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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2013 (03.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/003112 A1

(51) International Patent Classification:
G01N 33/50 (2006.01) *A61P 35/00* (2006.01)
A61K 31/00 (2006.01) *A61P 35/02* (2006.01)
A61K 31/255 (2006.01) *A61P 37/00* (2006.01)
A61K 31/26 (2006.01)

(21) International Application Number:
PCT/US2012/043074

(22) International Filing Date:
19 June 2012 (19.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/501,522 27 June 2011 (27.06.2011) US

(71) Applicant *(for all designated States except US)*: **THE JACKSON LABORATORY** [US/US]; 600 Main Street, Bar Harbor, Maine 04609 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MILLS, Kevin David** [US/US]; 41 Meadow Drive, Bar Harbor, Maine 04609 (US). **HASHAM, Muneer Gulamhusien** [US/US]; 106 Gary Moore Road, Ellsworth, Maine 04605 (US). **MCPHEE, Caroline Gardner** [US/US]; 13 Hodgdon Road, Seal Cove, Maine 04674 (US).

(74) Agents: **RESNICK, David S.** et al.; NIXON PEABODY LLP, 100 Summer St., Boston, Massachusetts 02110-2131 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report (Art. 21(3))*

[Continued on next page]

(54) **Title**: METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER AND AUTOIMMUNE DISEASE

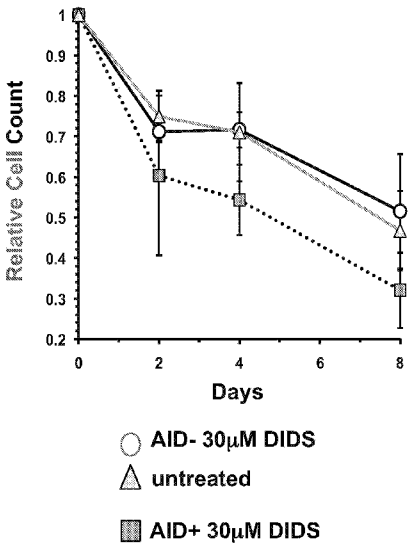


FIG. 17

(57) **Abstract**: The technology described herein relates to methods of inducing cell death. The technology described herein further relates to treating conditions including cancers and autoimmune diseases comprising administering inhibitors of double strand break repair. Also described herein are inhibitors of double strand break repair and methods of screening for such inhibitors.

WO 2013/003112 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER AND AUTOIMMUNE DISEASE

Cross-Reference to Related Applications

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/501,522 filed June 27, 2011, the contents of which are incorporated herein by reference in their entirety.

Sequence Listing

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 7, 2012, is named 060636PC.txt and is 547,092 bytes in size.

Technical Field

[0003] The technology described herein relates to methods of treating cancers and autoimmune diseases expressing activation-induced cytidine deaminase (AID) by inhibiting DNA double strand break repair mechanisms.

Background

[0004] In 2010, there were an estimated 137,000 new cases of leukemia, lymphoma and multiple myeloma, and more than 54,000 deaths from these cancers in the United States alone. The current standard of care in leukemia/lymphoma treatment often involves intensive, long-term chemotherapy, which can be physically taxing for the patient. Common side effects of conventional chemotherapy include immune system disruption, myelosuppression, bone marrow destruction, nausea, fatigue, liver toxicity, weight loss, hair loss, long-term cognitive impairment and therapy-related secondary tumors. A major problem with standard chemotherapy is the damage done to otherwise healthy cells and tissues in the cancer patient. Current treatment often fails to achieve long-term remission, and patients who do survive routinely experience long-lasting chemotherapy-related health concerns that prevent them from ever being truly well.

[0005] Selective targeting of the therapy specifically to the cancer cells could ameliorate most of these devastating side effects. Unfortunately, with few exceptions, selective targeting is technically difficult or impossible. Additional or alternative approaches to selectively target cancer cells, while minimizing off-target side effects, are therefore desperately needed.

Summary

[0006] The technology described herein is directed to treating cells having an active DNA editing enzyme with an inhibitor of DNA repair. As used herein, "DNA editing enzyme"

refers to an enzyme which normally catalyzes the mutation, exchange or excision of DNA segments, particularly enzymes which can generate or promote the generation of point mutations, DNA single strand breaks, DNA double-strand breaks or protein-DNA adducts. A DNA editing enzyme, as referred to herein, is not necessarily site-specific in its action. Similarly, it is not necessarily cell specific. In some embodiments, the cell is a B cell expressing a detectable amount of such an enzyme. Non-limiting examples of DNA editing enzymes include, but are not limited to Recombination Activating Gene 1 (RAG1; NCBI Gene ID: 5896, e.g. SEQ ID NO: 0157; NCBI Ref: NM_000448 (mRNA) and SEQ ID NO 0158; NCBI Ref: NP_000439 (polypeptide)), Recombination Activating Gene 1 (RAG2; NCBI Gene ID: 5897, e.g. SEQ ID NO: 0159; NCBI Ref: NM_001243785(mRNA) and SEQ ID NO: 160; NCBI Ref: NP_001230714 (polypeptide)), Sporulation-specific protein 11 (SPO11; NCBI Gene ID: 23626, e.g. SEQ ID NO: 0161; NCBI Ref: NM_012444 (mRNA) and SEQ ID NO 0162; NCBI Ref: NP_036576 (polypeptide)), APOBEC family members and/or AID. In some embodiments, the DNA editing enzyme can be AID.

[0007] In some embodiments, the DNA editing enzyme can be a member of the APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) family. As used herein "APOBEC family" refers to a family of cytidine deaminase enzymes having an N-terminal zinc-dependent cytidine deaminase catalytic domain comprising and a C-terminal pseudocatalytic domain. Non-limiting examples of APOBEC family members include AID, APOBEC1, APOBEC2, APOBEC3A, APOBEC3C, APOBEC3E, APOBEC3F, APOBEC3G, APOBEC3H, and APOBEC4.

[0008] Embodiments of the technology described herein utilize a DNA editing enzyme such as activation-induced cytidine deaminase (AID, or AICDA), a B-cell recombinase, which causes widespread genomic breaks when expressed in cells. Further, the inventors have discovered that when DNA homologous recombination ability (double strand break repair) is diminished and/or inhibited, this activity of a DNA editing enzyme , such as AID will cause cell death. Specifically, as demonstrated herein, inhibition of DNA double-strand break (DSB) repair in a cell expressing AID results in cytotoxicity due to the uncorrected off-target double strand breaks generated by AID.

[0009] Provided herein, in one aspect, is a cancer treatment paradigm that selectively induces self-destruction of cells expressing AID, e.g. cancerous B-cells or B-cells of an autoimmune disease, or other cancerous cells such as intestine cancer cells, colon cancer cells, lung cancer cells, liver cancer cells, epithelial cancer cells, breast cancer cells, esophageal cancer cells, thyroid cancer cells, prostate cancer cells, renal cancer, melanoma

etc. In some embodiments, the method selectively treats, e.g. cancer cells (while sparing normal cells), by exploiting DNA recombination systems to induce tumor cell self-destruction. This approach takes advantage of the finding that AID induces widespread genomic breaks and cell death in cells that have diminished DNA homologous recombination ability. As described herein, the inventors have determined that when a population of cells characterized by elevated expression of AID is treated with an inhibitor of double strand break repair (DSB), cell death occurs. Accordingly, methods for treating patients with cancers or autoimmune diseases having elevated AID expression with an inhibitor of double strand break repair are provided.

[0010] The inhibitor of DSB repair can be an inhibitor which reduces the expression or activity of any gene or protein necessary for DSB repair. In certain embodiments provided herein, the inhibitor of DSB repair is an inhibitor which reduces or inhibits the expression or activity of Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4 (DNA Ligase 4); XRCC4; PRKDC (DNA-PKcs7 XRCC7); DCLRE1C; XRCC6 (Ku70); XRCC5 (Ku80) and/or XLF (NHEJ1; XRCC4-like factor). In certain embodiments provided herein, the inhibitor of DSB repair is an inhibitor which reduces the expression or activity of Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4 (DNA Ligase 4); XRCC4; PRKDC (DNA-PKcs7 XRCC7); DCLRE1C; XRCC6 (Ku70); XRCC5 (Ku80) and/or XLF (NHEJ1; XRCC4-like factor). In some embodiments, the inhibitor of double strand break repair can inhibit a Rad51 family member (e.g. Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3). In some embodiments, the inhibitor of double strand break repair can inhibit a Non-homologous end joining (NHEJ) protein member (e.g. LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5;XLF).

[0011] In certain embodiments provided herein the DSB repair inhibitor, is a RAD51-mediated strand exchange repair inhibitor and is a stilbene derivative. Stilbene derivatives can include, but are not limited to, stilbene ((*E*)-1,2-Diphenylethene), trans-stilbene, ((*E*)-stilbene, *trans*-1,2-diphenylethylene) derivatives, cis-stilbene derivatives, combretastatin (5-[(2*R*)-2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl]-2-methoxyphenol), resveratrol (trans-3,5,4'-Trihydroxystilbene; (*E*)-5-(4-hydroxystyryl)benzene-1,3-diol), diethylstilboestrol (4,4'-(3E)-hex-3-ene-3,4-diyldiphenol), colchicine, and ((S) N-(5,6,7,9-tetrahydro- 1,2,3, IO-tetramethoxy-9-oxobenzo [alpha] heptaien-7-yl) acetamide). In one embodiment, the inhibitor of RAD51-mediated strand exchange repair is 4,4'diisothiocyanostilbene-2,2'-

disulfonic acid (DIDS). It has been reported that DIDS disrupts Rad51 complexes and inhibits heteroduplex formation (Ishida, T., et al., Nucleic Acids Res, 2009, 37(10): p. 3367-76).

[0012] In some embodiments provided herein, the DSB repair inhibitor is salazinic acid or a derivative thereof. In certain embodiments provided herein, the DSB repair inhibitor is stictic acid or a derivative thereof. In some embodiments provided herein, the DSB repair inhibitor is STK856883 or a derivative thereof. In some embodiments provided herein, the DSB repair inhibitor is 4'-Bromo-3'nitropropiophenone (NS-123) or a derivative thereof (Lally et al, Cancer Res 2007, 67; 8791).

[0013] Any cancer with an elevated level of a DNA editing enzyme can be treated according to the methods and compositions described herein. For example, the cancer may be breast, prostate, ovarian, brain, skin, colorectal (colon; large intestine), liver, lymphoma, lung, oral, head and neck, spleen, lymph node, small intestine, blood cells, stomach, kidney, pancreatic, endometrium, testicle, skin, esophagus, bone marrow, blood, cervical, bladder, Ewing's sarcoma, thyroid, a glioma, and/or gastrointestinal. The invention is applicable to other cancers discussed herein, including pre-cancers. In certain embodiments the cancer to be treated is a cancer of B cell, e.g. chronic lymphocytic leukemia (CLL).

[0014] Any cancer expressing AID can be treated. In certain embodiments, the cancer to be treated is a lymphoma or leukemia. In certain embodiments, the lymphoma to be treated is a Non-Hodgkin's lymphoma, e.g. including but not limited to Burkitt's lymphoma, follicular lymphoma, chronic lymphocytic leukemia (CLL), B-cell acute lymphocytic leukemia (B-ALL), acute lymphoblastic leukemia, hairy cell leukemia, splenic marginal zone lymphoma, Diffuse large B-cell lymphoma (DLBCL, DLBL, DLCL) and/or plasmacytoma. In certain embodiments the cancer to be treated is a leukemia, e.g. including but not limited to Hodgkin's disease, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), MALT lymphoma and/or T-cell leukemia and lymphoma. In certain embodiments the cancer to be treated is a sarcoma, a carcinoma, colon cancer, liver cancer, gastric cancer, intestinal cancer, lung cancer, breast cancer, prostate cancer, renal cancer, melanoma, thyroid cancer, esophageal cancer, and/or cholangiocarcinoma.

[0015] Any autoimmune disease with an elevated level of a DNA editing enzyme can be treated. In certain embodiments the DNA editing enzyme is AID. In certain embodiments, the autoimmune disease to be treated is lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, subacute cutaneous lupus

erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, autoimmune mediated hematological disease, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, and/or inflammatory gastritis.

[0016] In certain embodiments the DSB repair inhibitor is contained in a composition comprising the inhibitor and a pharmaceutically acceptable carrier. In further embodiments the DSB repair inhibitor can be contained in a composition comprising a pharmaceutically acceptable carrier and another chemotherapeutic compound. In certain embodiments a composition comprising a DSB repair inhibitor can be administered to a patient who is also receiving another treatment for cancer. In certain embodiments a composition comprising a DSB repair inhibitor can be administered to a patient who is also receiving another treatment for an autoimmune disease.

[0017] In certain embodiments, treating a patient having a cancer with high AID expression with a DSB repair inhibitor decreases an indicator, a marker, a symptom, the severity, the rate of metastasis, recurrence and/or tumor size of the cancer by at least 10%, *e.g.*, by at least 20%, at least 30%, at least 50%, at least 75%, at least 80%, at least 90% or more as compared to the indicator, marker, symptom, severity, metastasis, recurrence and/or tumor size prior to treatment with the DSB repair inhibitor or as compared to patients not receiving treatment with a DSB repair inhibitor.

[0018] In certain embodiments, treating a patient having an autoimmune disease with high AID expression with a DSB repair inhibitor decreases an indicator, a marker, a symptom, and/or the severity, of the autoimmune disease by at least 10%, *e.g.*, by at least 20%, at least 30%, at least 50%, at least 75%, at least 80%, at least 90% or more as compared to the indicator, marker, symptom, severity, metastasis, recurrence and/or tumor size prior to treatment with the DSB repair inhibitor or as compared to patients not receiving treatment with a DSB repair inhibitor.

[0019] Also provided herein are methods for determining if a cancer or autoimmune disease in a patient would be responsive to treatment by a DSB repair inhibitor by determining the level of protein or mRNA of AID in cells of that patient. In some embodiments, the level of AID mRNA and/or protein in cancerous cells obtained from the subject is determined. In some embodiments, the level of AID mRNA and/or protein is determined in autoreactive cells obtained from the subject. A high level of an AID expression product, i.e. mRNA or protein, indicates the disease is treatable by a DSB repair

inhibitor. For example, a subject having cells that express elevated levels of AID may be identified by measuring the level of AID protein or mRNA in a test sample of cells obtained from a subject suspected of having elevated levels and comparing that level to the level of AID found in a sample of the same type of cells obtained from a healthy subject, wherein an increased amount of AID in the test sample is indicative of a subject in need of treatment with an inhibitor of double strand break repair.

[0020] In certain embodiments the determining of the level of AID protein involves the use of one or more of the following assays; Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay; fluorescence in situ hybridization (FISH); immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; *in situ* immunoassay; precipitation reaction; agglutination assay; complement fixation assay; immunofluorescence assay; protein A assay; mass spectroscopy and/or immunoelectrophoresis assay. In certain embodiments the determining of the level of AID protein involves the use of an antibody, an antibody fragment, a polypeptide comprising an epitope-binding fragment of an antibody, a monoclonal antibody, a monoclonal antibody fragment, a protein binding protein, and/or a AID-binding peptide.

[0021] In certain embodiments, the determining of the level of AID mRNA involves the use of one or more of the following assays; RT-PCR, quantitative RT-PCR, RNA-seq, Northern blot, microarray based expression analysis, transcription amplification and/or self-sustained sequence replication. In certain embodiments the determining of the level of AID mRNA involves the use of an antibody, an antibody fragment, a monoclonal antibody, and/or a monoclonal antibody fragment and/or a protein binding protein. In certain embodiments AID primers for RT-PCR include, but are not limited to SEQ ID NO:101 and SEQ ID NO:102.

[0022] In certain embodiments the level of AID is determined by its activity and can be determined by sequence analysis, PCR or FISH analysis of its target genes and/or the transcripts encoded by the target genes. AID target genes can include, but are not limited to IGH (NCBI Gene ID 3492), BCL6 (NCBI Gene ID 604; SEQ ID NO:001), MYC (NCBI Gene ID 4609; SEQ ID NO:002), BCL11A (NCBI Gene ID 53335; SEQ ID NO:003), CD93 (NCBI Gene ID 22918; SEQ ID NO:004), PIM1 (NCBI Gene ID 5292; SEQ ID NO:005) and/or PAX5 (NCBI Gene ID 5079; SEQ ID NO:006).

[0023] The detection of hypermutations in the gene loci is indicative of AID activity. In certain embodiments the activity of AID is determined by using whole genome sequencing or

full genome sequencing and determine the level of hypermutations over the whole genome or in the specific target genes including IGH, BCL6, MYC, BCL11a, CD93, PIM1 and/or PAX5.

[0024] In certain embodiments the activity of AID is determined by using FISH analysis to detect double strand break, e.g. DNA breakage detection fish (DBD-FISH) (Volpi and Bridger, BioTechniques, Vol. 45, No. 4, 385–409).

[0025] In certain embodiments the activity of AID is determined by using a phospho-H2AX assay (Rakiman et al., Advance Biotech 2008, 39-42).

[0026] In certain embodiments, the antibody, antibody fragment, monoclonal antibody, monoclonal antibody fragment, protein binding protein, and/or AID-binding peptide used to determine the level of AID mRNA or protein is labeled with a detectable label.

[0027] In certain embodiments, the effective dose of a DSB repair inhibitor can be administered to a patient once. In certain embodiments, the effective dose of a DSB repair inhibitor can be administered to a patient repeatedly.

[0028] In one aspect, the technology described herein relates to a method of causing cell death comprising: (a) administering to a cell an effective amount of a DNA editing enzyme; and (b) thereafter contacting the cell of step (a) with an inhibitor of double strand break repair, thereby causing cell death. In one aspect, the technology described herein relates to a method of sensitizing a cell to cell death comprising: (a) administering to a subject, a therapeutically effective amount of a DNA editing enzyme to sensitize a cell to cell death by use of an inhibitor of double strand break repair: and (b) thereafter administering to the subject an inhibitor of double strand break repair. In some embodiments, the DNA editing enzyme is administered in a form selected from the group consisting of: a polypeptide; a nucleic acid encoding a DNA editing enzyme; and a vector comprising a nucleic acid encoding a DNA editing enzyme. In some embodiments, the DNA editing enzyme can be a member of the APOBEC family. In some embodiments, the DNA editing enzyme can be activation-induced cytidine deaminase (AID).

[0029] The details of various embodiments are set forth in the description below. Other features, objects, and advantages of the technology described herein will be apparent from the description and the drawings, and from the claims.

Description of the Drawings

[0030] Figure 1 shows a flow cytometry data graph indicating that XRCC2 knockdown leads to activation induced cytotoxicity. Flow cytometry analysis of $eGFP^{+}$ cells from wild-type and $Trp53^{-/-}$ mouse splenocytes transduced with constructs expressing *Xrcc2*-specific

shRNA (XKD) or control shRNA (Ctrl), was performed 3 days after stimulation. Shown are wild-type (WT) cells transduced with Ctrl (white bars), wild-type cells transduced with XKD (black bars) and *Trp53*$^{-/-}$ cells transduced with XKD (grey bars). Data are representative of two experiments with three replicates, experiments (mean and s.e.m.).

[0031] Figure 2 shows a graph of flow cytometry data of activated (ACT) and non-activated (NON) wild-type (Aicda$^{+/+}$, open bars) or *Aicda*$^{-/-}$ mouse splenocytes (filled bars) transduced with *Xrcc2*-specific (XKD) or control shRNA (Ctrl). Flow cytometry analysis of eGFP^{+} cells was performed 3 days after stimulation. Data are representative of two experiments with four replicates, experiments (mean and s.e.m.).

[0032] Figure 3 shows a flow cytometry data graph from the B cells, transduced with *Xrcc2*-specific shRNA and stimulated for 0, 2 or 3 days with anti-CD40 plus IL-4; total counts of cells activated with anti-CD40 and IL-4 are normalized to those of cells stimulated with anti-CD40 alone. Day 0 data is shown in the white bars, Day 2 data is shown in the grey bars and Day 3 data is shown in the black bars. Data are representative of two experiments with four replicates, experiments (mean and s.e.m.). The x-axis shows the genotype of the cells.

[0033] Figure 4 shows foci of γ-H2AX in *Aicda*$^{+/+}$ and *Aicda*$^{-/-}$ XKD and control (Ctrl) splenic B cells grown in nonactivating (Non) or activating (Act) conditions, presented as the ratio of γ-H2AX^{+} cells (one or more foci; filled bar) to γ-H2AX^{-} cells (no foci; open bar).

[0034] Figure 5 shows a graph with the number of DSB repair foci in *Aicda*$^{+/+}$ and *Aicda*$^{-/-}$ XKD and control (Ctrl) splenic B cells. The y-axis represents the number of γ-H2AX foci; open bars represent the nonactivating and filled bars the activating conditions in *Aicda*$^{+/+}$ and *Aicda*$^{-/-}$ treated with XKD or control (Ctrl) shRNA splenic B cells. $*P < 0.05$ and $**P < 0.01$ (two-sample *t*-test). Data are representative of four experiments (error bars, s.e.m.).

[0035] Figure 6 shows the foci distribution of gamma-H2AX foci in activated XKD or control (Ctrl) mouse CH12-F3 cells.

[0036] Figure 7 shows a graph of cell counts indicating that DIDS treatment decreases survival of stimulated splenocytes. Cells isolated from the spleens of wild-type (AID+/+; filled markers) or AICDA knock-out (AID-/-, open markers) mice were stimulated with anti-CD40 antibodies and IL-4 on day 0 and day 2. DIDS was added on day 0 and day 2 at concentrations of 0 μM, 50 μM, 100 μM and 150 μM. The total number of viable cells was determined on days 1, 2, 3, 4 and 6 using Trypan blue staining.

[0037] Figures 8A-8B show graphs indicating that cancer cells display high levels of AICDA expression. Each column/tick on the x-axis represents a different cell or tissue type while the y-axis represents the level of AICDA expression as the fold change above the dataset medial level. Figure 8A shows expression data from a collection of 59 cancer-derived human cell lines. Figure 8B shows expression data from primary human tissues and cancers.

[0038] Figure 9 shows a graph of splenocyte viability using Guava EasyCyte Flow Cytometer. Cells isolated from the spleens of wild-type (WT) or AICDA knock-out (-/-) mice were stimulated with anti-CD40 antibodies and IL-4 on day 0 and day 2. DIDS was added on day 0 and day 2 at concentrations of 0 or 150 μM. WT cells stimulated with anti-CD40 antibodies plus IL-4 and treated with DIDS are shown as filled boxes, AICDA-/- cells stimulated with anti-CD40 antibodies plus IL-4 and treated with DIDS as circle; WT cells stimulated with anti-CD40 antibodies plus IL-4 are shown as open diamonds; and AICDA-/- cells stimulated with anti-CD40 plus IL-4 antibodies as open triangles. The total number of viable cells was determined every other day. Days are shown on the x-axis and the fraction of viable cells is shown on the y-axis.

[0039] Figure 10 shows screening results of DIDS derivatives using the MultiTox-Fluor Multiplex Cytotoxicity Assay. Compound identity is shown on the x-axis and the fraction of viable cells is shown on the y-axis.

[0040] Figure 11 shows primary human CLL cells from 14 primary chronic lymphocytic leukemia (CLL) patients treated with DIDS. CLL cells were treated with 0 uM (n=5, control), 150 uM (n=4), or 600 uM (n=2). DIDS with viable cell counts were determined by manual counting on a hemacytometer on days 2, 4, 6, and 8 of culture. Error bars indicate standard error of the mean.

[0041] Figure 12 shows a graph of primary AID-knockout mouse splenocytes seeded in cultures at day 0 at a concentration of 1X10^6 cells/ml in RPMI medium supplemented with aCD40 + IL-4 to activate the B-cells. Individual cultures were supplemented with 0 (circle), 0.5 (triangle), 5 (diamond), 50 (square), or 500 uM (circle) NS-123, and viable cells were counted after Trypan blue staining on days 1, 2, 3, and 4.

[0042] Figure 13 shows a graph for a dose response of NS-123 on viability of primary AID-knockout mouse splenocytes seeded in cultures at day 0 at a concentration of 1X10^6 cells/ml in RPMI medium supplemented with aCD40 + IL-4 to activate the B-cells. NS-123 concentration of 0, 5, 10, 20, 30 and 50 uM were tested.

[0043] Figure 14 shows a graph of primary mouse B-cells and their response to DIDS. Cells were then subjected to either 0 (filled circles) or 2.5 Gy (=250 rads; open circles). Error bars represent the standard error of the mean (S.E.M) from three independent experiments.

[0044] Figure 15A shows total cell numbers of non-activated CH12-F3 cells treated with the various DIDS concentrations. Figure 15B shows total cell numbers of activated CH12-F3 cells treated with the various DIDS concentrations. Results for 0 μM DIDS are shown by filled squares, 50 μM DIDS by filled circles, 100 μM DIDS by open squares, and 150 μM DIDS by open circles.

[0045] Figure 16A shows number of foci detected in AID-null (AID-/-) and AID positive (AID+/+) splenocytes isolated from AID-knockout mice and B6 wild type mice, activated and treated with 150 μM DIDS. Figure 16B shows the proportion of phospho-H2AX positive cells (filled bars) versus phospho-H2AX negative cells (open bars), quantified for AID+/+ in comparison to AID-/- cultures. Figure 16C shows the number of foci per cell was quantified for DIDS-treated AID+/+ (filled bars) versus AID-/- (open bars) cells.

[0046] Figure 17 shows cell viability of AID-expressing (AID+) or AID-negative (AID-) primary human CLL cells, untreated or treated with 30 μM DIDS.

[0047] Figure 18A shows RT-PCR expression of AID for primary human CLL cells. Figure 18B shows the cell viability of primary human CLL cells in response to DIDS.

[0048] Figure 19A shows the weight of BXSB.Yaa Cd8/IL15-/- mice treated with 25mg/kg DIDS. Figure 19B shows the IgG2b serum content in of BXSB.Yaa Cd8/IL15-/- mice treated with 25mg/kg DIDS.

[0049] Figures 20A-20B show a log-rank Mantel Cox survival plots after treatment of BXSB.Yaa Cd8/Il15-/- mice with either 25mg/kg DIDS (20A) or 50mg/kg DIDS (20B), shown as days after start of treatment.

[0050] Figures 21A-21B show survival of BXSB.Yaa Cd8/IL15-/- mice treated with either 25mg/kg DIDS (21A) or 50mg/kg DIDS (21B), plotted as age of the mice in days applying the Gehan-Breslow-Wilcoxan test.

[0051] Figure 22 shows that DIDS disrupts RAD51 focus formation after DNA damage. Irradiated cells not exposed to DIDS (0mM) show efficient focus formation. DIDS exposure (150mM) completely inhibits radiation-induced RAD51 focus formation, reducing the fraction of Rad51 focus+ cells to baseline levels (equivalent to those in the unirradiated, 0 Gy samples). Error bars show the standard error of the mean (S.E.M) from three independent experiments.

[0052] Figures 23A-23B show the number of phosphor-H2AX foci in AID-positive (AID+) and AID-negative (AID-) human cells depending on DIDS treatment. The number of foci are shown on the x-axis. Figure 23A depicts the results of treatment with a 0 μM DIDS control and Figure 23B depicts the results of treatment with 30 μM DIDS. Error bars represent the standard error of the mean (S.E.M.) for 4 independent cultures of the AID-/- (open bars) samples and 5 independent cultures of the AID+ samples (filled bars).

[0053] Figure 24 shows activated caspase 3 (AC3) positive cells depending on DIDS treatment and AID expression. Error bars represent standard error of the mean (S.E.M.) for 4 independent cultures of the AID- samples -/- (open bars) and 5 independent cultures of the AID+ samples filled bars).

[0054] Figure 25A shows the experimental design to test the effect of systemic DIDS treatment in a mouse model. Figure 25B shows the fraction change in body mass of control mice. Figure 25C shows the fraction change in body mass of mice treated with DIDS.

[0055] Figure 26 shows endpoint flow cytometry dot plot analysis of bone marrow, spleen, and peripheral blood from AID-/- and AID+/+ mice immunized with DNP-KLH and treated with 0, 10, or 50 mg/kg DIDS. Plots represent the population of cells in the lymphocyte gate stained for expression of B220 (y-axis) and CD19 (x-axis). The numbers in the upper right corner of each plot provide the percentage of B220+/CD19+ cells for each analysis. The progression of B-cell maturation from early/pre-GC to post-GC is indicated below.

[0056] Figure 27 shows RT-PCR expression analysis for AID and GAPDH (control) in Epstein-Barr virus transformed peripheral human B-lymphocytes.

Detailed Description

Definitions

[0057] For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in the art and its definition provided herein, the definition provided within the specification shall prevail.

[0058] Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 18th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-18-2); Robert S. Porter et al. (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-

569-8); The ELISA guidebook (Methods in molecular biology 149) by Crowther J. R. (2000); Fundamentals of RIA and Other Ligand Assays by Jeffrey Travis, 1979, Scientific Newsletters; Immunology by Werner Luttmann, published by Elsevier, 2006. Definitions of common terms in molecular biology are also be found in Benjamin Lewin, Genes IX, published by Jones & Bartlett Publishing, 2007 (ISBN-13: 9780763740634); Kendrew et al. (eds.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Intersciences, Coligan et al., eds..

[0059] Unless otherwise stated, the technology described herein was performed using standard procedures, as described, for example in Methods in Enzymology, Volume 289: Solid-Phase Peptide Synthesis, J. N. Abelson, M. I. Simon, G. B. Fields (Editors), Academic Press; 1st edition (1997) (ISBN-13: 978-0121821906); U. S. Pat. Nos: 4,965,343, and 5,849,954; Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (1982); Sambrook et al., Molecular Cloning: A Laboratory Manual (3 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2000); Davis et al., Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol.152, S. L. Berger and A. R. Kimmel Eds., Academic Press Inc., San Diego, USA (1987); Current Protocols in Protein Science (CPPS) (John E. Coligan, et. al., ed., John Wiley and Sons, Inc.), Current Protocols in Cell Biology (CPCB) (Juan S. Bonifacino et. al. ed., John Wiley and Sons, Inc.), and Culture of Animal Cells: A Manual of Basic Technique by R. Ian Freshney, Publisher: Wiley-Liss; 5th edition (2005), Animal Cell Culture Methods (Methods in Cell Biology, Vol. 57, Jennie P. Mather and David Barnes editors, Academic Press, 1st edition, 1998) which are all incorporated by reference herein in their entireties.

[0060] The singular terms “a”, “an” and “the” include plural referents unless context clearly indicates otherwise. Similarly, the word “or” is intended to include “and” unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, “e.g.” is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation “e.g.” is synonymous with the term “for example”.

[0061] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood

as modified in all instances by the term "about". The term "about" when used in connection with percentages can mean ±1%.

[0062] As used herein, the term "administer" refers to the placement of a composition into a subject by a method or route which results in at least partial localization of the composition at a desired site such that desired effect is produced. A compound or composition described herein can be administered by any appropriate route known in the art including, but not limited to, oral, enteral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary, nasal, intranasal, rectal, and topical (including buccal and sublingual) administration.

[0063] Exemplary modes of administration include, but are not limited to, injection, infusion, instillation, inhalation, or ingestion. "Injection" includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intra-cerebrospinal, and intrasternal injection and infusion. In preferred embodiments, the compositions are administered by intravenous infusion or injection.

[0064] As used herein, the terms "autoimmune disease" or "autoimmune disorder" refer to a condition that is immune-mediated due to an attack on self-tissues, such as when a subject's own antibodies react with host tissue, but can also involve an immune response to a microorganism. Such conditions include, but are not limited to, lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, discoid lupus, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis , autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease.

[0065] The terms "decrease", "reduce", "reduction", "inhibit" or "inhibition" are all used herein generally to mean a decrease by a statistically significant amount. However, for avoidance of doubt, "decrease", "reduced", "reduction", "inhibit" or "inhibition" means a decrease by at least 5 % as compared to a reference level, for example a decrease by at least about 10 %, or at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least

about 90% or at least about 95%, or at least about 98% or at least about 99%, or more as compared to a reference level.

[0066] The terms "increased", "increase" or "enhance" or "activate" or "elevated" are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms "increased", "increase" or "enhance" or "activate" or "elevated" means a statistically significant increase, such as an increase of at least 5% as compared to a reference level, for example an increase of at least about 10%, at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 5-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

[0067] The term "statistically significant" or "significantly" refers to statistical significance and generally means a two standard deviation (2SD) below or above normal, or lower, or higher concentration of the marker. The term refers to statistical evidence that there is a difference. It is defined as the probability of making a decision to reject the null hypothesis when the null hypothesis is actually true. The decision is often made using the p-value.

[0068] As used herein, the terms "compound" or "agent" are used interchangeably and refer to molecules and/or compositions that inhibit DSB repair. The compounds/agents include, but are not limited to, chemical compounds and mixtures of chemical compounds, e.g., small organic or inorganic molecules; saccharide; oligosaccharides; polysaccharides; biological macromolecules, e.g., peptides, proteins, and peptide analogs and derivatives; peptidomimetics; nucleic acids; nucleic acid analogs and derivatives; extracts made from biological materials such as bacteria, plants, fungi, or mammalian cells or tissues; naturally occurring or synthetic compositions; peptides; aptamers; and antibodies, or fragments thereof.

[0069] As used herein, the terms "test compound" or "test agent" refer to a compound or agent and/or compositions thereof that are to be screened for their ability to inhibit the expression and/or activity of a gene or protein involved in DSB repair, as identified herein.

[0070] As used herein, the term "DSB repair inhibitor" is any compound or agent that inhibits the repair of double-strand DNA breaks. In certain embodiments, such inhibitors can include inhibiting homologous recombination and non-homologous end joining (NHEJ). In certain embodiments, such inhibitors can include inhibitors of RAD51-mediated strand

exchange. In some embodiments, such inhibitors can include inhibitors of, e.g. Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

[0071] As used herein, the term "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically bind an antigen comprising one or more epitopes. The terms also refers to antibodies comprised of two immunoglobulin heavy chains and two immunoglobulin light chains as well as a variety of forms besides antibodies; including, for example, Fv, Fab, and F(ab)'2 as well as bifunctional hybrid antibodies (e.g., Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)) and single chains (e.g., Huston et al., Proc. Natl. Acad. Sci. U.S.A., 85, 5879-5883 (1988) and Bird et al., Science 242, 423-426 (1988), which are incorporated herein by reference) and single domain antibodies (sdAb) including for example nanobodies, camelids (VHH fragments) and immunoglobulin new antigen receptor (IgNAR) (Harmsen et al. 2007, Appl. Microbiol. Biotechnol. 77 (1): 13–22; Holt et al. 2003, Trends in Biotechnology 21 (11): 484–490; which are incorporated by reference herein in their entireties). (See, generally, Hood et al., Immunology, Benjamin, N.Y., 2ND ed. (1984), Harlow and Lane, Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory (1988) and Hunkapiller and Hood, Nature, 323, 15-16 (1986), which are incorporated herein by reference). The term also includes intrabodies, i.e. antibodies that work within the cell and bind to intracellular protein. Intrabodies can include whole antibodies or antibody binding fragments thereof, e.g. single Fv, Fab and F(ab)'2, etc. As used herein, the term "epitope" refers to a fragment of a polypeptide or protein or a non-protein molecule having antigenic or immunogenic activity in an animal, preferably in a mammal, and most preferably in a human. An epitope having immunogenic activity is a fragment of a polypeptide or protein that elicits an antibody response in an animal. An epitope to which an antibody immunospecifically binds can be determined by any method well-known to one of skill in the art, for example by immunoassays. Antigenic epitopes need not necessarily be immunogenic.

[0072] The term "protein binding protein" refers to a non-immunoglobulin binding protein and is selected from the group consisting of antibody substructure (e.g. Fc fragment), minibody, adnectin, anticalin, affibody, affilin, ankyrin repeat proteins, DARPin, knottin, glubody, C-type lectin-like domain protein, tetranectin, kringle domain (KD), kunitz domain protein, thioredoxin, cytochrome b562, zinc finger scaffold, Staphylococcal nuclease

scaffold, fibronectin or fibronectin dimer, tenascin, N-cadherin, E-cadherin, ICAM, titin, GCSF-receptor, cytokine receptor, glycosidase inhibitor, antibiotic chromoprotein, myelin membrane adhesion molecule P0, CD8, CD4, CD2, class I MHC, T-cell antigen receptor, CD1, C2 and I-set domains of VCAM-1,1-set immunoglobulin domain of myosin-binding protein C, 1-set immunoglobulin domain of myosin-binding protein H, I-set immunoglobulin domain of telokin, NCAM, twitchin, neuroglian, growth hormone receptor, erythropoietin receptor, prolactin receptor, interferon-gamma receptor, β-galactosidase/glucuronidase, β-glucuronidase, transglutaminase, T-cell antigen receptor, superoxide dismutase, tissue factor domain, cytochrome F, green fluorescent protein, GroEL, and thaumatin. Methods for preparation of such non-immunoglobulin binding proteins are well-known in the art (Binz et al. 2005, Nat Biotechnol 1257-6; Lee et al. 2010, Proc Natl Acad Sci USA 107(21):9567-71; Gebauer and Skerra 2009, Curr Opin Chem Biol. 13(3):245-255).

[0073] The term "expression" refers to the cellular processes involved in producing RNA and proteins and as appropriate, secreting proteins, including where applicable, but not limited to, for example, transcription, translation, folding, modification and processing. The terms "expression product" or "expression products" include RNA transcribed from a gene, and polypeptides obtained by translation of mRNA transcribed from a gene. In some embodiments, an expression product is transcribed from a sequence that does not encode a polypeptide, such as a microRNA or RNAi.

[0074] As used herein, the term "complementary" or "complementary base pair" refers to A:T and G:C in DNA and A:U in RNA. Most DNA consists of sequences of nucleotide only four nitrogenous bases: base or base adenine (A), thymine (T), guanine (G), and cytosine (C). Together these bases form the genetic alphabet, and long ordered sequences of them contain, in coded form, much of the information present in genes. Most RNA also consists of sequences of only four bases. However, in RNA, thymine is replaced by uridine (U).

[0075] The term "nucleic acids" or "nucleic acid sequence" used herein refers to any molecule, preferably a polymeric molecule, incorporating units of ribonucleic acid, deoxyribonucleic acid or an analog thereof, polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA), polymers thereof in either single- or double-stranded form. A single-stranded nucleic acid can be one strand nucleic acid of a denatured double- stranded DNA. Alternatively, it can be a single-stranded nucleic acid not derived from any double-stranded DNA. In one aspect, the template nucleic acid is DNA. In another aspect, the template is RNA. Suitable nucleic acid molecules are DNA, including genomic DNA, ribosomal DNA and cDNA. Other suitable nucleic acid molecules are RNA,

including mRNA, rRNA and tRNA. The nucleic acid molecule can be naturally occurring, as in genomic DNA, or it may be synthetic, i.e., prepared based up human action, or may be a combination of the two. Unless specifically limited, the term encompasses nucleic acids containing known analogs of natural nucleotides, which have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer, et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka, et al., J. Biol. Chem. 260:2605-2608 (1985), and Rossolini, et al., Mol. Cell. Probes 8:91-98 (1994)). The nucleic acid molecule can also have certain modification such as 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O--N-methylacetamido (2'-O-NMA), cholesterol addition, and phosphorothioate backbone as described in US Patent Application 20070213292; and certain ribonucleoside that are is linked between the 2'-oxygen and the 4'-carbon atoms with a methylene unit as described in US Pat No. 6,268,490, wherein both patent and patent application are incorporated hereby reference in their entirety. The term "nucleic acid" should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, and, single (sense or antisense) and double-stranded polynucleotides.

[0076] The term "gene" means the nucleic acid sequence (DNA) which is transcribed to RNA in vitro or in vivo when operably linked to appropriate regulatory sequences. The gene may or may not include regions preceding and following the coding region, e.g. 5' untranslated (5'UTR) or "leader" sequences and 3' UTR or "trailer" sequences, as well as intervening sequences (introns) between individual coding segments (exons).

[0077] As used herein, the terms "protein" and "polypeptide and "peptide" are used interchangeably herein to designate a series of amino acid residues connected to the other by peptide bonds between the alpha-amino and carboxy groups of adjacent residues. The terms "protein", and "polypeptide and "peptide", which are used interchangeably herein, refer to a polymer of amino acids, including modified amino acids (e.g., phosphorylated, glycated, glycosylated, etc.) and amino acid analogs, regardless of its size or function. Although

"protein" is often used in reference to relatively large polypeptides, and "peptide" is often used in reference to small polypeptides, usage of these terms in the art overlaps and varies. The term "peptide" as used herein refers to peptides, polypeptides, proteins and fragments of proteins, unless otherwise noted. The terms "protein" and "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product and fragments thereof. Thus, exemplary peptides or proteins include gene products, naturally occurring proteins, homologs, orthologs, paralogs, fragments and other equivalents, variants, fragments, and analogs of the foregoing.

[0078] The term "vector", as used herein, refers to a nucleic acid construct designed for delivery to a host cell or transfer between different host cells. As used herein, a vector can be viral or non-viral. A vector can include, but is not limited to, a cloning vector, an expression vector, a plasmid, a phage, a transposon, a cosmid, a bacterial artificial chromosome (BAC), a yeast artificial chromosome (YAC), a virus, a virion, a retrovirus etc. In some embodiments, the vector is episomal. The use of a suitable episomal vector provides a means of maintaining the nucleotide of interest in the subject in high copy number extra chromosomal DNA thereby eliminating potential effects of chromosomal integration.

[0079] As used herein, the term "expression vector" refers to a vector that has the ability to incorporate and express heterologous nucleic acid fragments in a cell. An expression vector may comprise additional elements, for example, the expression vector may have two replication systems, thus allowing it to be maintained in two organisms, for example in human cells for expression and in a prokaryotic host for cloning and amplification. An expression vector may direct expression of an RNA or polypeptide from sequences linked to transcriptional regulatory sequences on the vector. The sequences expressed will often, but not necessarily, be heterologous to the cell. An expression vector may comprise additional elements, for example, the expression vector may have two replication systems, thus allowing it to be maintained in two organisms, for example in human cells for expression and in a prokaryotic host for cloning and amplification.

[0080] As used herein, the term "viral vector" refers to a nucleic acid vector construct that includes at least one element of viral origin and has the capacity to be packaged into a viral vector particle. The viral vector can contain the target gene in place of non-essential viral genes. The vector and/or particle may be utilized for the purpose of transferring any nucleic acids into cells either in vitro or *in vivo*. Numerous forms of viral vectors are known in the art, including but not limited to cytomegalovirus, adenovirus, lentivirus, pox virus, herpes virus, retrovirus (e.g. MMLV, HIV-1 or ALV). Viral can be used as carriers of a

nucleic acid modulatory compound into the cell. For example, constructs containing the modulatory compound may be integrated and packaged into non-replicating, defective viral genomes like Adenovirus, Adeno-associated virus (AAV), or Herpes simplex virus (HSV) or others, including retroviral and lentiviral vectors, for infection or transduction into cells. Alternatively, the construct may be incorporated into vectors capable of episomal replication, e.g. EPV and EBV vectors. The nucleic acid incorporated into the vector can be operatively linked to an expression control sequence when the expression control sequence controls and regulates the transcription and translation of that polynucleotide sequence.

[0081] The term "operatively linked" or "operably linked" as used herein refers to a nucleic acid in functional relationship with a second nucleic acid. The term "operably linked" encompasses functional connection of two or more nucleic acid molecules, such as an oligonucleotide or polynucleotide to be transcribed and a regulatory element such as a promoter or an enhancer element, which allows transcription of the oligonucleotide or polynucleotide to be transcribed. In some examples, transcription of a nucleic acid modulatory compound is under the control of a promoter sequence (or other transcriptional regulatory sequence) which controls the expression of the nucleic acid in a cell- type in which expression is intended. It will also be understood that the modulatory nucleic acid can be under the control of transcriptional regulatory sequences which are the same or which are different from those sequences which control transcription of the naturally-occurring form of a protein. In some instances the promoter sequence is recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required for initiating transcription of a specific gene. The promoter sequence may be a "tissue-specific promoter", which means a nucleic acid sequence that serves as a promoter, i.e., regulates expression of a selected nucleic acid sequence operably linked to the promoter, and which affects expression of the selected nucleic acid sequence in specific cells, e.g. lymphocytes or epithelial cells. The term also covers so-called "leaky" promoters, which regulate expression of a selected nucleic acid primarily in one tissue, but cause expression in other tissues as well.

[0082] As used herein, the term "heterologous nucleic acid fragments" refers to nucleic acid sequences that are not naturally occurring in that cell. For example, when a heterologous gene, such as DNA editing enzyme (e.g. AID) is inserted into the genome of a bacteria or virus, that gene is heterologous to that recipient bacteria or virus because the bacteria and viral genome do not naturally have the DNA editing enzyme gene.

[0083] The term "replication incompetent" as used herein means the viral vector cannot further replicate and package its genomes. For example, when the cells of a subject are

infected with replication incompetent recombinant adeno-associated virus (rAAV) virions, the heterologous (also known as transgene) gene is expressed in the patient's cells, but, the rAAV is replication defective (e.g., lacks accessory genes that encode essential proteins from packaging the virus) and viral particles cannot be formed in the patient's cells.

[0084] The term "isolated" or "partially purified" as used herein refers, in the case of a nucleic acid or polypeptide, to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) that is present with the nucleic acid or polypeptide as found in its natural source and/or that would be present with the nucleic acid or polypeptide when expressed by a cell, or secreted in the case of secreted polypeptides. A chemically synthesized nucleic acid or polypeptide or one synthesized using in vitro transcription/translation is considered "isolated."

[0085] As used herein in the context of disease, the terms "treat", "treatment", "treating" and the like, refer to a decrease in severity of indicators, symptoms, markers, physical parameters, tumor size or recurrence of a cancer as described herein. In the context of the technology described herein insofar as it relates to any of the conditions recited herein, the terms "treat", "treatment", "treating" and the like mean to relieve, alleviate, ameliorate, inhibit, slow down, delay, reverse, or stop the progression, aggravation, deterioration, progression, anticipated progression or severity of at least one symptom or complication associated with such cancer or autoimmune disorder or delaying the onset of the disease or disorder. In one embodiment, the symptoms of a cancer or an autoimmune disorder are alleviated by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%.

[0086] By "lower" in the context of a disease or disorder marker or symptom is meant a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably down to a level accepted as within the range of normal for an individual without such disease or disorder.

[0087] By "higher" in the context of a disease or disorder marker or symptom is meant a statistically significant increase in such level. The decrease can be, for example, at least 10%, at least 20%, at least 30%, at least 40%, at least 50 % or more, and is preferably up from a level accepted as within the range of normal for an individual without such disease or disorder.

[0088] As used herein, the phrase "therapeutically effective amount", "effective amount" or "effective dose" refers to an amount that provides a therapeutic benefit in the treatment, prevention, or management of a condition described herein, (e.g. cancer or an autoimmune

disease), e.g. an amount that provides a statistically significant decrease in at least one symptom of such a condition. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, a therapeutically effective amount can vary with the subject's history, age, condition, sex, as well as the severity and type of the medical condition in the subject, and administration of other pharmaceutically active agents.

[0089] As used herein, the term "pharmaceutical composition" refers to the active agent in combination with a pharmaceutically acceptable carrier commonly used in the pharmaceutical industry.

[0090] As used here, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, 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.

[0091] The term "pharmaceutically acceptable carrier" as used herein means any pharmaceutically acceptable material, composition, media, or vehicle, such as a liquid or solid filler, diluent, excipient (e.g., dyes, flavors, binders, emollients, fillers, lubricants, preservatives, cornstarch, lactose, talc, magnesium stearate, sucrose, gelatin, calcium stearate, silicon dioxide, shellac and glaze), solvent or encapsulating material, coating, surfactant, absorption delaying agents, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, salts, preservative, stabilizers, gels, disintegration agents, sweetening agents, such like materials and combinations thereof, as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. For example, the carrier does not decrease the impact of the agent on the treatment. In other words, a carrier is pharmaceutically inert. Some examples of materials which can serve as pharmaceutically-acceptable carriers include, but are not limited to: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository

waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C_2-C_{12} alcohols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, binding agents, fillers, lubricants, coloring agents, disintegrants, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative, water, salt solutions, alcohols, antioxidants, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like can also be present in the formulation. The terms such as "excipient", "carrier", "pharmaceutically acceptable carrier" or the like are used interchangeably herein.

[0092] As used herein, the term "small molecule" refers to a chemical agent which can include, but is not limited to, a peptide, a peptidomimetic, an amino acid, an amino acid analog, a polynucleotide, a polynucleotide analog, an aptamer, a nucleotide, a nucleotide analog, an organic or inorganic compound (i.e., including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

[0093] As used herein, a "subject" means a human or an animal. In one embodiment, the animal is a vertebrate such as a primate, rodent, domestic animal, avian species, fish or game animal. The terms, "patient", "individual" and "subject" are used interchangeably herein.

[0094] Preferably, the subject is a mammal. The mammal can be a human, non-human primate, mouse, rat, dog, cat, horse, or cow, but are not limited to these examples. Mammals other than humans can be advantageously used as subjects that represent animal models of cancer, an autoimmune disease, or an inflammatory disease. In addition, the methods described herein can be used to treat domesticated animals and/or pets. A subject can be male or female. A subject can be one who has been previously diagnosed with cancer or an

autoimmune disease, or a subject identified as having one or more complications related to cancer or an autoimmune disease, and optionally, but need not have already undergone treatment for the cancer or an autoimmune disease or the one or more complications related to the cancer or an autoimmune disease. A subject can also be one who is not suffering from cancer or an autoimmune disease. For example, a subject can be one who exhibits one or more risk factors for cancer or an autoimmune disease or one or more complications related to cancer or an autoimmune disease. A subject can be asymptomatic for cancer or an autoimmune disease or one or more complications related to cancer or an autoimmune disease. In one embodiment, the subject is selected for having, or being at risk for having, cancer or an autoimmune disease. A subject can also be one who has been diagnosed with or identified as having one or more complications related to cancer or an autoimmune disease, or alternatively, a subject can be one who has not been previously diagnosed with or identified as having one or more complications related to cancer or an autoimmune disease.

[0095] As used herein, the term "alkyl" refers to saturated straight-chain, branched-chain, or cyclyl hydrocarbon radicals. The term "alkyl" includes cycloalkyl or cyclic alkyl. In addition, backbone of the alkyl can comprise one or more heteroatoms, such as O, N, or S. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, neopentyl, n-hexyl, and n-octyl radicals.

[0096] As used herein, the term "alkenyl" refers to unsaturated straight-chain, branched-chain, or cyclyl hydrocarbon radicals having at least one carbon-carbon double bond. The term "alkenyl" includes cycloalkyl or cyclic alkenyl. In addition, backbone of the alkenyl can comprise one or more heteroatoms, such as O, N, or S. Examples of alkenyl radicals include, but are not limited to, allyl, butenyl, and hexenyl radicals.

[0097] As used herein, the term "alkynyl" refers to unsaturated hydrocarbon radicals having at least one carbon-carbon triple bond. In addition, backbone of the alkynyl can comprise one or more heteroatoms, such as O, N, or S. Representative alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 1-butynyl, isopentynyl, 1,3-hexadiynyl, n-hexynyl, 3-pentynyl, 1-hexen-3-ynyl and the like.

[0098] As used herein, the term "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine. The term "halogen radioisotope" refers to a radionuclide of an atom selected from fluorine, chlorine, bromine and iodine.

[0099] As used herein, the term "cyclyl" refers to a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cyclyl group may be optionally substituted. Examples

of cyclyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[00100] As used herein, the term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1 -6 heteroatoms if bicyclic, or 1 -9 heteroatoms if tricyclic, sAICD heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1 -6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0,1, 2 or 3 atoms of each ring can be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like.

[00101] As used herein, the term "aryl" refers to a 6-carbon monocyclic, 10-carbonbicyclic, 14-carbon tricyclic aromatic ring system wherein each ring can have 1 to 4 substituents. Examples of aryl groups include, but are not limited to, phenyl, methylphenyl, naphthyl, and anthracenyl.

[00102] As used herein, the term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1 -6 heteroatoms if bicyclic, or 1 -9 heteroatoms if tricyclic, sAICD heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1 -6, or 1 -9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein each ring may have 1 to 5 substituents. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, pyrrolyl, pyrazinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like.

[00103] As used herein, the term "substituted" refers to independent replacement of one or more of the hydrogen atoms on the substituted moiety with substituents independently selected from, but not limited to, alkyl, alkenyl, heterocycloalkyl, alkoxy, aryloxy, hydroxy, amino, amido, alkylamino, arylamino, cyano, halo, mercapto, nitro, carbonyl, acyl, aryl and heteroaryl groups.

[00104] As used here in the term "isomer" refers to compounds having the same molecular formula but differing in structure. Isomers which differ only in configuration and/or conformation are referred to as "stereoisomers." The term "isomer" is also used to refer to an enantiomer.

[00105] The term "enantiomer" is used to describe one of a pair of molecular isomers which are mirror images of each other and non-superimposable. Other terms used to designate or refer to enantiomers include "stereoisomers" (because of the different arrangement or stereochemistry around the chiral center; although all enantiomers are

stereoisomers, not all stereoisomers are enantiomers) or "optical isomers" (because of the optical activity of pure enantiomers, which is the ability of different pure enantiomers to rotate planepolarized light in different directions). Enantiomers generally have identical physical properties, such as melting points and boiling points, and also have identical spectroscopic properties. Enantiomers can differ from each other with respect to their interaction with plane-polarized light and with respect to biological activity.

[00106] The term "racemic mixture", "racemic compound" or "racemate" refers to a mixture of the two enantiomers of one compound. An ideal racemic mixture is one wherein there is a 50:50 mixture of both enantiomers of a compound such that the optical rotation of the (+) enantiomer cancels out the optical rotation of the (-) enantiomer.

[00107] The term "resolving" or "resolution" when used in reference to a racemic mixture refers to the separation of a racemate into its two enantiomorphic forms (i.e., (+) and (-); or (R) and (S) forms). The terms can also refer to enantioselective conversion of one isomer of a racemate to a product.

[00108] The term "enantiomeric excess" or "ee" refers to a reaction product wherein one enantiomer is produced in excess of the other, and is defined for a mixture of (+)- and (-)-enantiomers, with composition given as the mole or weight or volume fraction $F_{(+)}$ and $F_{(-)}$ (where the sum of $F_{(+)}$ and $F_{(-)} = 1$). The enantiomeric excess is defined as $* F_{(+)} - F_{(-)}^{*}$ and the percent enantiomeric excess by $100x* F_{(+)} - F_{(-)}^{*}$. The "purity" of an enantiomer is described by its ee or percent ee value (% ee).

[00109] Whether expressed as a "purified enantiomer" or a "pure enantiomer" or a "resolved enantiomer" or "a compound in enantiomeric excess", the terms are meant to indicate that the amount of one enantiomer exceeds the amount of the other. Thus, when referring to an enantiomer preparation, both (or either) of the percent of the major enantiomer (e.g. by mole or by weight or by volume) and (or) the percent enantiomeric excess of the major enantiomer may be used to determine whether the preparation represents a purified enantiomer preparation.

[00110] The term "enantiomeric purity" or "enantiomer purity" of an isomer refers to a qualitative or quantitative measure of the purified enantiomer; typically, the measurement is expressed on the basis of ee or enantiomeric excess.

[00111] The terms "substantially purified enantiomer", "substantially resolved enantiomer" "substantially purified enantiomer preparation" are meant to indicate a preparation (e.g. derived from non-optically active starting material, substrate, or intermediate) wherein one enantiomer has been enriched over the other, and more preferably,

wherein the other enantiomer represents less than 20%, more preferably less than 10%, and more preferably less than 5%, and still more preferably, less than 2% of the enantiomer or enantiomer preparation.

[00112] The terms "purified enantiomer", "resolved enantiomer" and "purified enantiomer preparation" are meant to indicate a preparation (e.g. derived from non-optically active starting material, substrates or intermediates) wherein one enantiomer (for example, the R-enantiomer) is enriched over the other, and more preferably, wherein the other enantiomer (for example the S-enantiomer) represents less than 30%, preferably less than 20%, more preferably less than 10% (e.g. in this particular instance, the R-enantiomer is substantially free of the S-enantiomer), and more preferably less than 5% and still more preferably, less than 2% of the preparation. A purified enantiomer may be synthesized substantially free of the other enantiomer, or a purified enantiomer may be synthesized in a stereopreferred procedure, followed by separation steps, or a purified enantiomer may be derived from a racemic mixture.

[00113] The term "enantioselectivity", also called the enantiomeric ratio indicated by the symbol "E", refers to the selective capacity of an enzyme to generate from a racemic substrate one enantiomer relative to the other in a product racemic mixture; in other words, it is a measure of the ability of the enzyme to distinguish between enantiomers. A nonselective reaction has an E of 1, while resolutions with E's above 20 are generally considered useful for synthesis or resolution. The enantioselectivity resides in a difference in conversion rates between the enantiomers in question. Reaction products are obtained that are enriched in one of the enantiomers; conversely, remaining substrates are enriched in the other enantiomer. For practical purposes it is generally desirable for one of the enantiomers to be obtained in large excess. This is achieved by terminating the conversion process at a certain degree of conversion.

[00114] Compounds of the present invention may exist in prodrug form. As used herein, "prodrug" is intended to include any carriers which release the active parent drug or compounds that are metabolized in vivo to an active drug or other compounds employed in the methods of the invention in vivo when such prodrug is administered to a subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds employed in some methods of the invention may, if desired, be delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the invention may be 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. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Other examples include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkyl aryl esters such as methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, sec-butyl, tertbutyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

[00115] As used herein, the term "pharmaceutically-acceptable salts" refers to the inorganic and organic salts, conventional nontoxic salts or quaternary ammonium salts of a therapeutic agent or compound or prodrug, e.g., from non-toxic organic or inorganic acids. These salts can be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting a therapeutic agent in its free base or acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed during subsequent purification. Conventional nontoxic salts include those derived from inorganic acids such as sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, adipic, aspartic, carbonic, gluconic, glucuronic, malonic, oleic, pamoic and the like. See, for example, Berge et al., "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19 (1977) or P. H. Stahl and C. G. Wermuth, editors, Handbook of Pharmaceutical Salts: Properties, Selection and Use, Weinheim/Zürich:Wiley-VCH/VHCA, 2002, content of which is herein incorporated by reference in its entirety. The terms "salt" or "salts" is used interchangeably with "pharmaceutically acceptable salts".

[00116] In some embodiments of the aspects described herein, representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, succinate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, monohydrogenphosphate, glucoheptonate, lactobionate, laurylsulphonate, pyrophosphate, pyrosulfate, and sodium salts and the like.

[00117] All patents and other publications identified are expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with the

technology described herein. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

DNA-editing enzymes and double strand DNA break repair

[00118] Embodiments of the technology described herein are based on the discovery that activation-induced cytidine deaminase (AID, or AICDA, also known as ARP2, CDA2 or HIGM2), a DNA-editing enzyme that is a member of the apolipoprotein B mRNA editing enzymes, catalytic polypeptide-like (APOBEC), will cause widespread genomic breaks and cell death in cells with diminished homologous recombination ability (e.g. cells with diminished DNA double strand break repair abilities). Accordingly, provided herein is a method of causing cell death comprising detecting increased expression of a DNA-editing enzyme (e.g. AID) in a cell and thereafter contacting the cell with an inhibitor of double strand break repair; thereby resulting in cell death. Accordingly, provided herein is a method of causing cell death comprising increasing expression of a DNA-editing enzyme (e.g. AID) in a cell and thereafter contacting the cell with an inhibitor of double strand break repair; thereby resulting in cell death. Accordingly, provided herein is a method of causing cell death comprising administering to a cell a therapeutically effective amount of a DNA editing enzyme (e.g. AID) and thereafter contacting the cell with an inhibitor of double strand break repair; thereby resulting in cell death.

[00119] AID, encoded by the AICDA gene (NCBI Gene ID: 57379), is required for proper B-cell function and is most prominently expressed in centroblast B-cells. The protein is involved in somatic hypermutation, gene conversion, and class-switch recombination of immunoglobulin genes. AID is normally expressed almost exclusively in antigen-activated germinal center B-cells, where it initiates immunoglobulin isotype class switching (Manis et al. 2002, Trends Immunol, 23, 31-39; Chaudhuri and Alt, Nat Rev Immunol, 2004, 4, 541-552; Longerich et al., Curr Opin Immunol, 2006, 18, 164-174; Chaudhuri et al., Adv Immunol 2007, 94, 157-214). AID is required for somatic hypermutation and immunoglobulin class switching in activated B cells. AID expression is regulated by CD40 ligand, B-cell receptor, IL4R, or Toll-like receptor stimulation (Crouch et al., J Exp Med 2007 204:1145-1156; Muramatsu et al., J Biol Chem 1999 274:18470-6). After activation, AID is transiently upregulated, induces point mutations or DNA double strand breaks in a

sequence non-specific manner within immunoglobulin genes, and is then downregulated (Longerich et al., Curr Opin Immunol, 2006, 18, 164-176; Chaudhuri et al., Adv Immunol 2007, 94, 157-214). Overall, AID is active in only a tiny population of normal cells (antigen-activated B-cells) at any given time. The genomic rearrangements and mutations controlled by AID lead to the development of antigen-recognition diversity, receptor editing and lymphoid effector function required for functional adaptive immunity (Mills, et al. Immunol Rev 2003 194:77-95). Recently it has been reported that AID has off-target point mutation activities (Liu, M. et al., Nature 2008, 451, 841–845; Liu and Schatz, Trends Immunol. 2009, 30, 173–181; Pérez-Durán et al., Carcinogenesis. 2007, 28(12):2427-33). Robbiani et al. has reported off-target activities of AID in B- cells, especially c-myc/IgH translocations (Robbiani et al., Mol Cell 2009, 36(4):631-41). AID expression accelerates the rate of tumor development in Bcl6 transgenic mice (Pasqualucci et al., 2008, Nat. Genet. 40, 108–112). However, deregulated AID does not necessarily cause malignancy or translocation-associated cancer on its own in B cells (Muto et al., 2006, Proc. Natl. Acad. Sci. USA 103, 2752–2757; Okazaki et al., 2003, J. Exp. Med. 197, 1173–1181; Shen et al., 2008, Mol. Immunol. 45, 1883–1892). In addition, despite its obligate role in c-myc/IgH translocation, AID is not required for the development of plasmacytosis or plasmacytoma in IL-6 transgenic or pristane-treated mice, respectively (Kovalchuk et al., 2007, J. Exp. Med. 204, 2989–3001; Ramiro et al., 2004, J. Exp. Med. 200, 1103–1110). However, most human B cell lymphoma-associated translocations do not involve c-myc, and many do not involve Ig genes (Kuppers, 2005, Oncogene 20, 5580–5594).

[00120] Overexpression of AID has been reported in chronic lymphocytic leukemia (CLL) (Hancer et al. Leuk Lymphoma. 2011 Jan;52(1):79-84; Heintel et al., Leukemia. 2004 Apr;18(4):756-62). Further, AID expression has been shown to be correlated with blast crisis B lineage leukemia and therapy resistance in myeloid leukemia and to be associated with generally poor prognosis in chronic B lymphocytic leukemia (Mao et al., Br J Dermatol 2001, 145:117-122; Chaudhuri et al., Nature 2004, 430:992-8). Further expression of AID in tumor cells from a variety of cancers has been reported including but not limited to lung, breast, gastric, colon, intestinal, liver cancer and choriangiocarcinoma (Greeve et al., Blood 2003, 1010, 3574-3580; Feldhahn et al., J Exp Med 2007, 204, 1157-1166; Kotani et al., PNAS USA 2007, 104, 1616-1620; Engels et al., 2008, Appl Immunohistochem Mol Morphol 16, 521-529; Klemm et al., 2009, Cancer Cell 6, 232-245; Palacios et al., 2010, Blood 115(22), 4488-4496; Leuenberger et al., 2009, Mod Pathol 32, 177-186; Gruber et al., 2010, Cancer Res 70, 7411-7420; inflammatory cancer (Marusawa 2008, Int J Biochem Cell Biol.40, 399-

402); follicular lymphoma (Hardianti et al., 2004, Leukemia 18, 826-831; Shikata et al., 2012, Cancer Sci. 103(3):415-21); thyroid cancer (Qiu et al. 2012, Mod Pathol 25(1),36-45); breast cancer (Borchert et al. 2011, BMC Cancer 11:347); Marusawa, et al., 2011, Adv Immunol 111:109-41; Zhang et al. 2012, Hum Pathol 43(3):423-34; Komori et al., 2008, Hepatology 47(3):888-896; Hockley 2010, Leukemia 24(5):1084-6; adult T-cell leukemia (Nakamura et al., 2011, Br J Dermatol. 165(2):437-9). All of the references in the foregoing paragraph are incorporated by reference herein in their entireties.

[00121] Elevated levels of AID have been reported in arthritis (Xu et al. Scand. J. Immunol. 2009, 296, 2033-6) and in the MRL/Fas(lpr/lpr) mouse lupus model (White et al. 2011, Autoimmunity 44(8), 585-98). All of the references in the foregoing paragraph are incorporated by reference herein in their entireties.

[00122] It is demonstrated herein that when DSB repair is inhibited, the extent of the DSBs generated by AID is much higher than previously suspected and the extent of genomic damage is so severe as to result in cell death. Accordingly, in one embodiment of the technology described herein, there is provided a method of treatment comprising; (a) selecting a subject having cells that express elevated levels of activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level of AID is a level of AID that is higher than the level of AID in cells of the same type from a healthy individual. In some embodiments, the cells expressing elevated levels of AID are B cells. In some embodiments, the B cell expressing elevated levels of AID is a cancerous B cells or a B cell associated with autoimmune disease. In some embodiments, the subject can be a human subject.

[00123] Methods provided herein treat cancers and/or autoimmune disorders by inhibiting DNA double strand break repair. This inhibition proves lethal to cells expressing AID, as AID generates widespread genomic breaks, and the treatment with a double strand break repair inhibitor prevents the repair of these lesions which are being generated by the cell itself. This results in cell death in the subject which is specific to the cells expressing AID, e.g. cancerous B cells and/or autoimmune cells. Accordingly, as described herein, in one embodiment there is a provided a treatment paradigm that selectively induces self-destruction of certain diseased cells, while reducing the unintended side effects in healthy tissues.

[00124] RAD51-mediated strand exchange repair is a component of homologous recombination, which is used to repair DNA double strand breaks (DSBs) generated by

irradiation, cross-linking drugs or as a consequence of the activity of enzymes such as AID (Klein2008, DNA Repair, 7:686-93).

[00125] RAD51 (NCBI Gene ID: 5888) is a eukaryotic recombinase with ATP-dependent DNA binding activity and plays a role in meiotic recombination and DNA repair in mammals. RAD51 binds to the 3'-tailed single strands of the DSB and promotes pairing with homologous sequences. Further steps involve strand invasion and repair (see San Filippo et al., Annual Review of Biochemistry 2008, 77:229-257). Further RAD51 has been shown to have a function in class switch recombination during antibody maturation (Li et al., PNAS 1996, 93:10222-7). In certain embodiments, the DSB repair inhibitor inhibits the expression or activity of RAD51.

[00126] In certain embodiments, the DSB repair inhibitor inhibits the expression or activity of one or more of the following proteins and/or transcripts including, but not limited to: Rad51AP1 (NCBI Gene ID:10635; e.g. SEQ ID NO:007 (mRNA) and SEQ ID NO:114 (protein)); Rad51B (NCBI Gene ID: 5890; e.g. SEQ ID NO:008 (mRNA) and SEQ ID NO:115 (protein)); Rad51C (NCBI Gene ID: 5889 e.g. SEQ ID NO: 0163 (mRNA; NM_058216) and SEQ ID NO: 0164 (protein; NP_478123) or SEQ ID NO:0165 (mRNA; NM_002876) and SEQ ID NO:0166 (protein; NP_002867); Rad51D (NCBI Gene ID: 5892; e.g. SEQ ID NO:009 (mRNA) and SEQ ID NO:116 (protein)) ; XRCC2 (NCBI Gene ID: 7516; e.g. SEQ ID NO:010 (mRNA) and SEQ ID NO:117 (protein)); XRCC3 (NCBI Gene ID: 7517; e.g. SEQ ID NO:011 (mRNA) and SEQ ID NO:118 (protein)); RAD54 (NCBI Gene ID: 546; e.g. SEQ ID NO:012 (mRNA) and SEQ ID NO:119 (protein)); RAD52 (NCBI Gene ID: 5893; e.g. SEQ ID NO:013 (mRNA) and SEQ ID NO:120 (protein)); BRCA1 (NCBI Gene ID: 672; e.g. SEQ ID NO:014 (mRNA) and SEQ ID NO:121 (protein)); BRCA2 (NCBI Gene ID: 675; e.g. SEQ ID NO:015 (mRNA) and SEQ ID NO:122 (protein)); ATM (NCBI Gene ID: 472; e.g. SEQ ID NO:016 (mRNA) and SEQ ID NO:123 (protein)); ATR (NCBI Gene ID: 545; e.g. SEQ ID NO:017 (mRNA) and SEQ ID NO:124 (protein)); MRE11 (NCBI Gene ID: 4361; e.g. SEQ ID NO:018 (mRNA) and SEQ ID NO:125 (protein)); RAD50 (NCBI Gene ID:10111: e.g. SEQ ID NO:019 (mRNA) and SEQ ID NO:126 (protein)); NBS1 (NCBI Gene ID: 4683; e.g. SEQ ID NO:020 (mRNA) and SEQ ID NO:127 (protein)); WRN (NCBI Gene ID: 7486; e.g. SEQ ID NO:021 (mRNA) and SEQ ID NO:128 (protein)); BLM (NCBI Gene ID: 641; e.g. SEQ ID NO:022 (mRNA) and SEQ ID NO:129)); RECQ4 (NCBI Gene ID: 9401; e.g. SEQ ID NO:023 (mRNA) and SEQ ID NO:130 (protein)); LIG4 (DNA Ligase 4; NCBI Gene ID: 3981; e.g. SEQ ID NO:024 (mRNA) and SEQ ID NO:131 (protein)); XRCC4 (NCBI Gene ID: 7518; e.g. SEQ ID NO:025 (mRNA)

and SEQ ID NO:132 (protein)); PRKDC (DNA-PKcs7; XRCC7; NCBI Gene ID: 5591; e.g. SEQ ID NO:026 (mRNA) and SEQ ID NO:133 (protein)); DCLRE1C (NCBI Gene ID: 64421; e.g. SEQ ID NO:027 (mRNA) and SEQ ID NO:134 (protein)); XRCC6 (Ku70; NCBI Gene ID: 2547; e.g. SEQ ID NO:028 (mRNA) and SEQ ID NO:135 (protein)); XRCC5 (Ku80; NCBI Gene ID: 7520; e.g. SEQ ID NO:029 (mRNA) and SEQ ID NO:136 (protein)) and/or XLF (NHEJ1; XRCC4-like factor; NCBI Gene ID: 79840; e.g. SEQ ID NO:030 (mRNA) and SEQ ID NO:137 (protein)).

[00127] In certain embodiments, the DSB repair inhibitor inhibits the expression or activity of one or more proteins and/or transcripts encoded by a gene selected from the group consisting of: Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

[00128] In certain embodiments, the DSB repair inhibitor inhibits the expression or activity of one or more proteins and/or transcripts encoded by a gene selected from the group consisting of: Rad51AP1; Rad51B; Rad51C; Rad51D; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; and PRKDC.

[00129] In certain embodiments, the DSB repair inhibitor binds to one or more of the following proteins and/or transcripts including, but not limited to: Rad51AP1; Rad51B; Rad51C; and/or Rad51D.

[00130] In some embodiments, the inhibitor of double strand break repair can inhibit the expression or activity of a Rad51 family member (e.g. Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3). In some embodiments, the inhibitor of double strand break repair can inhibit a Non-homologous end joining (NHEJ) protein member (e.g. LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5;XLF).

[00131] In yeast Rad52 has been shown to mediate binding of Rad51 to ssDNA. BRCA2 also appears to function as a recombination mediator; promoting the binding of RAD51 to ssDNA and possibly mediating the translocation of RAD51 to the nucleus. RAD51B, Rad51C , RAD51D, XRCC2 and XRCC3 are paralogs of RAD51 and are all functioning in HR of DSBR pathway (Yokoyama et al. J Biol Chem. 2003, 278(4):2767-72; Thacker, Trends Genet. 1999, 15:166–168; Schild D, et al., J. Biol. Chem. 2000, 275:16443–16449). Rad51AP1 is a RAD51 associated protein that promotes binding to branched DNA molecules (Modesti et al., Mol Cell 2007, 28:468-481; Dunlop et al., 2012, J Biol Chem 6, 287, 12343-7). RAD54 is a protein with dsDNA-dependent ATPase activity and this activity is enhanced by the presence of RAD51. In yeast, Rad54 promotes the search for DNA homology,

remodeling of chromatin, formation of the invasion complex, and eventual removal of Rad51 from the dsDNA. In humans it has been shown to function in branch migration of the Holliday junction, a key intermediate in DNA repair and recombination (San Filippo et al., Annual Review of Biochemistry 2008, 77:229-257; Mazina et al., 2012, J Biol Chem 6, 287(15):11820-32). BRCA1 promotes RAD51-mediated repair of DSBs and suppresses crossover type repair (Cousineau et al., Cancer Res 2005 65:11384-91). ATM and ATR are protein kinases. ATM phosphorylates targets when DSBs are detected, halting the cell cycle. MRE11, RAD50 and NBS1 form the MRN complex which recruits ATM to DSBs. In contrast, ATR is activated by ssDNA. WRN, BLM, and RECQ4 are members of the RECQ helicase family. WRN is a helicase and exonuclease which is believed to unwind the Holliday junctions formed during HR, thus decreasing inappropriate recombination (Yang et al., J Biol Chem 2002, 277, 31980-7). BLM and RECQ4 are both helicases which are activated by interaction with RAD51 (Brosh et al., 2000, J Biol Chem, 275:23500-8; Rossi et al., 2010, DNA Repair 9:796-804).

[00132] XRCC2 is a key member of the RAD51 family of mammalian homologous-recombination factors (Thacker, Biochimie 1999, 81: 77-85; Braybrooke et al., J Biol Chem 2000, 275:29110-6; Deans et al., EMBO J 2000, 19:6675-6685), and is known for its DSB repair functions (Johnson et al., Nature 1999, 401:397-9). In the human genome, *XRCC2* is located on cytoband q36 of chromosome 7 (7q36), a region frequently rearranged in various cancers (Dohner et al., Blood 1998, 92:4031-5; Simmons et al., Leukemia 2002, 16:2408-2416; Mao et al., Br J Dermatol 2001, 145:117-122). XRCC2-deficient cells show proliferation defects, hypersensitivity to ionizing radiation and other DNA-damaging agents, and spontaneous chromosomal instability (Deans et al., EMBO J 2000, 19:6675-6685; Liu et al., J Biomed Biotechnol 2002, 2:106-113; Deans et al., Cancer Res 2003, 63:8181-7). XRCC2 is required for successful proliferation and genomic integrity in early developing B cells (Caddle, et al., 2008, Mol. Cell. Biol. 28, 2295–2303). Mice with homozygous deletion of Xrcc2 die during mid-gestation, associated with widespread cellular apoptosis (Deans et al., EMBO J 2000, 19:6675-6685; Orii et al., PNAS 2006 ,103:10017-10022; Adam et al., DNA Repair (Amst.) 2007, 6:224-234). As described herein and in Hasham et al. (Nature Immunology, 2010, 11 (9), 820-826), the inventors have found that AID expression in XRCC2-defective mature B cells lead to widespread, highly cytotoxic DSBs.

[00133] XRCC3 is a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage.

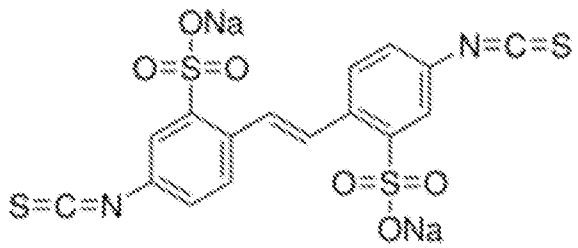
XRCC4 is a DNA double strand break repair gene and important for genome stability. It is known to interact with DNA ligase IV.

Inhibitors of DSB repair

[00134] In certain embodiments, the DSB repair inhibitor, e.g. is an inhibitor of RAD51-mediated strand exchange repair, can be a stilbene derivative. Stilbene derivatives can include, but are not limited to, stilbene, trans-stilbene derivatives, cis-stilbene derivatives, cis-stilbene oxide, trans-stilbene oxide, 4,4'-bis(2-benzoxazolyl)stilbene, 4-nitro-4'-(octadecylamino)stilbene, α,β-bis(phenylazo)stilbene, meso-1,2-dibromo-1,2-diphenylethane, (Z)-1,2-diphenyl-1,2-ethylenediboronic acid bis(pinacol) ester, 2,4-dinitro-3',4'-(methylenedioxy)-stilbene, polymethoxystilbenes, dihydrostilbenes, combretastatin, combretastatin A-4, 3,5,4'-trimethoxy-trans-stilbene, 3,4,5,4'-tetramethoxystilbene, resveratrol, diethylstilboestrol, 2,4,6-trihydrophenanthrene-2-O-glucoside, resveratrol-2-C-glucosides, cis-ε-viniferin diglucoside, trans-ε-viniferin diglucoside, pallidol glucoside, pallidol diglucoside, cis-3,4',5-trimethyoxy-3'-aminostilbene, cis-3,4',5-trimethoxy-3'-hydroxystilbene, cholchicine, combretastatin A4-phosphate, desoxyrhapontigenin, dimethylaminonitrostilbene, rhapontigenin, piceatannol, 4-hydroxystilbene, 4,4'-dihydroxystilbene, 3,5-dihydroxystilbene, trimethylresveratrol, silbamidine, diethylstilbestrol, parthenocissine, pallidol, quadrangularin A, quadrangularin B, quadrangularin C, ZD6126. Non-limiting examples of stilbene derivatives include those structures disclosed in U.S. Patent Nos. 4,723,034, 4,326,055, 4,723,028, 4,892,949, 6,562,834, 5,589,506, 7,655,696, 4,996,237, 5,561,122, 5,525,632, 5,430,062, 5,731,353, 7,781,580, US Patent Publications US2004/0147788, US2008/071364, Japanese Patent Kokai Publications JP-A-7-225558, JP-A-8-301831 and JP-A-10-81673, Roberti et al., J. Med. Chem 2003 46:3546-54; Baderschneider and Winterhalter J of Agricultural and Food Chem 2000 48:2681-6; Hillis and Ishikura, Journal of Chromatography A 1968 32:323-336; Kim et al., J Med Chem 2002 45:160-4; Young et al., J Am Chem Soc 1972 94:3976-81; Iliya et al., Phytochemistry 2003 62:601-6; Aguamah et al., Phytochemistry 1981 20:1381-3; and Kim et al., J Biol Chem2002 277:16340-4; which are incorporated by reference herein in their entireties. Known compounds, as well as stilbene compounds which will be found in the future, are included in the stilbene derivatives in the technology described herein provided that such newly found compounds are classed as stilbene derivatives. The stilbene derivatives of the technology described herein also include bioprecursors or compounds which may be converted in a subject body into a stilbene derivative. The manufacture of stilbene derivatives, which can be in the form of pharmaceutically acceptable salts, esters, hydrates and solvates, and the

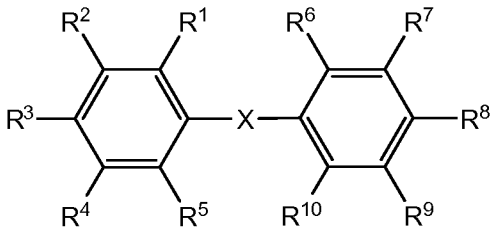
manufacture of pharmaceutical compositions comprising a stilbene derivative, its inert pharmaceutically acceptable carrier(s) and/or diluent(s), are disclosed in U.S. Patent No. 5,525,632 and in the publications listed above. Certain stilbene derivatives are also available commercially, for example; cis-stilbene (#S2259 Sigma-Aldrich, St. Louis MO), trans-stilbene (#S6382 Sigma-Aldrich, St. Louis MO), resveratrol (#R5010 Sigma-Aldrich, St. Louis MO), or 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (#D3514 Sigma-Aldrich, St. Louis MO).

[00135] In certain embodiments, the inhibitor of DSB repair can be the RAD51-mediated strand exchange repair inhibitor 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS; Formula XXVI).



Formula XXVI

[00136] In some embodiments, described herein is a stilbene or derivative thereof of formula (V):



Formula V

[00137] R^1 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^1 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4

alkyl. In some embodiments, R^1 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

[00138] R^2 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^2 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^2 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

[00139] R^3 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^3 is hydrogen, hetercyclyl, OR^{21}, NO_2, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHSO_2R^{21}$, $N(R^{22})_2$, $NHC(O)N(R^{22})_2$, $NHC(S)N(R^{22})_2$, or $NHSO_2N(R^{22})_2$, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^3 is hydrogen, OH, OCH_3, N=C=S, NH_2, $NHCH_3$, NO_2, NH-octadecane, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, benzoxazolyl, or NHC(O)NH-cyclopropane.

[00140] R^4 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^4 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4

alkyl. In some embodiments, R^4 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

R^5 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^5 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^5 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

[00141] R^6 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^6 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^6 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

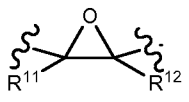
[00142] R^7 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^7 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^7 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

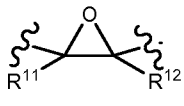
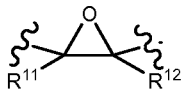
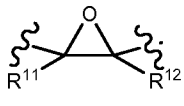
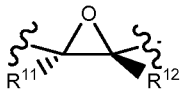
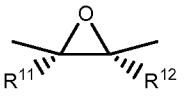
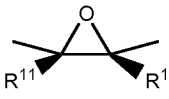
[00143] R^8 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally

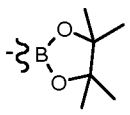
substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^8 is hydrogen, hetercyclyl, OR^{21}, NO_2, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHSO_2R^{21}$, $N(R^{22})_2$, $NHC(O)N(R^{22})_2$, $NHC(S)N(R^{22})_2$, or $NHSO_2N(R^{22})_2$, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^8 is hydrogen, OH, OCH_3, N=C=S, NH_2, $NHCH_3$, NO_2, NH-octadecane, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, benzoxazolyl, or NHC(O)NH-cyclopropane.

[00144] R^9 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^9 is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^9 is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

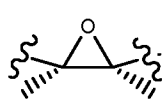
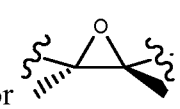
[00145] R^{10} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^{10} is hydrogen, OR^{21}, NO_2, $N(R^{22})_2$, $OP(O)(OH)_2$, or SO_3R^{21}, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. In some embodiments, R^{10} is hydrogen, OH, OCH_3, NO_2, NH_2, $OP(O)(OH)_2$, SO_3H, or SO_3Na.

[00146] X can be selected from the group consisting of $C(R^{21})_2$, $-C(O)N(R^{22})-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-SO_2-$ $-CH(R^{11})CH(R^{12})-$, $-C(R^{11})=C(R^{12})-$, and  . Preferably

X is -C(R^{11})=C(R^{12})- or  . It is to be understood that when X is -C(R^{11})=C(R^{12})- or  , the substituents R^{11} and R^{12} can be present in either the cis- or the trans-conformation. Further, when X is  , the carbons to which R^{11} and R^{12} are attached can independently have the R or the S configuration. Thus, X can be  ,  , or  .

[00147] R^{11} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. Preferably, R^{11} is hydrogen, C_1-C_{10} alkyl, halogen, OR^{21}, cyclyl, or heterocyclyl. In some embodiments, R^{11} is hydrogen, methyl, ethyl, OH, OCH_3, Br, N_2-phenyl,  ,

[00148] R^{12} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. In some embodiments, R^{12} is hydrogen.

[00149] Further, R^{11} and R^{12} both can be the same or both different. In some embodiments, R^{11} and R^{12} are both hydrogen. In some embodiments, X is -CH_2CH_2-, -CH=CH-,  , or  .

[00150] Each R^{21} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or

branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof. Preferably, R^{21} is hydrogen or a linear or branched C_1-C_{10} alkylene. In some embodiments, R^{21} can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, t-butyl, cyclopropyl, or CH_2OCH_3.

[00151] Each R^{22} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof. Preferably, R^{22} is hydrogen or a linear or branched C_1-C_{10} alkylene. In some embodiments, R^{22} can be hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, t-butyl, or cyclopropyl.

[00152] R^3 and R^8 can be the same or different. Accordingly, in some embodiments, R^3 and R^8 are selected independently from the group consisting of hydrogen, hetercyclyl, OR^{21}, NO_2, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHSO_2R^{21}$, $N(R^{22})_2$, $NHC(O)N(R^{22})_2$, $NHC(S)N(R^{22})_2$, and $NHSO_2N(R^{22})_2$, wherein R^{21} can be H or C_1-C_4alkyl and R^{22} can be H or C_1-C_{10} alkyl. For example, R^3 and R^8 can be selected independently from the group consisting of hydrogen, OH, OCH_3, N=C=S, NH_2, $NHCH_3$, NO_2, NH-octadecane, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, benzoxazolyl, or NHC(O)NH-cyclopropane.

[00153] In some embodiments, at least one of R^3 and R^8 is not hydrogen. In some embodiments, both of R^3 and R^8 are not hydrogen.

[00154] In some embodiments, R^3 and R^8 are different and selected independently from the group consisting of hydrogen, OH, OCH_3, N=C=S, NH_2, $NHCH_3$, NO_2, NH-octadecane, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, benzoxazolyl, or NHC(O)NH-cyclopropane. For example, one of R^3 and R^8 can be H and the other can be NH_2, one of R^3 and R^8 can be H and the other can be $NHCH_3$, one of R^3 and R^8 can be H and the other can be $N(CH_3)_2$, one of R^3 and R^8 can be H and the other can be $NHC(O)CH_3$, one of R^3 and R^8 can be H and the other can be $NHC(O)CH(CH_3)_2$, one of R^3 and R^8 can be H and the other can be $NHC(O)CH_2OCH_3$, one of R^3 and R^8 can be H and the other can be $NHSO_2$-CH_3, one of R^3 and R^8 can be H and the other can be $NHSO_2$-$CH(CH_3)_2$, one of R^3 and R^8 can be H and the

other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be H and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be H and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be H and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be H and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be H and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be H and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be H and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be H and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be H and the other can be NHC(O)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be H and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be NH_2 and the other can be $NHCH_3$, one of R^3 and R^8 can be NH_2 and the other can be $N(CH_3)_2$, one of R^3 and R^8 can be NH_2 and the other can be NHC(O)CH_3, one of R^3 and R^8 can be $NH_2$and the other can be NHC(O)$CH(CH_3)_2$, one of R^3 and R^8 can be NH_2 and the other can be NHC(O)CH_2OCH_3, one of R^3 and R^8 can be NH_2 and the other can be $NHSO_2$-CH_3, one of R^3 and R^8 can be NH_2 and the other can be $NHSO_2$-$CH(CH_3)_2$, one of R^3 and R^8 can be NH_2 and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be NH_2 and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NH_2$and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be NH_2 and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NH_2$and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be NH_2 and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NH_2$and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NH_2$and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be NH_2 and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NH_2$and the other can be NHC(O)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NH_2$and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be $N(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)CH_3, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)$CH(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)CH_2OCH_3, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-CH_3, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHCO)NH-CH_3, one of

R^3 and R^8 can be $NHCH_3$ and the other can be $NHC(O)NH\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(O)CH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(O)CH(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(O)CH_2OCH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2\text{-}CH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2\text{-}NHCH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2\text{-}N(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2\text{-}NHCH(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(S)NH\text{-}CH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(S)NH\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(O)NH\text{-}CH_3$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be $NHC(O)NH\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $N(CH_3)_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(O)CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(O)CH_2OCH_3$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2\text{-}CH_3$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2\text{-}NHCH_3$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2\text{-}N(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2\text{-}NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(S)NH\text{-}CH_3$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(S)NH\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(O)NH\text{-}CH_3$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be $NHC(O)NH\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_3$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHC(O)CH_2OCH_3$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2\text{-}CH_3$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2\text{-}CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2\text{-}NHCH_3$, one of R^3 and R^8 can be

$NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHC(S)NH$-CH_3, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHC(S)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHC(O)NH$-CH_3, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be $NHC(O)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH(CH_3)_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-CH_3, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHC(S)NH$-CH_3, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHC(S)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHC(O)NH$-CH_3, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be $NHC(O)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHC(O)CH_2OCH_3$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHC(S)NH$-CH_3, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHC(S)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHC(O)NH$-CH_3, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be $NHC(O)NH$-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-CH_3 and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be $NHSO_2$-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the

other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(O)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$CH(CH_3)_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be $NHSO_2$-$NHCH_3$, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(O)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-cyclopropane and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be $NHSO_2$-$N(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(O)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$NHCH_3$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be $NHSO_2$-$NHCH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be NHC(S)NH-$CH(CH_3)_2$, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-$N(CH_3)_2$ and the other can be

NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHSO_2$-N(CH_3)$_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be $NHSO_2$-NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(S)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHSO_2$-NHCH(CH_3)$_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(S)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(S)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHSO_2$-NH-cyclopropane and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(S)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be $NHCH_3$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be NHC(S)NH-CH(CH_3)$_2$ and the other can be NHC(S)NH-cyclopropane, one of R^3 and R^8 can be NHC(S)NH-CH(CH_3)$_2$ and the other can be NHC(O)NH-CH_3, one of R^3 and R^8 can be NHC(S)NH-CH(CH_3)$_2$ and the other can be NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be NHC(S)NH-CH(CH_3)$_2$ and the other can be NHC(O)NH-cyclopropane, one of R^3 and R^8 can be NHC(O)NH-CH_3 and the other can be NHC(O)NH-CH(CH_3)$_2$, one of R^3 and R^8 can be NHC(O)NH-CH_3 and the other can be NHC(O)NH-cyclopropane, or one of R^3 and R^8 can be NHC(O)NH-CH(CH_3)$_2$ and the other can be NHC(O)NH-CH(CH_3)$_2$.

[00155] In some embodiments, R^3 and R^8 are both N=C=S, NH_2, $NHC(O)CH_3$, NHC(O)CH(CH_3)$_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, or NHC(O)NH-cyclopropane.

[00156] In some embodiments, at least one of R^1 and R^6 (e.g., one or both) is SO_3R^{21}. For example, at least one (e.g., one or both) of R^1 and R^6 is SO_3H or a salt thereof.

[00157] In some embodiments, at least one of R^1 and R^6 (e.g., one or both) can be SO_3R^{21}

and R^3 and R^8 can be selected independently from the group consisting of hydrogen, hetercyclyl, OR^{21}, NO_2, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHSO_2R^{21}$, $N(R^{22})_2$, $NHC(O)N(R^{22})_2$, $NHC(S)N(R^{22})_2$, and $NHSO_2N(R^{22})_2$, wherein R^{21} and R^{22} are independently H or C_1-C_4 alkyl. For example, at least one (e.g., one or both) of R^1 and R^6 can be SO_3H and R^3 and R^8 can be selected independently from the group consisting of hydrogen, OH, OCH_3, N=C=S, NH_2, $NHCH_3$, NO_2, NH-octadecane, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, benzoxazolyl, or NHC(O)NH-cyclopropane.

[00158] In some embodiments, at least one of R^1 and R^6 (e.g., one or both) can be SO_3R^{21} and R^3 and R^8 are both same and selected from the group consisting of hydrogen, N=C=S, $NHC(O)R^{21}$, $NHSO_2R^{21}$, $N(R^{22})_2$, $NHC(O)N(R^{22})_2$, $NHC(S)N(R^{22})_2$, and $NHSO_2N(R^{22})_2$. For example, at least one (e.g., one or both) of R^1 and R^6 can be SO_3H and R^3 and R^8 are the same and can be selected from the group consisting of hydrogen, N=C=S, NH_2, $NHC(O)CH_3$, $NHC(O)CH(CH_3)_2$, $NHC(O)CH_2OCH_3$, $NHSO_2CH_3$, $NHSO_2$-cyclopropane, $NHSO_2CH(CH_3)_2$, $NHSO_2N(CH_3)_2$, $NHC(S)NHCH_3$, $NHC(S)NHCH(CH_3)_2$, NHC(S)NH-cyclopropane, $NHC(O)NHCH_3$, $NHC(O)NHCH(CH_3)_2$, and NHC(O)NH-cyclopropane.

[00159] In some embodiments, 1, 2, 3, 4, 5, or 6 of R^1-R^{10} are OH or OCH_3.

[00160] The compounds of formula (V) include pharmaceutically acceptable salts, stereoisomer mixtures, and enantiomers thereof. The compounds of the technology described herein can also include physiologically acceptable salts of the compounds of formula (V). The compounds of formula (V) can be present as a racemic mixture or as a substantially pure stereoisomer or enantiomer.

[00161] Methods of making stilbenes are well known in the art and are described, for example in U.S. Patent Nos. 7,321,050; 6,022,998; 6,177,220; 5,068,300; 3,387,050; 5,563,298; 7,820,848; 8,101,804; 6,218,108; and 7,714,161; U.S. Patent Publications 2007/0276172 and 2004/0143023; Likhtenstein, Gertz I. "Stilbenes Synthesis and Applications" in Kirk-Othmer Encyclopedia of Chemical Technology. 2000, John Wiley & Sons, Inc.; Likhtenshtein, G. "Stilbenes Preparation and Analysis" in "Applications in Chemistry, Life Sciences and Materials Science" 2010, Wiley-VCH; which are incorporated by reference herein in their entireties. Synthesis of stilbenes and stilbene derivatives is also available as a commercial service (e.g. Mercachem, Nijmegen, Netherlands; Proteros, Martinsried, Germany; AMRI, Albany, NY; WuXi Apptec, Shanghai, China; and Richman Chemical Inc., Gwynedd, PA). In some embodiments, a stilbene may be further

functionalized to amide and sulfonamide derivatives.

[00162] Some exemplary compounds of formula (V) are (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))diacetamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methylpropanamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methoxyacetamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dimethanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dicyclopropanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide); (E)-N-(4-(4-aminostyryl)phenyl)propane-2-sulfonamide; (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-methylthiourea); (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-isopropylthiourea); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)acetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)isobutyramide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)-2-methoxyacetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)methanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; N'-(4-{(E)-2-[4-(dimethylamino)phenyl]-1-ethenyl}phenyl)-N,N-dimethylsulfamide; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylthiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylthiourea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)thiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylurea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylurea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)urea; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(methylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-

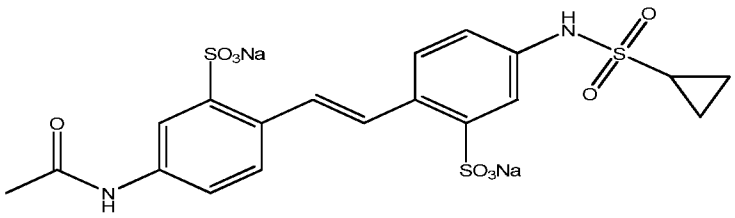
cyclopropylthioureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-acetamido-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-

cyclopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(methylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-methylthioureido)-2-(2-

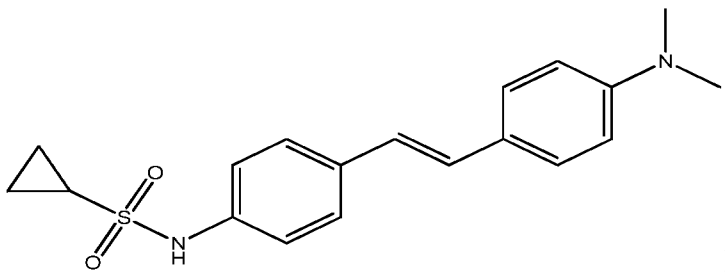
sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-methylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N-isopropylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N,N-dimethylbenzamide); (E)-(ethene-1,2-diylbis(4,1-phenylene))bis(morpholinomethanone); and (E)-5-(4-hydroxystyryl)benzene-1,3diol(3,5,4'-trihydroxy-trans-stilbene).

[00163] In some embodiments, the stilbene derivative can be selected from the group consisting of (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate (Formula VI, also referred to herein as BB5-4); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide (Formula VII, also referred to herein as BB2-5); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide) (Formula VIII, also referred to herein as BB1-6); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide) (Formula IX, also referred to herein as BB1-7); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide (Formula X, also referred to herein as BB2-6); (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate (Formula XI, also referred to herein as BB5-39); 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate) (Formula XII, also referred to herein as BB4B-2); (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate (Formula XIII, also referred to herein as BB5-47); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide) (Formula XIV, also referred to herein as BB8-1); (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate (Formula XXIII, also referred to herein as BB5-6); sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXVII); sodium (E)-5-

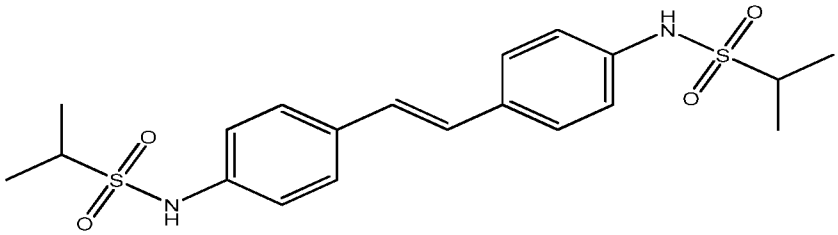
(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXVIII); sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXIX); and sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXX).



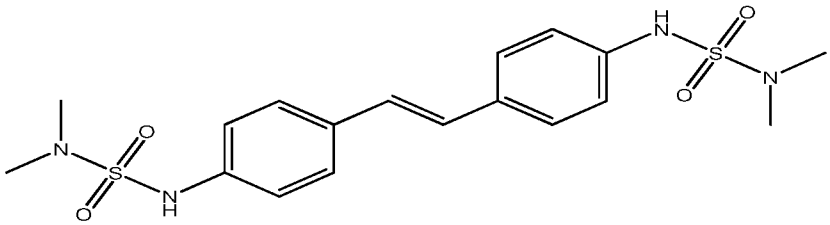
Formula VI



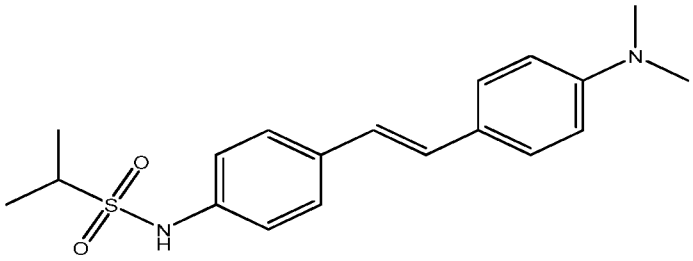
Formula VII



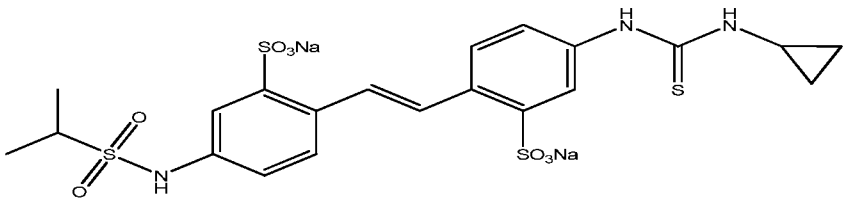
Formula VIII



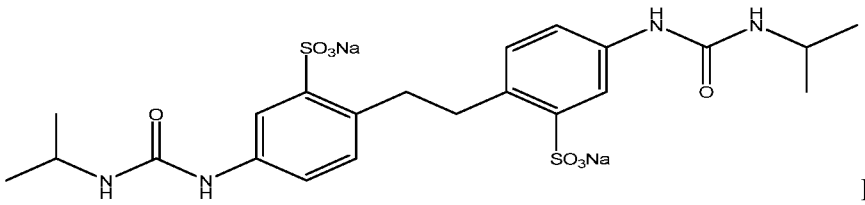
Formula IX



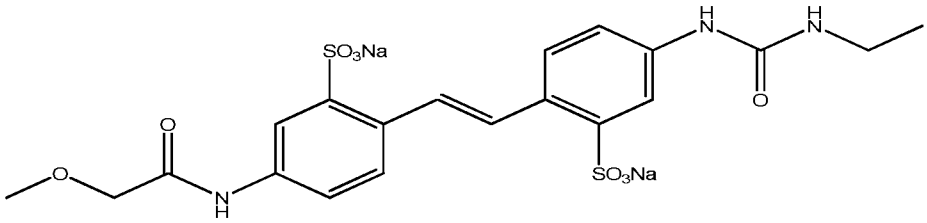
Formula X



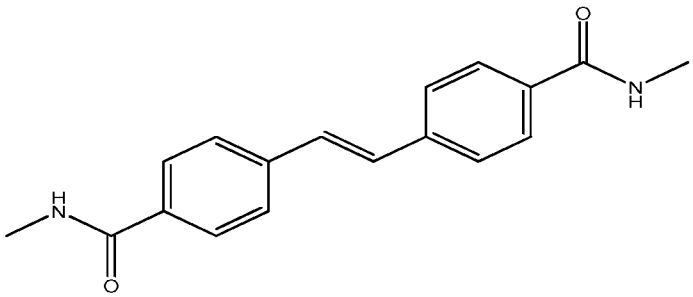
Formula XI



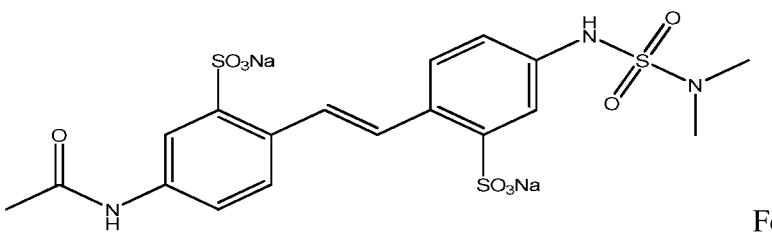
Formula XII



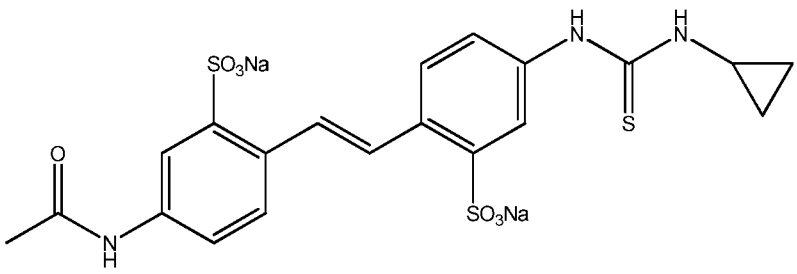
Formula XIII



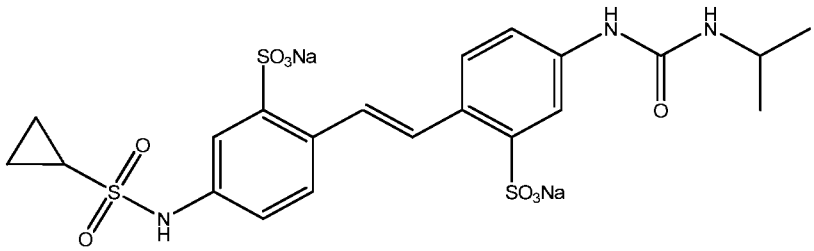
Formula XIV



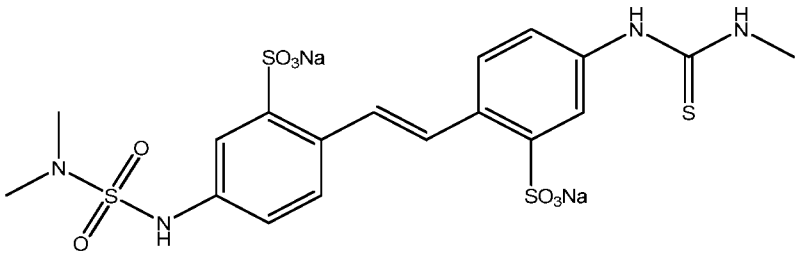
Formula XXIII



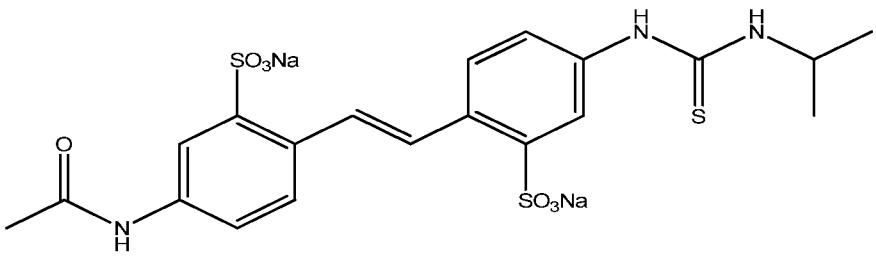
Formula XXVII



Formula XXVIII



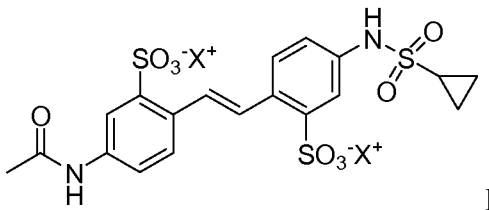
Formula XXIX



Formula XXX

[00164] In certain embodiments, the stilbene derivative can be selected from the group consisting of sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate (Formula VI); sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXVII); sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXIX); sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate (Formula XXVIII); and sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate (Formula XII, also referred to herein as BB4B-2).

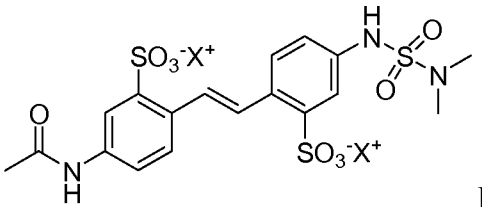
[00165] In some embodiments, the stilbene derivative can be (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXIV:



Formula XXIV

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

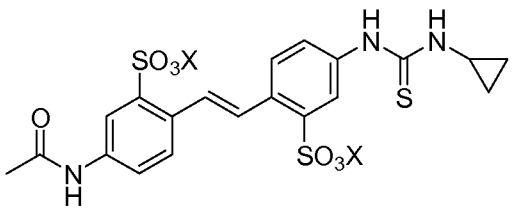
[00166] In some embodiments, the stilbene derivative can be (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXV:



Formula XXV

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

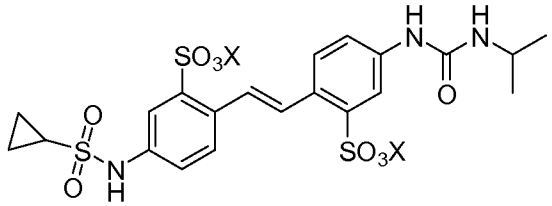
[00167] In some embodiments, the stilbene derivative can be (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXXI:



Formula XXXI

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

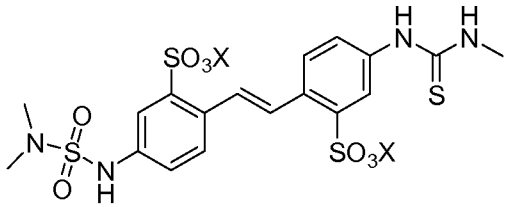
[00168] In some embodiments, the stilbene derivative can be (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXXII:



Formula XXXII

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

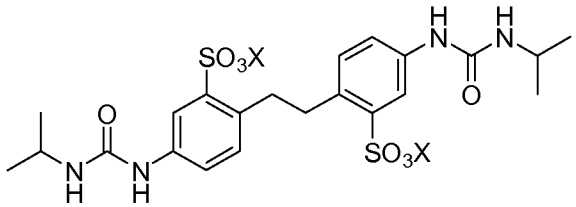
[00169] In some embodiments, the stilbene derivative can be (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXXIII:



Formula XXXIII

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

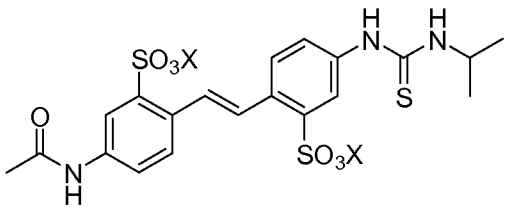
[00170] In some embodiments, the stilbene derivative can be 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate). In some embodiments, the stilbene derivative can have the structure of Formula XXXIV:



Formula XXXIV

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

[00171] In some embodiments, the stilbene derivative can be (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate. In some embodiments, the stilbene derivative can have the structure of Formula XXXV:



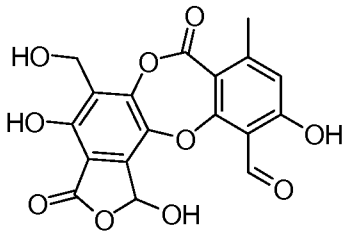
Formula XXXV

wherein X can be any pharmaceutically acceptable salt cation. By way of non-limiting example, X can be sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

[00172] In some embodiments, the stilbene and stilbene derivatives described above herein can be inhibitors of double strand break repair. In some embodiments, the stilbenes and stilbene derivatives described above can be used in the methods described herein.

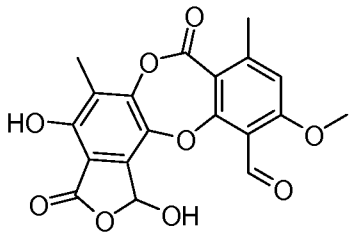
[00173] In some embodiments, the inhibitor of double strand break repair can be a stilbenoid. As used herein, a "stilbenoid" is a hydroxylated stilbene derivative. Non-limiting examples of stilbenoids include, but are not limited to, resveratrol; aglycones; picetannol; pinosylvin; pterostilbene; alpha-viniferin; ampelopsin A; ampelopsin E; diptoindonesin C; diptoindonesin F; epsilon-viniferin; flexuosol A; gnetin H; hemsleyanol D; hopeaphenol; trans-diptoindonesin B; vaticanol B; astringin; piceid; diptoindonesin A.

[00174] In certain embodiments provided herein, the inhibitor can be salazinic acid (Formula I)(Pubchem Substance ID: 24840333; Compound A03). Salazinic acid can also be referred to as 1,4,10-trihydroxy-5-(hydroxymethyl)-8-methyl-3,7-dioxo-1,3-dihydro-7H-2,6,12-trioxabenzo[5,6]cyclohepta[1,2-e]indene-11-carbaldehyde.



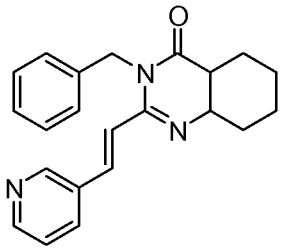
Formula I

[00175] In certain embodiments provided herein, the inhibitor can be stictic acid (Formula II)(Pubchem Substance ID: 24840609; Compound A10). This compound is also known as NSC-87511, scopularic acid, sterocaulonic acid; and 1,3-dihydro-1,4-dihydroxy-10-methoxy-5,8-dimethyl-3,7-dioxo-7H-isobenzofuro[4,5-b][1,4]benzodioxepin-11-carbaldehyde.



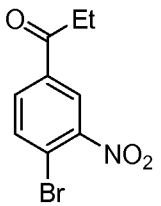
Formula II

[00176] In certain embodiments provided herein, the inhibitor can be STK856883 (Formula III)(Pubchem Substance ID: 24787209; Compound B02). This compound can also be referred to as 3-benzyl-2-[(E)-2-pyridin-3-ylethenyl]quinazolin-4-one. STK856883 has been identified as a RAD51 inhibitor (Huang et al. ACS Chem Biol. 2011 Mar 23).



Formula III

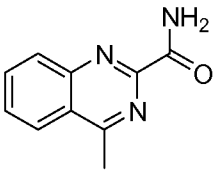
[00177] In certain embodiments provided herein, the inhibitor can be 4'-bromo-3'nitropropiophenone (Formula IV)(Calbiochem Cat: No. 323115). 4'-Bromo-3'-nitropropiophenone, also known as NS-123 or 1-(4-bromo-3-nitrophenyl)propan-1-one, is a cell-permeable nitro-ropiophenone compound as described in WO2009036297 that preferentially enhances tumor growth-inhibitory effects of ionizing radiation (~ 5 μM in U251, HT-29 and A549 tumor cells and in U251 xenograft mouse model, 50 mg/kg, i.p.) with no apparent effect on normal human glial cells, Zebrafish embryos and nude mice. It has been shown to increase the accumulation of unrepaired double-strand DNA breaks and prolong the damage-dependent signaling.



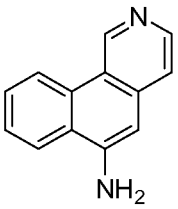
Formula IV

[00178] In some embodiments, the inhibitor can be selected from the group consisting of 4-methylquinazoline-2-carboxamide (Formula XV); benz[h]isoquinolin-6-amine (Formula XVI); 5,6-dimethyl-2-mercaptomethylbenzimidazole (Formula XVII); (E)-1-(2-

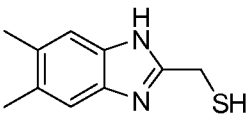
hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one (Formula XVIII); N4-butyl-6-chloropyrimidine-2,4-diamine (Formula XIX); 1-thermopsine (Formula XX); 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one (Formula XXI); and 4-(2-amino-4-nitrophenylamino)phenyl (Formula XXII).



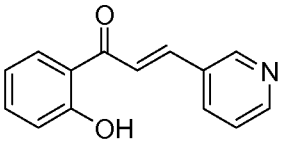
Formula XV



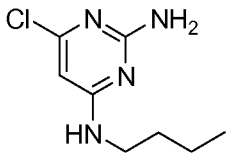
Formula XVI



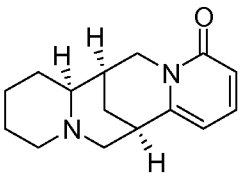
Formula XVII



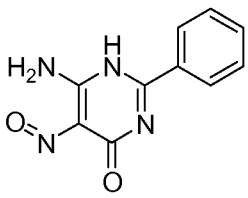
Formula XVIII



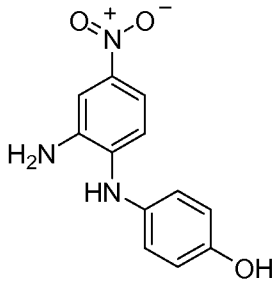
Formula XIX



Formula XX



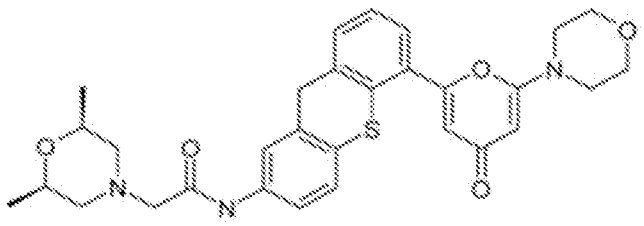
Formula XXI



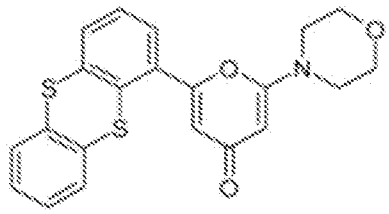
Formula XXII

[00179] In some embodiments, the inhibitor can be selected from the group consisting of 7-Aazaindole-3-carboxaldehyde (CAS4649-09-6); 2-Amino-4-phenylphenol (CAS1134-36-7); 3-(1-methyl-3-pyrrolidinyl)indole (CAS3671-00-9); 1-methyl- [1,2,4]Triazolo[4,3-a]quinolone (CAS35359-22-9); 2-amino-5-nitro-1H-benzimidazole (CAS6232-92-4); 2-(5-nitro-2-furfurylidene)aminoethanol-N-oxide (CAS19561-70-7; Nifuratrone); alpha-mercapto-N,2-naphthylacetamide (CAS93-42-5; Thionalide); (CAS486-90-8; 1-thermospine); N4-butyl-6-chloro-2,4-Pyrimidinediamine (CAS5457-91-0); 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid (CAS7248-04-6); 6-amino-5-nitroso-2-phenyl-1H-pyrimidin-4-one (CAS5466-66-0); 4-amino-2-hydroxyphenyl)arsonic acid (CAS6318-57-6); spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione (CAS6252-98-8); N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-diamine (CAS93001-35-5); 2-amino-9-pentyl-3H-purine-6-thione (CAS24397-98-6); 2-(4-methoxyphenyl)-3-(pyridin-3-yl)prop-2-enenitrile (CAS92437-25-7); 2-chloropyrimidine-4,6-dicarboxamide (CAS7150-30-3); 2-amino-3H-Phenoxazin-3-one (CAS1916-59-2); 2-methyl-N-benzyl-7H-pyrrolo[2,3-d]pyrimidine-4-amine; 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine;NSC-106570 (CAS1866-43-9; Rolodine); 2-amino-1-naphthalenesulfonic acid (CAS81-16-3); N-sec-butyl-3-methylbenzamide (NSC 34983); benz[h]isoquinolin-6-amine; and 2-(2-methylcyclohexylidene) hydrazinecarboxamide.

[00180] In certain embodiments, the DSB repair inhibitor can be an ATM inhibitor. In some embodiments the inhibitor is 2-morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (KU-55933, S1092 Selleck Chemicals LLC: Houston, TX; WO/03070726) or 2-((2R, 6S)-2, 6-Dimethyl-morpholin-4-yl)-N-[5-(6-morpholin-4-yl-4-oxo-4H-pyran-2-yl)-9H-thioxanthen-2-yl]-acetamide (KU-60019 or KU60019; WO/2007/026157; S1570 Selleck Chemicals LLC; Houston TX; Mol Cancer Ther 2009, 8(10): 2894–2902). Also by way of a non-limiting example, the DSB repair inhibitor can be compounds such as those disclosed in European Patent EP1946757 and WO 03/070726 and WO 2005/016919.



KU-60019



KU-55933

[00181] In certain embodiments provided herein, the DSB repair inhibitor is an inhibitor which reduces the expression or activity of any gene or protein which promotes DSB repair. These genes or proteins may be enzymes that participate in DSB repair, in RAD51-mediated strand exchange or regulatory or scaffolding genes or proteins that control the activity of enzymes which participate in DSB repair. A gene or protein is considered to be a gene or protein which promotes DSB repair if a decrease in the expression or activity of that gene or protein results in a decrease in DSB repair. The reduction in DSB repair can be by about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, about 125%, about 150% or more compared to a control with normal expression or activity of the gene or protein being tested. DSB repair can be measured by methods well known to those skilled in the art. By way of non-limiting example, DSB repair can be measured by colorimetric or immunofluorescence detection of H2AX-S139PO4 (γ-H2AX, a phosphorylated histone 2A) foci (Rogakou et al., J Biol Chem 1998, 273:5858-5868; Rothkamm and Löbrich, Proc Natl Acad Sci USA, 2003, 100(9): 5057–5062; Redon et al., Aging 2011, 3(2):168-74; Rakiman et al. 2008, Advanced Biotech 39). By way of non-limiting example, DSB repair can be measured by detection of gamma-H2AX phosphorylation. By way of non-limiting example, DSB repair can be measured by the COMET assay (Orlow et al.2008, J. Clin. Oncol. 26, 3560-3566; Muller et al 1994, International Journal of Radiation Biology 65, 315-319; Fairbairn et al. 1995, Mutation Research/Reviews in Genetic Toxicology 339, 37–59). By way of non-limiting example, DSB repair can be assessed by measuring RAD51-mediated strand exchange, a component of DSB repair. RAD51-mediated strand exchange can be measured by the *in vitro* strand-exchange assay described in Ishida et al., Nucleic Acids Res 2009 37:3367-3376. All of the references in the foregoing paragraph are incorporated by reference herein in their entireties.

[00182] In certain embodiments provided herein, the DSB repair inhibitor is an inhibitor which reduces the expression or activity of one or more of the following proteins; including, but not limited to: Rad51AP1 (NCBI Gene ID:10635; SEQ ID NO:007); Rad51B (NCBI

Gene ID: 5890; SEQ ID NO:008); Rad51D (NCBI Gene ID: 5892; SEQ ID NO; 009); Rad51C (NCBI Gene ID: 5889 e.g. SEQ ID NO:0163 (mRNA; NM_058216) and SEQ ID NO:0164 (protein; NP_478123) or SEQ ID NO:0165 (mRNA; NM_002876) and SEQ ID NO:0166 (protein; NP_002867); XRCC2 (NCBI Gene ID: 7516; SEQ ID NO:010); XRCC3 (NCBI Gene ID: 7517; SEQ ID NO:011); RAD54 (NCBI Gene ID: 546; SEQ ID NO:012); RAD52 (NCBI Gene ID: 5893; SEQ ID NO:013); BRCA1 (NCBI Gene ID: 672; SEQ ID NO:014); BRCA2 (NCBI Gene ID: 675; SEQ ID NO:015); ATM (NCBI Gene ID: 472; SEQ ID NO:016); ATR (NCBI Gene ID: 545; SEQ ID NO:017); MRE11 (NCBI Gene ID: 4361; SEQ ID NO:018); RAD50 (NCBI Gene ID:10111: SEQ ID NO:019); NBS1 (NCBI Gene ID: 4683; SEQ ID NO:020); WRN (NCBI Gene ID: 7486; SEQ ID NO:021); BLM (NCBI Gene ID: 641; SEQ ID NO:022); RECQ4 (NCBI Gene ID: 9401; SEQ ID NO:023); LIG4 (DNA Ligase 4; NCBI Gene ID: 3981;SEQ ID NO:024; XRCC4 (NCBI Gene ID: 7518; SEQ ID NO:025); PRKDC (DNA-PKcs7; XRCC7; NCBI Gene ID: 5591; SEQ ID NO:026); DCLRE1C (NCBI Gene ID: 64421; SEQ ID NO:027); XRCC6 (Ku70; NCBI Gene ID: 2547; SEQ ID NO:028); XRCC5 (Ku80; NCBI Gene ID: 7520; SEQ ID NO:029) and/or XLF (NHEJ1; XRCC4-like factor; NCBI Gene ID: 79840; SEQ ID NO:030).

[00183] An inhibitor of DSB repair can be a nucleic acid (DNA or RNA), a small molecule, an aptamer, a protein, a peptide, an antibody, a polypeptide comprising an epitope-binding fragment of an antibody, an antibody fragment, a peptide-nucleic acid (PNA), a locked nucleic acid (LNA) or a ribozyme. In some embodiments, an inhibitor of DSB repair can be selected from the group consisting of a small molecule, an aptamer, a protein, a peptide, an antibody, a polypeptide comprising an epitope-binding fragment of an antibody, an antibody fragment, and a peptide-nucleic acid (PNA).

[00184] LNA bases are ribonucleotide analogs containing a methylene linkage between the 2′ oxygen and the 4′ carbon of the ribose ring (Koshkin A.A., 1998, Tetrahedron, 54:3607–3630; Obika S., 1998, Tetrahedron Lett., 39:5401–5404). The constraint on the sugar moiety results in a locked 3′-endo conformation that preorganizes the base for hybridization and increases melting temperature (Tm) values as much as 10°C per base (Wengel J., 1999, Acc. Chem. Res., 32:301–310; Braasch D.A. and Corey, D.R., 2001, Chem. Biol., 8:1–7). LNA bases can be incorporated into oligonucleotides using standard protocols for DNA synthesis. Introduction of LNA bases also confers resistance to nucleases when incorporated at the 5′ and 3′ ends of oligomers (Crinelli R., et. al., 2002, Nucleic Acids Res., 30:2435–2443). In some embodiments, the gene silencing agent is an LNA-DNA chimera. The syntheses of LNA-containing oligomers are known in the art, for examples, those described in U. S.

Patents No. 6316198, 6670461, 6794499, 6977295, 6998484, 7053195, and U. S Patent Publication No. US 2004/0014959, and all of which are hereby incorporated by reference in their entirety.

[00185] In some embodiments, the DSB inhibitor comprises an RNA interfering sequence selected from the group consisting of : SEQ ID NO:050, SEQ ID NO:051, SEQ ID NO:052, SEQ ID NO:053, SEQ ID NO:054, SEQ ID NO:055, SEQ ID NO:056, SEQ ID NO:057, SEQ ID NO:058, SEQ ID NO:059, SEQ ID NO:060, SEQ ID NO:061, SEQ ID NO:062, SEQ ID NO:063, SEQ ID NO:064, SEQ ID NO:065, SEQ ID NO:066, SEQ ID NO:067, SEQ ID NO:068, SEQ ID NO:069, SEQ ID NO:070, SEQ ID NO:071, SEQ ID NO:072, SEQ ID NO:073, SEQ ID NO:074, SEQ ID NO:075, SEQ ID NO:076, SEQ ID NO:077, SEQ ID NO:078, SEQ ID NO:079, SEQ ID NO:080, SEQ ID NO:081, SEQ ID NO:082, SEQ ID NO:083, SEQ ID NO:084, SEQ ID NO:085, SEQ ID NO:086, SEQ ID NO:087, SEQ ID NO:088, SEQ ID NO:089, SEQ ID NO:090, SEQ ID NO:091, SEQ ID NO:092, SEQ ID NO:093, SEQ ID NO:094, SEQ ID NO:095, SEQ ID NO:096, SEQ ID NO:097, and SEQ ID NO:098.

[00186] Inhibitors of DSB repair can be produced recombinantly using methods well known to those of skill in the art (see Sambrook et al., Molecular Cloning: A Laboratory Manual (2 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (1989)). Alternatively, DSB repair can be obtained commercially e.g. DIDS (#38440 Sigma-Aldrich; St. Louis, MO); 4'-Bromo-3'nitropropiophenone (Calbiochem Cat: No. 323115) or chemically synthesized.

[00187] Test compounds and agents can be screened for their ability to inhibit DSB repair. The inhibition of DSB repair can be monitored *in vivo* or *in vitro*. In one embodiment, the disruption of DSB repair is monitored by assessing the level of double strand breaks (DSBs) present in cells expressing a DNA editing enzyme, e.g. AID in the presence and absence of a test compound, e.g. by karyotyping as described herein. In one embodiment DSB are measured by γ-H2AX foci formation. In one embodiment DSB repair is measured by 53BP1 or Rad50 foci formation. In one embodiment, the ability of a test compound to disrupt DSB repair is monitored *in vivo*, e.g. by determining the ability to prevent or reduce tumor growth, symptoms, or markers of a cancer wherein the cancerous cells express AID. DSB repair can also be measured *in vitro* by the strand-exchange assay described in Ishida et al., Nucleic Acids Res 2009 37:3367-3376.

[00188] In one embodiment, an *in vitro* strand exchange assay is performed that monitors the production of joined nucleic acid molecules. For example, the ϕX174 circular ssDNA (20

μM) is incubated with RAD51 (6 μM) in the presence of a test agent at 37°C for 10 min, in 10 μl of 26 mM HEPES buffer (pH 7.5), containing 45 mM NaCl, 0.03 mM EDTA, 0.6 mM 2-mercaptoethanol, 3% glycerol, 1 mM $MgCl_2$, 1 mM DTT, 1 mM ATP, 0.1 mg/ml bovine serum albumin, 2 mM $CaCl_2$, 20 mM creatine phosphate and 75 μg/ml creatine kinase. After this incubation, 2 μM RPA is added to the reaction mixture, and the mixture is incubated at 37°C for a further 10 min. The reactions are then initiated by the addition of 20 μM ϕX174 linear dsDNA, and are continued for 60 min. The reactions are stopped by the addition of 0.1% SDS and 1.97 mg/ml proteinase K (Roche Applied Science, Basel, Switzerland), and are further incubated at 37°C for 20 min. After adding 6-fold loading dye, the deproteinized reaction products are separated by 1% agarose gel electrophoresis in 1× TAE buffer at 3.3 V/cm for 4h. The products are visualized by SYBR Gold (Invitrogen, Carlsbad, CA, USA) staining.

[00189] In another embodiment of the assay, the reactions can be performed with ^{32}P-labeled dsDNA. Visualization is performed by drying the gels, exposing them to an imaging plate and visualizing the plate using an FLA-7000 imaging analyzer (Fujifilm, Tokyo, Japan).

[00190] When the reactions are visualized, the ssDNA and dsDNA molecules provided in excess will be visible. If DSB repair occurred, a larger, joint molecule will be detected. Inhibitors of DSB repair will cause a reduction in the amount of joint molecule visible.

[00191] Test agents are typically first screened for their ability to inhibit gene expression or protein activity *in vitro* and those test agents with inhibitory effect on gene expression or protein activity are identified. Positive inhibitory agents are then tested for efficacy with respect to inhibition of DSB repair by *in vitro* or *in vivo* assays.

[00192] Generally, compounds can be tested at any concentration that can modulate expression or protein activity relative to a control over an appropriate time period. In some embodiments, compounds are tested at concentration in the range of about 0.1 nM to about 1000 mM. In one embodiment, the compound is tested in the range of about 0.1 μM to about 20 μM, about 0.1 μM to about 10 μM, or about 0.1 μM to about 5 μM. In one embodiment, compounds are tested at 1 μM.

[00193] Depending upon the particular embodiment being practiced, the test compounds can be provided free in solution, or may be attached to a carrier, or a solid support, e.g., beads. A number of suitable solid supports may be employed for immobilization of the test compounds. Examples of suitable solid supports include agarose, cellulose, dextran (commercially available as, i.e., Sephadex, Sepharose) carboxymethyl cellulose, polystyrene, polyethylene glycol (PEG), filter paper, nitrocellulose, ion exchange resins, plastic films,

polyaminemethylvinylether maleic acid copolymer, glass beads, amino acid copolymer, ethylene-maleic acid copolymer, nylon, silk, etc. Additionally, for the methods described herein, test compounds may be screened individually, or in groups. Group screening is particularly useful where hit rates for effective test compounds are expected to be low such that one would not expect more than one positive result for a given group.

[00194] To screen test agents, an *in vitro* assay system and/or a cell-based assay system can be used. For example, test agents can be screened for binding to a gene or protein encoded by a gene, screened for altering the expression level of a gene, or screened for modulating activity/function of a protein encoded by a gene.

[00195] In one embodiment, protein/peptide test agents (including antibodies, or fragments thereof) can be assessed for their ability to bind an encoded protein *in vitro*. Examples direct binding assays include, but are not limited to, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, ELISA assays, co-immunoprecipitation assays, competition assays (e.g. with a known binder), and the like. See, e.g., U.S. Patents 4,366,241; 4,376,110; 4,517,288; and 4,837,168; and also Bevan et al., Trends in Biotechnology 13:115-122, 1995; Ecker and Crooke, 1995, Biotechnology (NY) 13:351-360; and Hodgson, Biotechnology (NY) 10:973-980, 1992. The test agent can also be identified by detecting a signal that indicates that the agent binds to a protein of interest e.g., fluorescence quenching or FRET. Test agent polypeptides can also be monitored for their ability to bind nucleic acid in vitro, e.g. ELISA-format assays can be a convenient alternative to gel mobility shift assays (EMSA) for analysis of protein binding to nucleic acid. Binding of a test agent to an encoded protein provides an indication the agent may be an inhibitor of protein activity.

[00196] In one embodiment, the test agent is assayed for the ability to downregulate the biological activity or function of a protein encoded by a gene. The assay used will be dependent on the function of the protein and can be readily determined by a skilled artisan, for example monitoring inhibition of RAD51-mediated repair *in vitro*.

[00197] In one embodiment the test agent is assayed for the ability to inhibit transcription of a gene. Transcriptional assays are well known to those of skill in the art (see e.g. United States Patents 7,319,933 and 6,913,880). For example, modulation of expression of a gene can be examined in a cell-based system by transient or stable transfection of a reporter expression vector into cultured cell lines. Test compounds can be assayed for ability to inhibit or increase expression of a reporter gene (e.g., luciferase gene) under the control of a transcription regulatory element (e.g., promoter sequence) of a gene. An assay vector bearing

the transcription regulatory element that is operably linked to the reporter gene can be transfected into any mammalian cell line for assays of promoter activity. Reporter genes typically encode polypeptides with an easily assayed enzymatic activity that is naturally absent from the host cell. Typical reporter polypeptides for eukaryotic promoters include, e.g., chloramphenicol acetyltransferase (CAT), firefly or Renilla luciferase, beta-galactosidase, beta-glucuronidase, alkaline phosphatase, Dendra2, mCherry, mRaspberry, mPlum, tdTomato, green fluorescent protein (GFP), yellow fluorescent protein (YFP), enhanced green fluorescent protein (eGFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP), etc. Vectors expressing a reporter gene under the control of a transcription regulatory element of a gene can be prepared using routinely practiced techniques and methods of molecular biology (see, e.g., e.g., Sambrook et al., supra; Brent et al., supra).

[00198] In addition to a reporter gene, the vector can also comprise elements necessary for propagation or maintenance in the host cell, and elements such as polyadenylation sequences and transcriptional terminators. Exemplary assay vectors include pGL3 series of vectors (Promega, Madison, WI; U.S. Patent No. 5,670,356), which include a polylinker sequence 5' of a luciferase gene. General methods of cell culture, transfection, and reporter gene assay have been described in the art, e.g., Sambrook et al., supra; and Transfection Guide, Promega Corporation, Madison, WI (1998). Any readily transfectable mammalian cell line may be used to assay expression of the reporter gene from the vector, e.g., 3T3, Caco-2, CCRF-CEM, CHO, COS-7, HCT 116, HEK 293, CH12-F3, MCF-7, HepG2, Jurkat, Mo-B, KG-1, K-562, MOLT-4 and HL-60 cells.

[00199] Alternatively, determining mRNA levels can be assessed using, e.g., biochemical and molecular biology techniques such as Northern blotting or other hybridization assays, nuclease protection assay, reverse transcription (quantitative RT-PCR) techniques, RNA-Seq, high throughput sequencing and the like. Such assays are well known to those in the art. In one embodiment, nuclear "run-on" (or "run-off") transcription assays are used (see e.g. Methods in Molecular Biology, Volume: 49 , Sep-27-1995, Page Range: 229-238). Arrays can also be used; arrays, and methods of analyzing mRNA using such arrays have been described previously, e.g. in EP0834575, EP0834576, WO96/31622, U.S. Pat. No. 5,837,832 or WO98/30883. WO97/10365 provides methods for monitoring of expression levels of a multiplicity of genes using high density oligonucleotide arrays.

[00200] In one embodiment, one or more cells from the subject to be tested are obtained and RNA is isolated from the cells. When obtaining the cells, it is preferable to obtain a sample containing predominantly cells of the desired type, e.g., a sample of cells in which at

least about 50%, preferably at least about 60%, even more preferably at least about 70%, 80% and even more preferably, at least about 90% of the cells are of the desired type. Tissue samples can be obtained according to methods known in the art.

[00201] It is also possible to obtain a cell sample from a subject, and then to enrich it in the desired cell type. For example, cells can be isolated from other cells using a variety of techniques, such as isolation with an antibody binding to an epitope on the cell surface of the desired cell type. Where the desired cells are in a solid tissue, particular cells can be dissected out, e.g., by microdissection , or laser capture microdissection (LCM).

[00202] When isolating RNA from tissue samples or cells from individuals, it may be important to prevent any further changes in gene expression after the tissue or cells has been removed from the subject. Changes in expression levels are known to change rapidly following perturbations, e.g., heat shock or activation with lipopolysaccharide (LPS) or other reagents. In addition, the RNA in the tissue and cells may quickly-become degraded. Accordingly, in a preferred embodiment, the tissue or cells obtained from a subject is snap frozen or treated with RNAlater as soon as possible.

[00203] RNA can be extracted from the tissue sample by a variety of methods, e.g., the guanidium thiocyanate lysis followed by CsCl centrifugation (Chirgwin et al., 1979, Biochemistry 18:5294-5299). RNA from single cells can be obtained as described in methods for preparing cDNA libraries from single cells, such as those described in Dulac, C. (1998) Curr. Top. Dev. Biol. 36, 245 and Jena et al. (1996) J. Immunol. Methods 190: 199. Care to avoid RNA degradation must be taken, e.g., by inclusion of RNAsin.

[00204] The RNA sample can then be enriched in a particular species. In one embodiment, poly(A)+ RNA is isolated from the RNA sample. In general, such purification takes advantage of the poly-A tails on mRNA. In particular and as noted above, poly-T oligonucleotides may be immobilized within on a solid support to serve as affinity ligands for mRNA. Kits for this purpose are commercially available, e.g., the QuickExtract® kit (Epicentre Biotechnologies, Madison, WI; Oligotex Direct mRNA kit, Qiagen, Valencia, CA).

[00205] Types of probes that can be used in the methods described herein include cDNA, riboprobes, synthetic oligonucleotides and genomic probes. The type of probe used will generally be dictated by the particular situation, such as riboprobes for in situ hybridization, and cDNA for Northern blotting, for example. In one embodiment, the probe is directed to nucleotide regions unique to the RNA. The probes may be as short as is required to differentially recognize mRNA transcripts of a regulatable protein, and may be as short as,

for example, 15 bases; however, probes of at least 17, 18, 19 or 20 or more bases can be used. In one embodiment, the primers and probes hybridize specifically under stringent conditions to a DNA fragment having the nucleotide sequence corresponding to the gene encoding the protein to be assayed. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% identity in nucleotide sequences. In another embodiment, hybridization under "stringent conditions" occurs when there is at least 97% identity between the sequences.

[00206] In one embodiment the test agent is assayed for the ability to inhibit translation of a gene. Gene translation can be measured by quantitation of protein expressed from a gene, for example by Western blotting, by an immunological detection of the protein, ELISA (enzyme-linked immunosorbent assay), radioimmunoassay (RIA) or other immunoassays and fluorescence-activated cell analysis (FACS), mass spectrometry, or protein sequencing to detect protein.

[00207] Methods for developing small molecule, polymeric and genome based libraries are described, for example, in Ding, et al., J Am. Chem. Soc. 124: 1594-1596 (2002) and Lynn, et al., J. Am. Chem. Soc. 123: 8155-8156 (2001). Commercially available compound libraries can be obtained from, e.g., ArQule, Pharmacopia, graffinity, Panvera, Vitas-M Lab, Biomol International, Selleck Chemicals and Oxford Chemicals Limited. These libraries can be screened for ability to inhibit DSB repair using methods described herein.

[00208] In certain embodiments, the DSB repair inhibitor is a nucleic acid which is able to inhibit the expression of a gene encoding a protein which promotes DSB repair. By way of non-limiting example, the DSB repair inhibitor can be an antisense inhibitor of DSB repair, for example an antisense inhibitor of RAD51 as disclosed in US Patent Publication 2002/0137698. Gene silencing or RNAi can be used. In certain embodiments, contacting a cell with the inhibitor of DSB repair results in a decrease in the mRNA level in a cell for a target gene by at least about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 99%, about 100% of the mRNA level found in the cell without the presence of the miRNA or RNA interference molecule. In one embodiment, the mRNA levels are decreased by at least about 70%, about 80%, about 90%, about 95%, about 99%, about 100%. In certain embodiments, the inhibitor of DSB repair comprises an expression vector or viral vector comprising the RNAi molecule.

[00209] As used herein, the term "RNAi" refers to any type of interfering RNA, including but are not limited to RNAi, siRNA, shRNA, endogenous microRNA and artificial microRNA. For instance, it includes sequences previously identified as siRNA, regardless of

the mechanism of down-stream processing of the RNA (i.e. although siRNAs are believed to have a specific method of *in vivo* processing resulting in the cleavage of mRNA, such sequences can be incorporated into the vectors in the context of the flanking sequences described herein). The term "RNAi" and "RNA interfering" with respect to an agent of the technology described herein, are used interchangeably herein.

[00210] As used herein an "siRNA" refers to a nucleic acid that forms a double stranded RNA, which double stranded RNA has the ability to reduce or inhibit expression of a gene or target gene when the siRNA is present or expressed in the same cell as the target gene. The double stranded RNA siRNA can be formed by the complementary strands. In one embodiment, a siRNA refers to a nucleic acid that can form a double stranded siRNA. The sequence of the siRNA can correspond to the full length target gene, or a subsequence thereof. Typically, the siRNA is at least about 15-50 nucleotides in length (e.g., each complementary sequence of the double stranded siRNA is about 15-50 nucleotides in length, and the double stranded siRNA is about 15-50 base pairs in length, preferably about 19-30 base nucleotides, preferably about 20-25 nucleotides in length, e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length).

[00211] As used herein "shRNA" or "small hairpin RNA" (also called stem loop) is a type of siRNA. In one embodiment, these shRNAs are composed of a short, e.g. about 19 to about 25 nucleotide, antisense strand, followed by a nucleotide loop of about 5 to about 9 nucleotides, and the analogous sense strand. Alternatively, the sense strand can precede the nucleotide loop structure and the antisense strand can follow.

[00212] RNAi may be delivered with the help of nanoparticles as described for example in Schiffelers and Storm, Expert Opin Drug Deliv. 2006 May;3(3):445-54 or liposomes (e.g. Hughes et al., Methods Mol Biol. 2010;605:445-59).

[00213] In certain embodiments, the DSB repair inhibitor which is a nucleic acid can be an antisense RNA.

[00214] In certain embodiments, the DSB repair inhibitor which is a nucleic acid can be a ribozyme. Ribozyme molecules designed to catalytically cleave cellular mRNA transcripts can also be used to prevent translation of cellular mRNAs and expression of cellular polypeptides, or both (See, e.g., PCT International Publication W090111364; Sarver et al. 1990, Science 247, 1222-1225 and US Pat. No. 5,093,246). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy cellular mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The

sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach 1988, Nature 334:585-591. The ribozyme may be engineered so that the cleavage recognition site is located near the 5' end of cellular mRNAs; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[00215] The ribozymes of the methods and compositions presented herein also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in Tetrahymena thermophil a (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Cech and collaborators (Zaug, et al. 1984, Science 224:574-578; Zaug, et al. 1986, Science 231:470-475; Zaug, et al. 1986 Nature 324:429-433; published International patent application No. W088/04300; Been, et al. 1986, Cell 47:207-216). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The methods and compositions of this invention includes those Cech-type ribozymes which target eight base-pair active site sequences that are present in cellular genes.

[00216] As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express DNA editing enzyme genes in vivo. A preferred method of delivery involves using a DNA construct encoding the ribozyme under the control of a strong constitutive pol HI or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous cellular messages and inhibit translation. Because ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[00217] The terms “microRNA” or “miRNA” are used interchangeably herein are endogenous RNAs, some of which are known to regulate the expression of protein-coding genes at the posttranscriptional level. Endogenous microRNAs are small RNAs naturally present in the genome which are capable of modulating the productive utilization of mRNA. The term artificial microRNA includes any type of RNA sequence, other than endogenous microRNA, which is capable of modulating the productive utilization of mRNA. MicroRNA sequences have been described in publications such as Lim, et al., Genes & Development, 17, p. 991-1008 (2003); Lim et al., Science 299, 1540 (2003); Lee and Ambros, Science, 294, 862 (2001); Lau et al., Science 294, 858-861 (2001); Lagos-Quintana et al., Current Biology, 12, 735-739 (2002); Lagos Quintana et al., Science 294, 853-857 (2001); and Lagos-Quintana

et al., RNA, 9, 175-179 (2003), which are incorporated by reference. Multiple microRNAs can also be incorporated into a precursor molecule. Furthermore, miRNA-like stem-loops can be expressed in cells as a vehicle to deliver artificial miRNAs and short interfering RNAs (siRNAs) for the purpose of modulating the expression of endogenous genes through the miRNA and or RNAi pathways.

[00218] As used herein, "double stranded RNA" or "dsRNA" refers to RNA molecules that are comprised of two strands. Double-stranded molecules include those comprised of a single RNA molecule that doubles back on itself to form a two-stranded structure. For example, the stem loop structure of the progenitor molecules from which the single-stranded miRNA is derived, called the pre-miRNA (Bartel et al., 2004, Cell 116:281-297), comprises a dsRNA molecule.

[00219] Means for selecting nucleotide sequences (e.g. RNAi, siRNA, shRNA) that can serve as inhibitors or activators of target gene expression are well known and practiced by those of skill in the art. Many computer programs are available to design RNAi agents against a particular nucleic acid sequence. The targeted region of RNAi (e.g. siRNA etc.) can be selected from a given target gene sequence, e.g., RAD51), beginning from about 25 to 50 nucleotides, from about 50 to 75 nucleotides, or from about 75 to 100 nucleotides downstream of the start codon. Nucleotide sequences can contain 5' or 3' UTRs and regions nearby the start codon. One method of designing a siRNA molecule of the technology described herein involves identifying the 23 nucleotide sequence motif AA(N19)TT (where N can be any nucleotide) (SEQ ID NO: 156), and selecting hits with at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75% G/C content. The "TT" portion of the sequence is optional. Alternatively, if no such sequence is found, the search can be extended using the motif NA(N21), where N can be any nucleotide. In this situation, the 3' end of the sense siRNA can be converted to TT to allow for the generation of a symmetric duplex with respect to the sequence composition of the sense and antisense 3' overhangs. The antisense RNAi molecule can then be synthesized as the complement to nucleotide positions 1 to 21 of the 23 nucleotide sequence motif. The use of symmetric 3' TT overhangs can be advantageous to ensure e.g. that the small interfering ribonucleoprotein particles (siRNPs) are formed with approximately equal ratios of sense and antisense target RNA-cleaving siRNPs (Elbashir et al. 2001 supra).

[00220] In some embodiments, the RNAi agent targets at least 5 contiguous nucleotides in the identified target gene sequence. In one embodiment, the RNAi agent targets at least 6, 7, 8, 9 or 10 contiguous nucleotides in the identified target sequence. In some embodiments, the

RNAi agent targets at least 11, 12, 13, 14, 15, 16, 17, 18 or 19 contiguous nucleotides in the identified target sequence.

[00221] In some embodiments, in order to increase nuclease resistance in an RNAi agent as disclosed herein, one can incorporate non-phosphodiester backbone linkages, as for example methylphosphonate, phosphorothioate or phosphorodithioate linkages or mixtures thereof, into one or more non-RNASE H-activating regions of the RNAi agents. Such non-activating regions may additionally include 2'-substituents and can also include chirally selected backbone linkages in order to increase binding affinity and duplex stability. Other functional groups may also be joined to the oligonucleoside sequence to instill a variety of desirable properties, such as to enhance uptake of the oligonucleoside sequence through cellular membranes, to enhance stability or to enhance the formation of hybrids with the target nucleic acid, or to promote cross-linking with the target (as with a psoralen photo-cross- linking substituent). See, for example, PCT Publication No. WO 92/02532 which is incorporated herein in by reference.

[00222] In certain embodiments, the inhibitor of DSB repair is an antibody, monoclonal antibody, or antibody fragment (See, generally, Hood et al., Immunology, Benjamin, N.Y., 2ND ed. (1984), Harlow and Lane, Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory (1988) and Hunkapiller and Hood, Nature, 323, 15-16 (1986), which are incorporated herein by reference). Antibodies are prepared using methods well known to those of skill in the art. Typically, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell (see, Kohler and Milstein (1976) Eur, J. Immunol. 6:511-519, incorporated herein by reference). Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode a monoclonal antibody or an antibody fragment or a binding fragment thereof by screening a DNA library from human B cells according, e.g., to the general protocol outlined by Huse, et al. (1989), Science 246:1275-1281, or by screening phage display libraries (See e.g. WO 91/17271 and WO 92/01047). In certain embodiments, the inhibitor of RAD51-mediated strand exchange repair is an intrabody. Methods for intrabody production are well known to those of skill in the art, e.g. as described in WO 2002/086096. Antibodies will usually bind with at least a KD of about 1

mM, e.g. 1 mM or lower, 300 μM or lower, 30 μM or lower, 10 μM or lower, 3 μM or lower, 1 μM or lower, 100 nM or lower, or 10 nM or lower.

[00223] In certain embodiments, the inhibitor of DSB repair is a protein or peptide. A peptide agent can be a fragment of a naturally occurring protein, or a mimic or pepetidomimetic of a protein of RAD51-mediated exchange repair. Agents in the form of a protein and/or peptide or fragment thereof can be designed to modulate a gene or protein involved in DSB repair described herein, i.e. modulate gene expression or encoded protein activity. Such agents are intended to encompass proteins which are normally absent as well as proteins normally endogenously expressed within a cell, e.g. expressed at low levels. Examples of useful proteins are mutated proteins, genetically engineered proteins, peptides, synthetic peptides, recombinant proteins, chimeric proteins, humanized proteins, modified proteins and fragments thereof. Modulation of gene expression or protein activity can be direct or indirect. In one embodiment, a protein/peptide agent directly binds to a protein encoded by a gene identified herein, or directly binds to a nucleic acid of a gene identified herein.

[00224] Peptides can be screened for inhibitory activity. Peptide libraries, e.g. combinatorial libraries of peptides or other compounds can be fully randomized, with no sequence preferences or constants at any position. Alternatively, the library can be biased, i.e., some positions within the sequence are either held constant, or are selected from a limited number of possibilities. For example, in some cases, the nucleotides or amino acid residues are randomized within a defined class, for example, of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, or to purines.

[00225] The test agents can be naturally occurring proteins or their fragments. Such test agents can be obtained from a natural source, e.g., a cell or tissue lysate. Libraries of polypeptide agents can also be prepared, e.g., from a cDNA library commercially available or generated with routine methods. The test agents can also be peptides, e.g., peptides of from about 5 to about 30 amino acids, with from about 5 to about 20 amino acids being preferred, and from about 7 to about 15 being particularly preferred. The peptides can be digests of naturally occurring proteins, random peptides, or "biased" random peptides. In some methods, the test agents are polypeptides, peptides or proteins. The test agents can also be nucleic acids. Nucleic acid test agents can be naturally occurring nucleic acids, random

nucleic acids, or "biased" random nucleic acids. For example, digests of prokaryotic or eukaryotic genomes can be similarly used as described above for proteins.

[00226] Libraries of test agents to be screened can also be generated based on structural studies of the proteins, or their fragments, encoded by the genes identified herein. Such structural studies allow the identification of test agents that are more likely to bind to the proteins and modulate their activity. The three-dimensional structures of the proteins can be studied in a number of ways, e.g., crystal structure and molecular modeling. Methods of studying protein structures using X-ray crystallography are well known in the literature. See Physical Bio-chemistry, Van Holde, K. E. (Prentice-Hall, New Jersey 1971), pp. 221-239, and Physical Chemistry with Applications to the Life Sciences, D. Eisenberg & D. C. Crothers (Benjamin Cummings, Menlo Park 1979). Computer modeling of structures provides another means for designing test agents to screen for modulators. Methods of molecular modeling have been described in the literature, e.g., U.S. Patent No. 5,612,894 entitled "System and method for molecular modeling utilizing a sensitivity factor", and U.S. Patent No. 5,583,973 entitled "Molecular modeling method and system". In addition, protein structures can also be determined by neutron diffraction and nuclear magnetic resonance (NMR). See, e.g., Physical Chemistry, 4th Ed. Moore, W. J. (Prentice-Hall, New Jersey 1972), and NMR of Proteins and Nucleic Acids, K. Wuthrich (Wiley-Interscience, New York 1986).

[00227] In some embodiments, the test compound that is screened and identified to inhibit expression of a gene identified herein, or identified to inhibit the activity of a protein encoded by a gene identified herein can inhibit DSB repair by at least 5%, 10%, 20%, 30%, 40%, 50%, 50%, 70%, 80%, 90%, 1-fold, 1.1-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 50-fold, 100-fold or more higher relative to an untreated control.

[00228] The DSB repair inhibitory compounds or agents may function directly in the form in which it is administered. Alternatively, the agent can be modified or utilized intracellularly to produce something which modulates the gene, e.g. introduction of a nucleic acid sequence into the cell and its transcription resulting in the production of an inhibitor or activator of gene expression or protein activity.

Treatment

[00229] In some embodiments, the technology described herein relates to a method of treatment comprising (a) selecting a subject having cells that express an elevated level of a DNA editing enzyme; and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level is a level of AID that is

higher than the level of a DNA editing enzyme in cells of the same type from a healthy individual. In some embodiments, the technology described herein relates to a method of treatment comprising (a) selecting a subject having B cells that express an elevated level of a DNA editing enzyme; and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject, wherein an elevated level is a level of a DNA editing enzyme that is higher than the level of a DNA editing enzyme in B cells of from a healthy individual. In some embodiments the DNA editing enzyme expression is not detectable in the healthy subject. In some embodiments, the subject can be a human subject.

[00230] In some embodiments, the subject having cells expressing elevated levels of a DNA editing enzyme as compared to the level of a DNA editing enzyme in cells of the same type from a healthy individual is identified by determining the level of a DNA editing enzyme protein and/or mRNA in a sample of cells obtained from the subject. In some embodiments, the levels of a DNA editing enzyme in the cells expressing an elevated level of a DNA editing enzyme are significantly higher than normal cells from a healthy subject. In some embodiments, the levels of a DNA editing enzyme in the cells expressing an elevated level of a DNA editing enzyme are significantly higher than the levels of a DNA editing enzyme expressed in unactivated B cells from a healthy subject. In some embodiments, the levels of a DNA editing enzyme in the B cells expressing an elevated level of a DNA editing enzyme are significantly higher than the levels of AID expressed in unactivated B cells from a healthy subject.

[00231] In some embodiments, the technology described herein relates to a method of treatment comprising (a) selecting a subject having cells that express an elevated level of activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level is a level of AID that is higher than the level of AID in cells of the same type from a healthy individual. In some embodiments, the technology described herein relates to a method of treatment comprising (a) selecting a subject having B cells that express an elevated level of AID; and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject, wherein an elevated level is a level of AID that is higher than the level of AID in B cells of from a healthy individual. In some embodiments the AID expression is not detectable in the healthy subject.

[00232] In some embodiments, the subject having cells expressing elevated levels of AID as compared to the level of AID in cells of the same type from a healthy individual is identified by determining the level of AID protein and/or mRNA in a sample of cells

obtained from the subject. In some embodiments, the levels of AID in the cells expressing an elevated level of AID are significantly higher than normal cells from a healthy subject. In some embodiments, the levels of AID in the cells expressing an elevated level of AID are significantly higher than the levels of AID expressed in unactivated B cells from a healthy subject. In some embodiments, the levels of AID in the B cells expressing an elevated level of AID are significantly higher than the levels of AID expressed in unactivated B cells from a healthy subject.

[00233] Also provided herein are methods for determining if a condition in a subject, e.g. a cancer or autoimmune disease, will be responsive to treatment by an inhibitor of DSB repair by determining the level of a DNA editing enzyme (e.g. AID) protein, mRNA and/or activity in the cells of that subject. The presence of high levels of a DNA editing enzyme in the subject's cells (test sample) can be indicative that the subject will be responsive to treatment by an inhibitor of DSB repair. The level of a DNA editing enzyme can be determined by assessing the level in a biological sample obtained from a subject and comparing the observed levels to the levels of a DNA editing enzyme found in a control reference sample. In some embodiments the DNA editing enzyme is AID.

[00234] In one embodiment, the condition (e.g. cancer or autoimmune disease) to be treated is already known to those of skill in the art to have high levels of a DNA editing enzyme, and thus treatment with an inhibitor of DSB repair is indicated without the need to measure levels of a DNA editing enzyme protein, mRNA, and/or expression in a biological sample obtained from the patient. In certain embodiments the DNA editing enzyme is AID. As used herein, a "biological sample" refers to a sample of biological material obtained from a patient, preferably a human patient, including a tissue sample (e.g., a tissue biopsy, such as, an aspiration biopsy, a brush biopsy, a surface biopsy, a needle biopsy, a punch biopsy, an excision biopsy, an open biopsy, an incision biopsy or an endoscopic biopsy) or cell samples (e.g. epithelial cells or lymphocytes). Biological samples can also be biological fluid samples e.g. semen, urine, blood, serum, saliva, cerebrospinal fluid, and supernatant from cell lysate, e.g. lymphocyte fraction. Some embodiments of the technology described herein also encompass the use of isolates of a biological sample in the methods described herein.

[00235] The control reference sample can be a biological sample (of the same type) that is obtained from a healthy individual, i.e. an individual that does not have cancer or an autoimmune disease. The control reference sample can also be a standard sample that contains the same concentration of a DNA editing enzyme that is normally found in a biological sample of the same type and that is obtained from a healthy individual. For

example, there can be a standard reference control sample for the amounts of a DNA editing enzyme normally found in biological samples such as particular cell fractions (e.g. lymphocytes), semen, urine, blood, cerebral spinal fluid, or tissue. In one embodiment, the control reference sample is a standard reference sample that contains a mean or median concentration of a DNA editing enzyme mRNA or a DNA editing enzyme protein found in cells from a population of healthy individuals that do not have cancer or an autoimmune disease. In one embodiment, e.g., when the cells are B cells, the reference level is the level of a DNA editing enzyme protein or mRNA found in a population of unactivated B-lymphocytes from a healthy individual. In one embodiment, the control reference sample is a biological sample of the patient from healthy cells or tissue from the patient, e.g. if the patient has lymphoma, a cheek swab or skin biopsy can be used as a reference sample. In some embodiments, the levels of a DNA editing enzyme mRNA, protein, and/or activity found in a population of B-cells undergoing class switching are not suitable control reference samples.

[00236] Cells obtained from a subject are characterized as having increased, or elevated levels of a DNA editing enzyme protein and/or mRNA if the level of a DNA editing enzyme protein, a DNA editing enzyme mRNA, and/or a DNA editing enzyme activity detected in the subject's cells (e.g. a biological sample comprising cancerous or autoimmune cells), is higher by a statistically significant amount, than the level of a DNA editing enzyme protein, mRNA and/or activity found in a reference control sample representative of the level of a DNA editing enzyme in cells of the same type from a healthy subject. The levels of a DNA editing enzyme can be represented by arbitrary units, for example as units obtained from a densitometer, luminometer, or an ELISA plate reader etc. In a certain embodiment the DNA editing enzyme is AID.

[00237] As used herein, the terms, a "high level" an "elevated level", and/or "increased level" of a DNA editing enzyme protein, mRNA, and/or activity are used interchangeably and refer to amounts of a DNA editing enzyme protein, mRNA, and/or activity that are significantly greater than the amounts of a DNA editing enzyme protein, mRNA, and/or activity present in a control reference sample representative of the levels of a DNA editing enzyme in cells of the same type from a healthy individual. In a certain embodiment the DNA editing enzyme is AID.

[00238] In some embodiments, the control reference sample can comprise healthy cells of the same type as the cells for which a DNA editing enzyme levels are to be determined. In some embodiments, the cells of the control reference sample can be of similar age, developmental status, sex, and/or cell type as the cells for which the level of a DNA editing

enzyme expression is to be determined. In some embodiments, the control reference sample can be obtained from a healthy organism of similar age, developmental status, and/or sex as the subject organism for which the level of a DNA editing enzyme expression is to be determined. In some embodiments, the test sample and control reference sample are of the same type, that is, obtained from the same biological source, and comprising the same composition, e.g. the same number and type of cells. In a certain embodiment the DNA editing enzyme is AID.

[00239] In some embodiments, the control reference sample can comprise healthy, unactivated and/or non-transformed B cells. In some embodiments, an elevated level of a DNA editing enzyme is a level significantly greater than that in a healthy, unactivated and/or non-transformed B cell. In some embodiments, B-cells undergoing class-switching are not considered to be useful reference samples. In a certain embodiment the DNA editing enzyme is AID.

[00240] In most normal cells AID protein/mRNA are not detectable, therefore in some embodiments, mere detection of AID can be considered to be an increased level as compared to there being no detectable levels in cells from a healthy individual. In some embodiments, an elevated level of AID can be the level of AID which is detectable using an RT-PCR assay using the primers SEQ ID NO:101 and SEQ ID NO:102, e.g. as described further in Example 11 herein.

[00241] In some embodiments, a detectable level of AID can be 1 pg of AID mRNA per 1 mL of blood or more, e.g. 10 pg/mL, 100 pg/mL, 1 ng/mL, 10 ng/mL or more. In some embodiments, a detectable level of AID can be 10 pg of AID mRNA per 1 mL of blood or more. In some embodiments, a detectable level of AID can be 100 pg of AID mRNA per 1 mL of blood or more. In some embodiments, a detectable level of AID can be 1 ng of AID mRNA per 1 mL of blood or more. In some embodiments, a detectable level of AID can be 10 ng of AID mRNA per 1 mL of blood or more. In some embodiments, a detectable level of AID can be 100 ng of AID mRNA per 1 mL of blood or more.

[00242] In some embodiments, a detectable level of AID can be 5 copies (e.g. transcripts) of AID mRNA per cell or more, e.g. 10 copies, 100 copies, 1,000 copies or more per cell.

[00243] In some embodiments, a detectable level of AID can be, as measured by immunohistochemistry, 1 AID polypeptide per 20 square microns in a tissue section or more e.g. 1 polypeptide, 10 polypeptides, 100 polypeptides, 1,000 polypeptides or more per 20 square microns in a tissue section

[00244] In some embodiments, a detectable level of AID can be 0.1 pg of AID polypeptide per mL of blood or serum or more, e.g. 0.1 pg, 1 pg, 10 pg, 100 pg, 1 ng, 10 ng, or more per mL of blood. In some embodiments, a detectable level of AID can be 0.1 pg or more of AID polypeptide per mL of blood or serum. In some embodiments, a detectable level of AID can be 10 pg or more of AID polypeptide per mL of blood. In some embodiments, a detectable level of AID can be 100 pg or more of AID polypeptide per mL of blood. In some embodiments, a detectable level of AID can be 1 ng or more of AID polypeptide per mL of blood. In some embodiments, a detectable level of AID can be 10 ng or more of AID polypeptide per mL of blood. In some embodiments, a detectable level of AID can be 100 ng or more of AID polypeptide per mL of blood.

[00245] In some embodiments, a sample comprising serum can first be depleted of serum albumin to increase sensitivity. In some embodiments, a sample comprising blood can be enriched for B-cells or for cancerous cells before detecting the level of a DNA editing enzyme. In some embodiments, numeric expression values can be quantified and analyzed with software (e.g., Microsoft EXCEL® spreadsheet and Affymetrix GENECHIP® software).

[00246] In some embodiments, a subject is a candidate for treatment according to the methods described herein if the levels of AID in the cells of a subject are significantly greater than the levels of AID present in the control reference sample. In some embodiments, a subject is a candidate for treatment according to the methods described herein if the levels of AID in the cells of a subject are at least 1.5- fold, 2-fold, 5-fold, 10-fold greater than the levels of AID present in the control reference sample, e.g. 1.5- fold or greater, 2-fold or greater, 3-fold or greater, 4-fold or greater, 5-fold or greater, or 6-fold or greater.

[00247] In some embodiments, a healthy subject and/or a subject not in need of treatment according to the methods described herein can be one whose cells do not express a detectable level of a DNA editing enzyme. In some embodiments, the DNA editing enzyme can be AID.

[00248] The levels of AID, as described herein, can be measured by any means known to those skilled in the art. In certain embodiments the determining of the level of AID protein involves the use of one or more of the following assays; Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay; fluorescence in situ hybridization (FISH); immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; in situ immunoassay; precipitation reaction; agglutination assay; complement fixation assay;

immunofluorescence assay; protein A assay; mass spectroscopy and/or immunoelectrophoresis assay. In certain embodiments the determining of the level of AID protein involves the use of an antibody, an antibody fragment, a monoclonal antibody, a monoclonal antibody fragment, a protein binding protein, and/or an AID-binding peptide.

[00249] In certain embodiments, the determining of the level of AID mRNA involves the use of one or more of the following assays; RT-PCR, quantitative RT-PCR, hybridization assays, RNA-Seq, Northern blot, high-throughput sequencing, microarray based expression analysis, transcription amplification and/or self-sustained sequence replication. In certain embodiments the determining of the level of AID mRNA involves the use of an antibody, an antibody fragment, a monoclonal antibody, and/or a monoclonal antibody fragment.

[00250] Methods for assessing levels of mRNA are well known to those skilled in the art. Preferred embodiments are herein described. Laser Capture Microdissection Laser Capture Microdissection (LCM) is known to those of skill in the art, see, for example, Simon et al. (1998) Trends in Genetics 14:272 and Emmert-Buck et al. (1996) Science 274:998-1001. In one embodiment of the technology described herein a tumor sample or biopsy is obtained and LCM is used to obtain genetic material, such as, mRNA, for analysis. Nucleic acid molecules can be isolated from a particular biological sample using any of a number of procedures, which are well known in the art, the particular isolation procedure chosen being appropriate for the particular biological sample. For example, freeze-thaw and alkaline lysis procedures can be useful for obtaining nucleic acid molecules from solid materials; heat and alkaline lysis procedures can be useful for obtaining nucleic acid molecules from urine; and proteinase K extraction can be used to obtain nucleic acid from blood (Rolff, A et al. PCR: Clinical Diagnostics and Research, Springer (1994).

[00251] Real time PCR is an amplification technique that can be used to determine levels of mRNA expression. (See, e.g., Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. For mRNA levels, mRNA is extracted from a biological sample, e.g. a tumor and normal tissue, and cDNA is prepared using standard techniques. Real-time PCR can be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, Calif.) 7700 Prism instrument. Matching primers and fluorescent probes can be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems (Foster City, Calif.). Optimal concentrations of primers and probes can be initially determined by those of ordinary skill in the art, and control (for

example, beta-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, Calif.).

[00252] To quantitate the amount of the specific nucleic acid of interest in a sample, a standard curve is generated using a control. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial concentration of the nucleic acid of interest used in the assay. Standard dilutions ranging from 10-106 copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial content of the nucleic acid of interest in a tissue sample to the amount of control for comparison purposes. Methods of real-time quantitative PCR using TaqMan probes are well known in the art. Detailed protocols for real-time quantitative PCR are provided, for example, for RNA in: Gibson et al., 1996 Genome Res., 10:995-1001; and for DNA in: Heid et al., 1996 Genome Res., 10:986-994.

[00253] A TaqMan-based assay also can be used to quantify the expression level. TaqMan based assays use a fluorogenic oligonucleotide probe that contains a 5' fluorescent dye and a 3' quenching agent. The probe hybridizes to a PCR product, but cannot itself be extended due to a blocking agent at the 3' end. When the PCR product is amplified in subsequent cycles, the 5' nuclease activity of the polymerase, for example, AmpliTaq, results in the cleavage of the TaqMan probe. This cleavage separates the 5' fluorescent dye and the 3' quenching agent, thereby resulting in an increase in fluorescence as a function of amplification.

[00254] In another embodiment, for example, detection of RNA transcripts may be achieved by Northern blotting, wherein a preparation of RNA is run on a denaturing agarose gel, and transferred to a suitable support, such as activated cellulose, nitrocellulose or glass or nylon membranes. Labeled (e.g., radiolabeled) cDNA or RNA is then hybridized to the preparation, washed and analyzed by methods such as autoradiography.

[00255] To monitor mRNA levels, for example, mRNA is extracted from the biological sample to be tested, reverse transcribed, and fluorescently-labeled cDNA probes are generated. The microarrays capable of hybridizing to cDNA generated from transcripts encoding a regulatable protein are then probed with the labeled cDNA probes, the slides scanned and fluorescence intensity measured. This intensity correlates with the hybridization intensity and expression levels.

[00256] The population of RNA, enriched or not in particular species or sequences, can further be amplified. As defined herein, an "amplification process" is designed to strengthen, increase, or augment a molecule within the RNA. For example, where RNA is mRNA, an amplification process such as RT-PCR can be utilized to amplify the mRNA, such that a

signal is detectable or detection is enhanced. Such an amplification process is beneficial particularly when the biological, tissue, or tumor sample is of a small size or volume.

[00257] Detection of RNA transcripts can further be accomplished using known amplification methods. For example, it is within the scope of the technology described herein to reverse transcribe mRNA into cDNA followed by polymerase chain reaction (RT-PCR); or, to use a single enzyme for both steps as described in U.S. Pat. No. 5,322,770, or reverse transcribe mRNA into cDNA followed by asymmetric gap lipase chain reaction (RT-AGLCR) as described by R. L. Marshall, et al., PCR Methods and Applications 4: 80-84 (1994). Real time PCR may also be used. Other suitable methods are isothermal detection methods including but not limited to ligase chain reaction (LCR) (see, e.g., Wu and Wallace 1989, Genomics 4, 560 Landegren et al. 1988, Science 241, 1077); self-sustained sequence replication (SSR) (see, e.g., Guatelli et al. 1990, PNAS USA, 87, 1874); transcription amplification (see, e.g., Kwoh et al. 1989, PNAS USA 86, 1173); strand displacement amplification (G. T. Walker et al., 1996, Clin. Chem. 42: 9-13 and European Patent Application No. 684315); rolling circle amplification; loop-mediated isothermal amplification; isothermal chimeric primer-initiated amplification of nucleic acids; Q-beta amplification systems (European Patent Application (EPA) No. 4544610); or OneCutEventAmplificatioN (OCEAN; Clinical Chemistry 52, 1855-1863 (2006)). The isothermal detection methods may further utilize Nuclease Chain Reaction (NCR), RNAse-mediated Nucleases Chain Reaction (RNCR), Polymerase Nuclease Chain Reaction (PNCR), RNAse-Mediated Detection (RMD), Tandem Repeat Restriction Enzyme Facilitated (TR-REF) Chain Reaction or Inverted reverse Complement Restriction Enzyme Facilitated (IRC-REF) Chain Reaction. Other known amplification methods which can be utilized herein include but are not limited to the so-called "NASBA" (nucleic acid sequence based amplification) or "3SR" (self-sustained sequence replication) technique described in PNAS USA 87: 1874-1878 (1990) and also described in Nature 350 (No. 6313): 91-92 (1991) and Mollasalehi et al., 2012, Anal Biochem, 425, 91-95; and target mediated amplification, as described by PCT Publication WO9322461 and PCT Publication WO2010/019898A1.

[00258] In some embodiments, AID nucleic acids can be detected using sequencing methods, e.g. high throughput sequencing, whole transcriptome shotgun sequencing or RNA-seq. RNA-seq can utilize any of a number of next-generation, commercially available sequencing technologies (e.g. 454 SEQUENCING™ or ILLUMINA™) to generate high-throughput sequencing of the entire transcriptome or portions thereof. RNA-seq is described, for example in Ryan et al. (2008).BioTechniques 45 (1): 81–94; Wang Z, et al.

(2009). Nature Reviews Genetics 10 (1): 57–63; Maher CA, et al. (2009).Nature 458 (7234): 97–101; which are incorporated by reference herein in their entireties.

[00259] In another embodiment, AID nucleic acids can be detected using "self-sustained sequence replication." This is a method of nucleic acid amplification using target nucleic acid sequences which are amplified (replicated) exponentially *in vitro* under isothermal conditions by using three enzymatic activities essential to retroviral replication: (1) reverse transcriptase, (2) RNase H, and (3) a DNA-dependent RNA polymerase (Guatelli, et al. 1990, *Proc. Natl. Acad. Sci.* USA 87:1874). By mimicking the retroviral strategy of RNA replication by means of cDNA intermediates, this reaction accumulates cDNA and RNA copies of the original target. Substantially isothermal means that the temperature may be varied over the course of an approximately one hour reaction time within the temperature range of about 37° C to 50° C. Alternatively, one temperature may be selected to carry out the entire reaction. Self-sustained sequence replication at 45° C is preferred.

[00260] In another embodiment, AID nucleic acids can be detected using "transcription amplification". In this method of nucleic acid amplification, each cycle is composed of two steps. In the first step, a cDNA copy of a RNA or DNA target is made and in the second step, multiple RNA transcripts of each cDNA copy are generated (see, e.g., Kwoh (1989) Proc. Natl. Acad. Sci. USA 86: 1173).

[00261] *In situ* hybridization visualization may also be employed, wherein a radioactively labeled antisense RNA probe is hybridized with a thin section of a biopsy sample, washed, cleaved with RNase and exposed to a sensitive emulsion for autoradiography. The samples may be stained with hematoxylin to demonstrate the histological composition of the sample, and dark field imaging with a suitable light filter shows the developed emulsion. Non-radioactive labels such as digoxigenin may also be used.

[00262] Alternatively, mRNA expression can be detected on a DNA array, chip or a microarray. Nucleic acids corresponding to a DNA editing enzyme are immobilized on a chip which is then hybridized with labeled nucleic acids of a test sample obtained from a patient. Positive hybridization signal is obtained with the sample containing a DNA editing enzyme transcript. Methods of preparing DNA arrays and their use are well known in the art. (See, for example U.S. Patent Nos: 6,618,6796; 6,379,897; 6,664,377; 6,451,536; 548,257; U.S. 20030157485 and Schena et al. 1995, Science 20:467-470; Gerhold et al. 1999, Trends in Biochem. Sci. 24, 168-173; and Lennon et al. 2000, Drug discovery Today 5: 59-65, which are herein incorporated by reference in their entirety). Serial Analysis of Gene Expression (SAGE) can also be performed (See for example U.S. Patent Application 20030215858). To

monitor mRNA levels, for example, mRNA is extracted from the biological sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes are generated. The microarrays capable of hybridizing to a DNA editing enzyme cDNA are then probed with the labeled cDNA probes, the slides scanned and fluorescence intensity measured. This intensity correlates with the hybridization intensity and expression levels. Quantitative PCR methods of "quantitative" amplification are well known to those of skill in the art. For example, quantitative PCR involves simultaneously co-amplifying a known quantity of a control sequence using the same primers. This provides an internal standard that may be used to calibrate the PCR reaction. Detailed protocols for quantitative PCR are provided, for example, in Innis et al. (1990), PCR Protocols, A Guide to Methods and Applications, Academic Press, Inc. N.Y.

[00263] DNA editing enzyme protein levels or DNA editing enzyme activity, can also be measured, in particular, when the biological sample is a fluid sample such as cell lysate. In one embodiment, levels of DNA editing enzyme protein can be measured by contacting the biological sample with an antibody moiety or protein-binding protein that specifically binds to a DNA editing enzyme, or to a fragment of a DNA editing enzyme. Formation of the antibody- DNA editing enzyme complex can then be detected as a measure of DNA editing enzyme levels. Antibodies which recognize a DNA editing enzyme (e.g. AID) can be obtained commercially or prepared according to the methods described elsewhere herein.

[00264] AID protein levels or AID activity can also be measured. In one embodiment, levels of AID protein are measured by contacting the biological sample with an antibody moiety or a protein-binding protein that specifically binds to AID, or to a fragment of AID. Formation of the antibody-AID complex is then detected as a measure of AID levels. Antibodies which recognize AID can be obtained commercially (ab59361, ab93596 or ab77401; AbCam Cambridge, MA) or prepared according to the methods described elsewhere herein. Tissues samples can be prepared as sections, for example as frozen or fixed sections and stained with an antibody. Liquid samples, can be analyzed for example in an ELISA or a flow cytometry analysis.

[00265] In one embodiment, the antibody moiety is detectably labeled. "Labeled antibody", as used herein, includes antibodies that are labeled by a detectable means and include, but are not limited to, antibodies that are enzymatically, radioactively, fluorescently, and chemiluminescently labeled. Antibodies can also be labeled with a detectable tag, such as c-Myc, HA, VSV-G, HSV, FLAG, V5, or HIS. In the diagnostic and prognostic methods described herein that use antibody based binding moieties for the detection of AID, the level

of AID present in the biological samples correlate to the intensity of the signal emitted from the detectably labeled antibody. In one preferred embodiment, the antibody-based binding moiety is detectably labeled by linking the antibody to an enzyme. The enzyme, in turn, when exposed to its substrate, will react with the substrate in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorometric or by visual means. Enzymes which can be used to detectably label the antibodies of the technology described herein include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-V-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-VI-phosphate dehydrogenase, glucoamylase and acetylcholinesterase.

[00266] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling an antibody, it is possible to detect the antibody through the use of radioimmunology assays. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography. Isotopes which are particularly useful for the purpose of the technology described herein are ^{3}H, ^{131}I, ^{35}S, ^{14}C, and preferably ^{125}I. It is also possible to label an antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wavelength, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are CYE dyes, fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. An antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA). An antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, luciferin, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[00267] In one embodiment, the levels of AID protein is detected by immunoassays, such as enzyme linked immunoabsorbant assay (ELISA), Western blotting, immunocytochemistry or flow cytometry. Immunoassays such as ELISA, flow cytometry or RIA, which can be extremely rapid. Antibody arrays or protein chips can also be employed, see for example U.S.

Patent Application Nos: 20030013208A1; 20020155493A1; 20030017515 and U.S. Patent Nos: 6,329,209; 6,365,418, which are herein incorporated by reference in their entirety.

[00268] The most common enzyme immunoassay is the Enzyme-Linked Immunosorbent Assay (ELISA). ELISA is a technique for detecting and measuring the concentration of an antigen using a labeled (e.g. enzyme linked) form of the antibody. There are different forms of ELISA, which are well known to those skilled in the art. The standard techniques known in the art for ELISA are described in "Methods in Immunodiagnosis", 2nd Edition, Rose and Bigazzi, eds. John Wiley & Sons, 1980; Campbell et al., "Methods and Immunology", W. A. Benjamin, Inc., 1964; and Oellerich, M. 1984, J. Clin. Chem. Clin. Biochem., 22:895-904.

[00269] In a "sandwich ELISA", an antibody (e.g. anti-AID) is linked to a solid phase (i.e. a microtiter plate) and exposed to a biological sample containing antigen (e.g. AID). The solid phase is then washed to remove unbound antigen. A labeled antibody (e.g. enzyme linked) is then bound to the bound-antigen (if present) forming an antibody-antigen-antibody sandwich. Examples of enzymes that can be linked to the antibody are alkaline phosphatase, horseradish peroxidase, luciferase, urease, and B-galactosidase. The enzyme-linked antibody reacts with a substrate to generate a colored reaction product that can be measured.

[00270] In a "competitive ELISA", antibody is incubated with a sample containing antigen (i.e. AID). The antigen-antibody mixture is then contacted with a solid phase (e.g. a microtiter plate) that is coated with antigen (i.e., AID). The more antigen present in the sample, the less free antibody that will be available to bind to the solid phase. A labeled (e.g., enzyme linked) secondary antibody is then added to the solid phase to determine the amount of primary antibody bound to the solid phase. In an "immunohistochemistry assay" a section of tissue or cells is tested for specific proteins by exposing the tissue to antibodies that are specific for the protein that is being assayed. An immunohistochemistry assay can include, but is not limited to, in situ immunofluorescence, or widefield epifluorescence microscopy, and immunofluorescence microscopy.

[00271] A "precipitation assay" or a "gel diffusion precipitation reaction" may also be used to detect AID protein. An antibody is incubated with a sample containing antigen (i.e. AID). A precipitate will form when the point of equivalence is reached. In a gel diffusion precipitation reaction, the antigen and antibody are introduced into an agar gel, typically at different points, and freely diffuse into the gel. When reactants are in contact at optimal proportions, a precipitate will form. Variations of the precipitation assay include but are not limited to, radial immunodiffusion, double diffusion gel precipitation and Ouchterlony double immunodiffusion. Quantitative precipitation assays are known to those skilled in the art

(Basic Techniques in Biochemistry and Molecular Biology, Sharma and Sangha (Eds), I.K. International Publishers Pvt. Lt, New Delhi, India (2009); Essentials of Immunology and Serology, Stanley, J. Thomson, Albany, New York, (2002)).

[00272] The antibodies are then visualized by any of a number of methods to determine the presence and amount of the protein present. Examples of methods used to visualize antibodies are, for example, through enzymes linked to the antibodies (e.g., luciferase, alkaline phosphatase, horseradish peroxidase, or beta-galactosidase), or chemical methods (e.g., DAB/Substrate chromagen). Alternatively, "radioimmunoassays" may be employed. A radioimmunoassay is a technique for detecting and measuring the concentration of an antigen using a labeled (e.g.. radioactively or fluorescently labeled) form of the antigen or epitope. Examples of radioactive labels for antigens include ^{3}H, ^{14}C, and ^{125}I. The concentration of antigen in a biological sample is measured by having the antigen or epitope in the biological sample compete with the labeled (e.g. radioactively) antigen for binding to an antibody to the antigen. To ensure competitive binding between the labeled antigen and the unlabeled antigen, the labeled antigen is present in a concentration sufficient to saturate the binding sites of the antibody. The higher the concentration of antigen in the sample, the lower the concentration of labeled antigen that will bind to the antibody.

[00273] In some embodiments, the level of a DNA editing enzyme can be measured by using protein in situ array (PISA). Briefly, PISA involves an array surface comprising free or immobilized PCR DNA to template protein synthesis in a cell-free system, (e.g. rabbit reticulocyte extract) and the proteins undergo simultaneous immobilization through a tag sequence which combines with a capture reagent which is already pre-coated on the array surface. PISA is described, for example, in patent publication WO 02/14860, which is incorporated by reference herein in its entirety. In certain embodiments the DNA editing enzyme is AID.

[00274] In some embodiments, the level of a DNA editing enzyme can be measured by using quantitative in situ protein analyses, for example, AQUA™. AQUA™ is described, for example in Stemmann O., Zou H., Gerber S. A., Gygi S. P., Kirschner M. W.; Dual inhibition of sister chromatid separation at metaphase, Cell 2001, Dec 14, 107: 715-726 and Keshishian, et al. 2007, Molecular & Cellular Proteomics 6.12, 2212-2229; which are incorporated by reference herein in their entireties. In certain embodiments the DNA editing enzyme is AID.

[00275] Other techniques may be used to detect a DNA editing enzyme , according to a practitioner's preference, based upon the present disclosure. One such technique is Western blotting (Towbin et al., Proc. Nat. Acad. Sci. 76:4350 (1979)), wherein a suitably treated

sample is run on an SDS-PAGE gel before being transferred to a solid support, such as a nitrocellulose filter. Detectably labeled anti-DNA editing enzyme antibodies can then be used to assess a DNA editing enzyme levels, where the intensity of the signal from the detectable label corresponds to the amount of a DNA editing enzyme present. Levels can be quantitated, for example by densitometry. In certain embodiments the DNA editing enzyme is AID.

[00276] In addition, a DNA editing enzyme may be detected using Mass Spectrometry such as MALDI/TOF (time-of-flight), SELDI/TOF, liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), high performance liquid chromatography-mass spectrometry (HPLC-MS), capillary electrophoresis-mass spectrometry, nuclear magnetic resonance spectrometry, or tandem mass spectrometry (e.g., MS/MS, MS/MS/MS, ESI-MS/MS, etc.). See for example, U.S. Patent Application Nos: 20030199001, 20030134304, and 20030077616, which are herein incorporated by reference. Mass spectrometry methods are well known in the art and have been used to quantify and/or identify biomolecules, such as proteins (see, e.g., Li et al. (2000), Tibtech 18:151-160; Rowley et al. (2000), Methods 20: 383-397; and Kuster and Mann (1998), Curr. Opin. Structural Biol. 8: 393-400). Further, mass spectrometric techniques have been developed that permit at least partial de novo sequencing of isolated proteins. Chait et al., Science 262:89-92 (1993); Keough et al., Proc. Natl. Acad. Sci. USA. 96:7131-6 (1999); reviewed in Bergman, EXS 88:133-44 (2000). In certain embodiments, a gas phase ion spectrophotometer is used. In certain embodiments the DNA editing enzyme is AID.

[00277] In other embodiments, laser-desorption/ionization mass spectrometry is used to analyze the sample. Modern laser desorption/ionization mass spectrometry ("LDI-MS") can be practiced in two main variations: matrix assisted laser desorption/ionization ("MALDI") mass spectrometry and surface-enhanced laser desorption/ionization ("SELDI"). In MALDI, the analyte is mixed with a solution containing a matrix, and a drop of the liquid is placed on the surface of a substrate. The matrix solution then co-crystallizes with the biological molecules. The substrate is inserted into the mass spectrometer. Laser energy is directed to the substrate surface where it desorbs and ionizes the biological molecules without significantly fragmenting them. However, MALDI has limitations as an analytical tool. It does not provide means for fractionating the sample, and the matrix material can interfere with detection, especially for low molecular weight analytes. See, e.g., U.S. Pat. No. 5,118,937 (Hillenkamp et al.), and U.S. Pat. No. 5,045,694 (Beavis & Chait). In SELDI, the substrate surface is modified so that it is an active participant in the desorption process. In one variant, the surface is derivatized with adsorbent and/or capture reagents that selectively

bind the protein of interest. In another variant, the surface is derivatized with energy absorbing molecules that are not desorbed when struck with the laser. In another variant, the surface is derivatized with molecules that bind the protein of interest and that contain a photolytic bond that is broken upon application of the laser. In each of these methods, the derivatizing agent generally is localized to a specific location on the substrate surface where the sample is applied. See, e.g., U.S. Pat. No. 5,719,060 and WO 98/59361. The two methods can be combined by, for example, using a SELDI affinity surface to capture an analyte and adding matrix-containing liquid to the captured analyte to provide the energy absorbing material.

[00278] For additional information regarding mass spectrometers, see, e.g., Principles of Instrumental Analysis, 3rd edition, Skoog, Saunders College Publishing, Philadelphia, 1985; and Kirk-Othmer Encyclopedia of Chemical Technology, 4.sup.th ed. Vol. 15 (John Wiley & Sons, New York 1995), pp. 1071-1094. Detection of the presence of a DNA editing enzyme mRNA or protein will typically involve detection of signal intensity. This, in turn, can reflect the quantity and character of a polypeptide bound to the substrate. For example, in certain embodiments, the signal strength of peak values from spectra of a first sample and a second sample can be compared (e.g., visually, by computer analysis etc.), to determine the relative amounts of particular biomolecules. Software programs such as the Biomarker Wizard program (Ciphergen Biosystems, Inc., Fremont, Calif.) can be used to analyzing mass spectra. The mass spectrometers and their techniques are well known to those of skill in the art.

[00279] In some embodiments, the activity of a DNA editing enzyme can be measured by determined the overall mutation status in all or a portion of the genome of a cell. An overall mutation status at least 2% greater, e.g. 2% greater or more, 3% greater or more, 5% greater or more, 10% greater or more, or 20% greater or more than the overall mutation status in a reference cell can be indicative of an increased, elevated, and/or significant level of a DNA editing enzyme activity. In some embodiments, the level of hyper mutations can be determined. In some embodiments, the overall mutation status in the whole genome or a portion thereof can be determined using FISH, whole genome sequencing, high throughput sequencing, exome sequencing, hybridization, and/or PCR. In some embodiments the activity of a DNA editing enzyme can be measured by determining the level of hypermutations in the specific target genes including, but not limited to IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5. In certain embodiments the DNA editing enzyme is AID. The detection of hypermutations in the gene loci is indicative of AID activity. In some embodiments, a level

of mutation in specific target genes including IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 which is at least 2% greater, e.g. 2% greater or more, 3% greater or more, 5% greater or more, 10% greater or more, or 20% greater or more than the level of mutation in IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 in a reference cell can be indicative of an increased, elevated, and/or significant level of AID activity.

[00280] In some embodiments the activity of a DNA editing enzyme is determined by using FISH analysis to detect DNA double strand breaks, e.g. DNA breakage detection fish (DBD-FISH) (Volpi and Bridger, BioTechniques, Vol. 45, No. 4, October 2008, pp. 385–409). In certain embodiments the DNA editing enzyme is AID.

[00281] In some embodiments the activity of a DNA editing enzyme is determined by using a phospho-H2AX assay (e.g. Rakiman et al., Advance Biotech 2008, 39-42; which is incorporated by reference herein in its entirety), 53BP1 assay (e.g. Schultz et al., Journal of Cell Biology 2000, 151:1381-1390; which is incorporated by reference herein in its entirety), or a RAD51 assay (e.g. Hochegger and Takeda (2006), Subcell Biochem., 40, 313-325; which is incorporated by reference herein in its entirety). In certain embodiments the DNA editing enzyme is AID.

[00282] As used herein, the phrase "subject in need of at least one inhibitor of DSB repair" can refer to a subject who is diagnosed with or identified as suffering from a cancer, the cells of which cancer have an increased level of a DNA editing enzyme protein or a DNA editing enzyme mRNA or a DNA editing enzyme activity. As used herein, the phrase "subject in need of at least one inhibitor of DSB repair" can also refer to a subject who is diagnosed with or identified as suffering from an autoimmune disease, the cells of which autoimmune disease have an increased level of a DNA editing enzyme protein or a DNA editing enzyme mRNA or a DNA editing enzyme activity. A subject in need of at least one inhibitor of DSB repair can be identified using any method used for determining the level of a mRNA or protein or a DNA editing enzyme activity present in a biological sample as described herein. Alternatively, the phrase "subject in need of at least one inhibitor of DSB repair" can refer to a subject who is diagnosed with or identified as suffering from a B-cell disease or autoimmune disorder or cancer. The cancer cells or B-cells of the subject can have an increased level of a DNA editing enzyme protein or a DNA editing enzyme mRNA or a DNA editing enzyme activity. Non-limiting examples of B-cell diseases include B cell cancers (e.g. lymphomas and leukemias), autoimmune diseases characterized by aberrant B cell proliferation, class switching, and/or activation. In some embodiments the autoimmune diseases are characterized by aberrant a DNA editing enzyme activity in cells. Autoimmune

diseases with aberrant a DNA editing enzyme activity include, but are not limited to lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis and autoimmune mediated hematological disease. In certain embodiments the DNA editing enzyme is AID.

[00283] In some embodiments, the methods described herein further comprise selecting a subject identified as being in need of an inhibitor of DSB repair. A subject in need of a DSB repair inhibitor can be selected based on the level of a DNA editing enzyme mRNA, or a DNA editing enzyme protein or a DNA editing enzyme activity. In certain embodiments the DNA editing enzyme is AID.

[00284] In some embodiments, a subject identified as being in need of an inhibitor of DSB repair may in addition to the increased level of or a DNA editing enzyme protein or a DNA editing enzyme mRNA or a DNA editing enzyme activity display hypermutations in IGH. In certain embodiments the DNA editing enzyme is AID.

Methods of treating cancers characterized by abnormal expression of DNA editing enzymes

[00285] As described above herein, some embodiments of the invention relate to methods of treatment comprising (a) selecting a subject having cells that express a DNA editing enzyme, e.g. activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject.

[00286] Some embodiments of the invention relate to methods of treatment comprising (a) selecting a subject having cells that express an elevated level of DNA editing enzyme, e.g. activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject wherein an elevated level of a DNA editing enzyme is a level of a DNA editing enzyme that is higher than the level of a DNA editing enzyme in cells of the same type from a healthy individual. In some embodiments, the methods of treatment comprise (a) selecting a subject having B cells that express a DNA editing enzyme; and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject. In some embodiments, the methods of treatment comprise (a) selecting a subject having B cells that express an elevated

level of a DNA editing enzyme; and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level of a DNA editing enzyme is a level of a DNA editing enzyme that is higher than the level of a DNA editing enzyme in B cells from a healthy individual. In some embodiments, the cells that express a DNA editing enzyme are cancerous cells. In some embodiments, the B cells that express a DNA editing enzyme are cancerous cells. In some embodiments the DNA editing enzyme is AID. As used herein, the term "cancerous cell" refers to cells that proliferate in an unregulated manner. In some embodiments, a subject having cancerous B cells that express elevated levels of a DNA editing enzyme can be a subject having or diagnosed as having a B-cell cancer (e.g. B cell lymphoma or leukemia), as described below herein. In some embodiments the DNA editing enzyme is AID. In some embodiments the high level of a DNA editing enzyme is detected in blood, serum or a biopsy sample.

[00287] In certain embodiments, the methods described herein selectively treat B-cell neoplasms, lymphomas, and leukemias by exploiting recombination and DNA repair systems to induce tumor cell self-destruction. This approach takes advantage of the finding that the DNA editing enzyme induces widespread genomic breaks and cell death in primary B-cells with diminished homologous recombination ability. As described herein, the inventors have determined that where a population of cells characterized by increased expression of AID is treated with an inhibitor of DSB repair, cell death results. Accordingly, provided herein are methods for treating patients with cancers having high DNA editing enzyme, e.g. AID, expression with an inhibitor of DSB repair.

[00288] In certain embodiments, the cancer to be treated is a type with high expression of a DNA editing enzyme. In certain embodiments, the cancer to be treated is a B-cell neoplasm. In certain embodiments, the cancer to be treated is a lymphoma. In certain embodiments, the cancer to be treated is Burkitt's lymphoma, follicular lymphoma, MALT lymphoma, multiple myeloma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, plasma cell myeloma, large B-cell lymphoma and/or T-cell lymphoma. Lymphoma is a malignancy in the lymphatic cells of the immune system (e.g. B cells, T cells, or natural killer (NK) cells). Lymphomas often originate in the lymph nodes and present as solid tumors. They can metastasize to other organs such as the brain, bone, or skin. Extranodal sites are often located in the abdomen. Lymphomas are closely related to the lymphoid leukemias and in some cases a particular form of cancer is categorized as both a lymphoma and a leukemia.

[00289] Several classification systems exist for lymphomas with the most recent being the World Health Organization classification developed in 2001 and updated in 2008 (Jaffe, E.S.,

et al., (Eds.) World Health Organization Classification of Tumors, Pathology and Genetics of tumors of hematopoietic and lymphoid tissues IARC Press: Lyon, France 2001). The WHO system divides lymphomas into three primary categories; mature B-cell lymphomas, mature T-cell lymphomas and mature NK cell lymphomas. Included in separate categories are Hodgkin lymphomas (comprised of abnormal B cells) and a number of other less common lymphomas.

[00290] Lymphoma can be diagnosed by a biopsy. Tissue obtained from the biopsy is subjected to histological examination to determine the presence, type, and arrangement of malignant cells. The cells are also tested to determine if they are lymphocytes and if so, what type of lymphocyte. Additional tests to determine the scope of the lymphoma and where it is located in the body can include additional biopsies, nuclear medicine, X-rays, CT scans or MRI (see US Patent Publication US2003/0129665). Hodgkin's lymphoma can be diagnosed by the presence of Reed-Sternberg cells in addition to other abnormal cell patterns characteristic of the disease. Markers and histological signs that differentiate each type of lymphoma are known to those skilled in the art (Jaffe, E.S., et al. (Eds.) World Health Organization Classification of Tumors, Pathology and Genetics of tumors of hematopoietic and lymphoid tissues IARC Press: Lyon, France 2001).

[00291] In certain embodiments the cancer to be treated is a leukemia. Leukemias are malignant neoplasms of hematopoietic tissues. Leukemias are categorized into two predominant forms: chronic and acute. Acute leukemia is characterized by the rapid increase of immature blood cells, which impairs the ability of the bone marrow to produce healthy blood cells. Chronic leukemia is characterized by the build up of relatively mature, yet abnormal, white blood cells. Abnormal cells are produced at a much higher rate than normal cells and result in the accumulation of abnormal white blood cells in the blood. Notwithstanding these classifications, however, the pathological impairment of normal hematopoiesis is the hallmark of all leukemias.

[00292] Further, leukemias are subdivided according to which blood cell is affected. For example, leukemias can be divided into lymphoblastic or lymphocytic leukemias and myeloid or myelogenous leukemias. In lymphoblastic or lymphocytic leukemias, a pre-lymphocyte cell is typically affected, which impairs the infection-fighting properties of cells derived from lymphocytes. Most lymphocytic leukemias involve B cells, a specific subtype of lymphocyte. In myeloid or myelogenous leukemias, white blood cell precursors are often affected as are some other types of red cells, and platelets. Thus, leukemias can be generally subdivided into four categories: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL),

and chronic myelogeneous leukemia (CML). Specific manifestations of each subtype can involve B cells. In some embodiments, the term leukemia includes Burkitt's leukemia; chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML); B-cell acute lymphocytic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL). In one embodiment, the term leukemia as described herein also encompasses hairy cell leukemia, which is often considered to be outside of the above-described classification scheme.

[00293] Leukemias can be diagnosed by any method known in the art. Typically, a complete blood count (CBC) test is initially performed. A CBC counts the number of white blood cells, red blood cells, and platelets in a blood sample. A sample of blood with high numbers of white blood cells and low levels of red blood cells or platelets can indicate leukemia, and abnormal liver and kidney function tests will indicate if the leukemia has affected those organs. Flow cytometry can also be used for a more precise diagnosis, for example, by using mature myeloid markers such as CD11b and Gr-1 to determine cell type, cell number, and/or cell morphology. Markers and histological signs that differentiate each type of cancer are known to those skilled in the art (Jaffe, E.S., et al. (Eds.) World Health Organization Classification of Tumors, Pathology and Genetics of tumors of hematopoietic and lymphoid tissues IARC Press: Lyon, France 2001). For AML, there would be a drop in red blood cells, platelets, and normal white blood cells. These symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. The symptoms of are caused by replacement of normal bone marrow with leukemic cells, which are mainly immature abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

[00294] In certain embodiments the cancer to be treated is B-cell neoplasms, B-cell leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Burkitt's leukemia, acute myelogenous leukemia and/or T-ALL. The maturation of B cells most typically ceases or substantially decreases when the foreign antigen has been neutralized. Occasionally, however, proliferation of a particular B cell will continue unabated; such proliferation can result in a cancer referred to as "B-cell lymphoma" or a "B-cell leukemia." In certain embodiments the cancer to be treated is chronic lymphocytic leukemia (CLL) or chronic myelogenous leukemia (CML).

[00295] In one embodiment, a bone marrow biopsy is used to assist in diagnosis of leukemia. A bone marrow biopsy sample can include bone marrow tissue or a mixture of bone marrow and bone. In another embodiment, cytogenetics is used to examine the chromosomes in individual cells. Cytogenetic testing uses a sample taken from a blood draw

or a bone marrow or lymph node biopsy. The sample's chromosomes are microscopically examined for abnormalities that indicate damage to the cells' DNA and to support a diagnosis of leukemia. In another embodiment, a spinal tap can be used in the diagnosis of leukemia. Typically, a sample of cerebrospinal fluid is taken from the lower back (the lumbar area). The fluid sample is then checked for leukemia cells and other abnormalities. MRIs (Magnetic Resonance Imaging), CT (Computerized Axial Tomography) scans, and X-rays are imaging techniques that can be used to support a diagnosis of leukemia.

[00296] In certain embodiments the cancer to be treated is a plasma cell neoplasm. Examples for plasma cell neoplasms include multiple myeloma; plasma cell myeloma; plasma cell leukemia and plasmacytoma.

[00297] Any cancer characterized by high levels of a DNA editing enzyme expression can be treated with an inhibitor of DSB repair. For example, sarcomas, epithelial cell cancer (carcinomas), colon cancer, gastric cancer, intestinal cancer, liver cancer, hepatocellular cancer, breast cancer, thyroid cancer, esophageal cancer, lung cancer, brain cancer, head and neck cancer, melanoma, renal cancer, prostate cancer, hemangioma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, fibrosarcoma and cholangiocarcinoma may be characterized by high levels of a DNA editing enzyme expression, e.g. AID. In certain embodiments the cancer to be treated is colon cancer, liver cancer, gastric cancer, intestinal cancer, breast cancer, lung cancer, thyroid cancer and/or cholangiocarcinoma. Any of these cancers can be diagnosed by any method known in the art. Biopsies, colonoscopies, stool samples, imaging or other means known in the art can be used to detect the presence of tumors and/or polyps. Tissue obtained by these methods is subjected to histological examination to determine the presence, type, and arrangement of malignant cells. Markers and histological signs that differentiate each type of lymphoma are known to those skilled in the art (Diagnostic Histopathology of Tumors, Fletcher, C.D.M. (Ed.), 3rd Edition, Churchill Livingstone Elsevier, China (2007); Methods of Cancer Diagnosis, Therapy and Prognosis. Hayat, M.A. (Ed), (Vol 3), Springer (2009)). Additional tests to determine the scope of the cancer and where it is located in the body can include additional biopsies, nuclear medicine, X-rays, CT scans or MRI.

[00298] In certain embodiments, treating a patient having a cancer with high DNA editing enzyme expression, e.g. AID, with a inhibitor of DSB repair decreases an indicator, marker, symptom, severity, metastasis, recurrence and/or tumor size of the cancer by at least 10%, e.g., by at least 20%, at least 30%, at least 50%, at least 75%, at least 100%, at least 200% or more as compared to the indicator, marker, symptom, severity, metastasis, recurrence and/or

tumor size prior to treatment with the inhibitor of DSB repair or as compared to patients not receiving treatment with a inhibitor of DSB repair.

[00299] The technology described herein can relate to the use of at least one inhibitor of DSB repair and compositions comprising at least one such inhibitor of DSB repair for the treatment of a cancer having increased levels of AID protein or mRNA. For example, a composition containing an inhibitor of DSB repair is used to reduce the tumor size, tumor growth, cancer cell count, cancer cell expansion or metastasis of a cancer. For example, a composition containing a inhibitor of DSB repair is used to reduce the severity, duration, or number of symptoms associated with one of the following, which are offered by way of example only; a B-cell cancer, a leukemia, a lymphoma, a colon cancer, a liver cancer, a gastric cancer, an intestinal cancer, a breast cancer, a lung cancer, a thyroid cancer, a brain cancer, a renal cancer, a melanoma, a prostate cancer or a cholangiocarcinoma.

[00300] The technology described herein can also relates to the use of at least one inhibitor of RAD51-mediated strand exchange repair or a composition comprising an inhibitor of RAD51-mediated strand exchange repair to increase life expectancy or increase time to remission in patients treated with the inhibitor of DSB repair as compared to patients not treated with the inhibitor of DSB repair.

[00301] In certain embodiments the inhibitor of DSB repair is contained in a composition comprising the inhibitor of DSB repair and a pharmaceutically acceptable carrier. In further embodiments the inhibitor of DSB repair can be contained in a composition comprising a pharmaceutically acceptable carrier and another pharmaceutically effective compound.

[00302] The pharmaceutical compositions of the technology described herein can be administered alone or in combination with other therapies, including without limitation immunotherapy or immunotherapeutic agents, or other therapies which can be beneficial to patients with cancer or combinations thereof. It is contemplated that the therapeutic agents of the technology described herein can be administered together with any other therapy effective against one of the cancers described herein. When two or more therapeutic agents are administered together, they can be administered simultaneously or with some delay between administrations thereof (i.e., according to an optimized delivery schedule). In further embodiments, the pharmaceutical compositions of the technology described herein can comprise at least one DSB repair inhibitor and at least one additional pharmaceutical agent.

[00303] As used herein, the term "immunotherapy" refers to treatment of a subject with an antibody or antibody-based therapeutic. As used herein, immunotherapy can be passive or active. Passive immunotherapy, as defined herein, is the passive transfer of antibody to a

subject (patient). Active immunization is the induction of antibody and/or T-cell responses in a subject (patient).

[00304] Exemplary immunotherapy agents include bevacizumab (Avastin®), Alemtuzumab (Campath®), cetuximab (Erbitux), Ibritumomab tiuxetan (Zevalin), Panitumumab (Vectibix), rituximab (Rituxan®), and tositumomab with ^{131}I(Bexxar®, Corixia Corp.). Rituximab works by selectively depleting $CD20^+$ B cells. The therapeutic effectiveness of rituximab is described in Collins-Burow et al., Rituximab and its Role as Maintenance Therapy in non-Hodgkin Lymphoma, *Expert Rev Anticancer Ther* 7(3):257-73 (2007); Marcus et al., The Therapeutic Use of Rituximab in non-Hodgkin's Lymphoma, *Eur J Haemotal Suppl* (67):5-14 (2007); Plosker et al., Rituximab: A Review of its Use in non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia, *Drugs* (2003), which are hereby incorporated by reference in their entirety. Bevacizumab (Avastin®, Genentech/Roche) blocks angiogenesis, and is used to treat various cancers, Cetuximab (IMC-C225; Erbitux®) is a chimeric (mouse/human) monoclonal antibody, against epidermal growth factor receptor (EGFR) inhibitor, given by intravenous infusion for treatment of metastatic colorectal cancer and squamous cell carcinoma of the head and neck. Ibritumomab tiuxetan (Zevalin), is a monoclonal antibody radioimmunotherapy treatment for some forms of B cell non-Hodgkin's lymphoma and binds to the CD20 antigen. Panitumumab is a fully human monoclonal antibody specific to the epidermal growth factor receptor (also known as EGF receptor, EGFR, ErbB-1 and HER1) for the treatment of colorectal cancer.

[00305] A further form of therapy for some cancers described herein is stem cell transplantation.

[00306] In some embodiments, the pharmaceutical compositions of the technology described herein can be administered after or before other therapies, including without limitation, immunotherapy agents, chemotherapy agents, radiation treatments or other therapies which can be beneficial to patients with cancer or combinations thereof.

[00307] In some embodiments, a subject is administered a cycle of treatment comprising administration of a composition comprising a DSB repair inhibitor as described herein. The subject is then administered a cycle of treatment comprising administration of another chemotherapy, immunotherapy, radiation or other therapy which can be beneficial to patients with cancers or combinations thereof. Each cycle of treatment can comprised 1 or more administrations of a composition or therapeutic, i.e. 1 administration, 2 administrations, 3 administrations, 5 administrations, 10 administrations, 20 administrations or more. Each cycle of treatment can last at least 1 day, i.e. at least 1 day, at least 2 days, at least 1 week, at

least 2 weeks, at least 3 weeks, at least 4 weeks, at least 6 weeks or more. In some embodiments, there is a hiatus or break between the cycles of treatment which can last at least 1 day, i.e. at least 1 day, at least 2 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 6 weeks or more. A course of treatment comprising a cycle of treatment with a DSB repair inhibitor as described herein, optionally a break, and a cycle of treatment with another chemotherapy, immunotherapy, radiation or other therapy which can be beneficial to patients with cancers or combinations thereof, and optionally a second break can be repeated in part or in whole. In some embodiments, the cycle of treatment with a DSB repair inhibitor is the second cycle and the other anti-cancer therapy is used in the first cycle. In some embodiments, the other chemotherapy, immunotherapy, radiation or other therapy which can be beneficial to patients with cancers or combinations thereof comprises a therapy which causes damage to the subject's DNA. In some embodiments, the other chemotherapy, immunotherapy, radiation or other therapy which can be beneficial to patients with cancers or combinations thereof comprises doxorubicin. In some embodiments, the other chemotherapy, immunotherapy, radiation or other therapy which can be beneficial to patients with cancers or combinations thereof comprises fludarabine.

[00308] Other therapies include, without limitation, chemotherapies may be done before, during or after the methods described herein. In one embodiment, the chemotherapy is administered before or after, but not during, treatment with a composition or method as described herein. Non-limiting examples of chemotherapies include radiation or treatment with chemotherapy agents such as actinomycin, amsacrine (Amsidine®), anthracyclines, bleomycin (Blenoxane®), busulfan, camptothecin, carboplatin (Paraplatin®), chlorambucil (Leukeran®), cisplatin, cyclophosphamide (Cytoxan®), cladribine, cytarabine (Cytosar-U®), cytoxan, dacarbazine (DTIC-Dome®), dactinomycin, daunorubicin, dexamethasone (Decadron®), docetaxel, doxorubicin (Adriamycin®), epirubicin, etoposide (Etopophos®), fludarabine (Fludara®), hexamethylmelamineoxaliplatin, ifosfamide (Ifex®), iphosphamide, melphalan, merchlorethamine, methotrexate, mitomycin, mitoxantrone, nitrosourea, paclitaxel, plicamycin, prednisone, procarbazine, teniposide, triethylenethiophosphoramide, etoposide (VPI6), vincristine (Oncovin®), vinblastine, bendamustine (Ribomustin and Treanda), CHOP therapy, monoclonal antibodies and inhibitors of the c-myc gene, DNA methyltransferase, proteasomes and cyclin-dependent kinases.

[00309] Chemotherapeutics can include agents which induce DNA damage. Non-limiting examples of such agents can include alkylating agents, nitrosourea, anti-metabolites, plant alkaloids, plant extracts, or radioisotopes.

[00310] Also included are courses of therapy which include, but are not limited to, 1) the CODOX-M/IVAC regimen (Magrath protocol)—two cycles of CODOX-M (cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate) alternating with IVAC (ifosfamide, etoposide and high-dose cytarabine), 2) three cycles of CODOX-M. Also included are modified versions of such combination therapies such as the adapted Magrath protocols of the United Kingdom Lymphoma Group and the Dana-Farber Cancer Institute.

[00311] **Methods of Treating Autoimmune Disorders**

[00312] As described above herein, some embodiments of the invention relate to methods of treatment comprising (a) selecting a subject having cells that express an elevated level of activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level of AID is a level of AID that is higher than the level of AID in cells of the same type from a healthy individual. In some embodiments, the cells that express an elevated level of AID are autoimmune cells. As used herein, "autoimmune cell" or "autoreactive cell" refers to immune cells that have activity towards and/or recognize cells or biological components of the organism from which the cell is derived. Examples of cells which can be autoimmune cells include, but are not limited to, adult splenocytes, T cells, and B cells. In some embodiments, the subject can be a human subject.

[00313] In some embodiments, the methods of treatment comprise (a) selecting a subject having B cells that express an elevated level of activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair to the subject; wherein an elevated level of AID is a level of AID that is higher than the level of AID in B cells from a healthy individual. In some embodiments, the B cells that express an elevated level of AID are B cells associated with autoimmune disease. As used herein, the term "B cell associated with autoimmune disease" refers to B cells with abnormal function, behavior, and/or proliferation in a particular autoimmune disease. In some embodiments, the B cells associated with autoimmune disease can be B cells which cause the disease due to their abnormal function, behavior, and/or proliferation. In some embodiments, the B cells associated with autoimmune disease can be B cells which cause one or more symptoms of an autoimmune disease due to their abnormal function, behavior, and/or proliferation. In some embodiments, a subject having B cells associated with an autoimmune disease can be a subject having or diagnosed as having an autoimmune disease characterized or caused by B cells with abnormal function, behavior, and/or proliferation. By way of non-limiting example, in systemic lupus erythematosus, a subject's B cells

abnormally produce antibodies specific for auto-antigens and in rheumatoid arthritis, a subject's B cells interact abnormally with the subject's T cells.

[00314] In certain embodiments, the methods described herein selectively treat autoimmune diseases by exploiting lymphoid recombination systems to induce self-destruction of diseased B-cells while sparing normal cells. This approach takes advantage of the finding that the B-cell recombinase AID induces widespread genomic breaks and cell death in primary B-cells with diminished homologous recombination ability. As described herein, it has been determined that where a population of cells characterized by increased expression of a DNA editing enzyme, e.g. AID is treated with an inhibitor of DSB repair, cell death results. Accordingly, provided herein are methods for treating patients with autoimmune diseases characterized by aberrant B cell proliferation, class switching, or activation. In some embodiments, the autoimmune disease can be characterized by increased B cell proliferation, class switching, or activation. In some embodiments, the autoimmune disease can be characterized by having B cells with high AID expression. In some embodiments, the method relates to treating a subject with an autoimmune disease and cells with high DNA editing enzyme expression with a DSB repair inhibitor. In some embodiments, the method relates to treating a subject with an autoimmune disease and B cells with high AID expression with a DSB repair inhibitor. In certain embodiments, the autoimmune disease to be treated is a type with B cells having high expression of AID. Autoimmune diseases known to be characterized by aberrant B cell proliferation, class switching and/or activation include, but are not limited to lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis; discoid lupus; subacute cutaneous lupus erythematosus; cutaneous lupus erythematosus including chilblain lupus erythematosus; chronic arthritis; Sjogren's syndrome; autoimmune nephritis; autoimmune vasculitis; autoimmune hepatitis; autoimmune carditis; autoimmune encephalitis; and autoimmune mediated hematological disease. In certain embodiments, autoimmune diseases are characterized by aberrant expression of a DNA editing enzyme. In certain embodiments, the autoimmune disease to be treated is Crohn's disease, ulcerative colitis, vasculitis; ankylosing spondylitis; Behçet's disease; paraneoplastic autoimmunity or dermatomyositis. In some embodiments, the autoimmune disease to be treated according to the methods described herein is an autoimmune disease characterized by aberrant B cell proliferation.

[00315] Lupus or lupus erythematosus or systemic lupus erythematosus (SLE) is an autoimmune disorder that can cause chronic inflammation in various parts of the body, especially the skin, joints, blood, and kidneys. The body's immune system normally makes proteins called antibodies to protect the body against viruses, bacteria, and other foreign materials (i.e., antigens). In an autoimmune disorder such as lupus, or lupus erythematosus or SLE, the immune system loses the ability to discriminate between antigens and its own cells and tissues and can thus make antibodies directed against its own cells and tissues to form immune complexes. These immune complexes can build up in the tissues and cause inflammation, injury to tissues and/or pain. The three most common types of lupus include systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE) and drug-induced lupus. Additional types of autoimmune disorders include, but are not limited to subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, rheumatoid arthritis, chronic arthritis, Sjogren's syndrome, autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease. More detailed descriptions of lupus or lupus erythematosus can be found in Wallace, 2000, *The Lupus Book: A Guide for Patients and Their Families,* Oxford University Press, Revised and Expanded Edition; Kuhn et al., 2004, *Cutaneous Lupus Erythematosus,* Springer, First Edition; and Lahita, 1999, *Systemic Lupus Erythematosus,* Academic Press, Third Edition; which are incorporated by reference herein in their entireties.

[00316] Methods of diagnosing lupus erythematosus are well known in the art. Laboratory tests for the presence of lupus include the LE Cell Test, the Anti-Nuclear Antibody Test, and the test for anti-DNA antibodies. Lupus is, however, often recognized by particular clinical manifestations including: (i) arthritis (occurring in 90-95% of persons with systemic lupus), (ii) skin changes, such as a photosensitive induced "butterfly" rash across the bridge of the nose, across the cheeks and/or beneath the eyes, and/or red, raised and scaly patches, known as discoid lupus, anywhere on the body (occurring in 75-80% of persons with lupus), (iii) hematologic abnormalities, such as anemia, leukopenia, and thrombocytopenia (occurring in about 50% of persons with lupus), (iv) kidney impairment (occurring in about 50% of persons with lupus), (v) heart or lung disease, such as an irritation of the heart or lung lining causing pericarditis or pleurisy (occurring in about 30% of persons with lupus), and (vi) neuropsychiatric changes (occurring in about 10% to 20% of persons with lupus). By way of non-limiting example, a subject can be diagnosed with systemic erythematosus lupus by having elevated levels of at least one autoantibody relative to the level of the autoantibody in

a subject not diagnosed with systemic erythematosus lupus. Exemplary autoantibodies for diagnosis of systemic erythematosus lupus include, but are not limited to, antinuclear antibody (ANA), anti-double strand DNA antibody (anti-dsDNA), anti Sm nuclear antigen antibody (anti-Sm), anti-phsopholipid antibody, and any combinations thereof. Such elevated levels can be at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 1-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 10-fold or higher compared to a subject not diagnosed with systemic erythematosus lupus. Alternatively, a subject can be diagnosed with systemic erythematosus lupus by having elevated levels of interferon-beta and or interferon-beta gene expression relative to levels in a subject not diagnosed with systemic erythematosus lupus. Such elevated levels can be at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 1-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 10-fold or higher compared to a subject not diagnosed with systemic erythematosus lupus.

[00317] In certain embodiments, treating a patient having an autoimmune disease or an autoimmune disorder having B cells with high AID expression with a inhibitor of DSB repair decreases an indicator, marker, symptom, and/or severity of the autoimmune disease by at least 10%, e.g., by at least 20%, at least 30%, at least 50%, at least 75%, at least 80%, at least 90%, at least 95% or more as compared to the indicator, marker, symptom, and/or severity prior to treatment with the inhibitor of DSB repair or as compared to patients not receiving treatment with a inhibitor of DSB repair.

[00318] The technology described herein can relate to the use of at least one inhibitor of DSB repair and compositions comprising at least one such inhibitor of DSB repair for the treatment of an autoimmune disease or an autoimmune disorder having B cells having increased levels of AID protein or mRNA. For example, a composition containing an inhibitor of DSB repair is used to reduce the severity, duration, or number of symptoms associated with one of the following, which are offered by way of example only; lupus erythematosus; systemic lupus erythematosus (SLE); cutaneous lupus erythematosus (CLE); drug-induced lupus; subacute cutaneous lupus erythematosus; cutaneous lupus erythematosus including chilblain lupus erythematosus; rheumatoid arthritis; Sjogren's syndrome; autoimmune nephritis; autoimmune vasculitis;, autoimmune hepatitis; autoimmune carditis; autoimmune encephalitis; and autoimmune mediated hematological disease. By “reduce” in

this context is meant a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at least 50%, at least 90% or more.

[00319] In certain embodiments the inhibitor of DSB repair is contained in a composition comprising the inhibitor of DSB repair and a pharmaceutically acceptable carrier. In further embodiments the inhibitor of DSB repair can be contained in a composition comprising a pharmaceutically acceptable carrier and another pharmaceutically effective compound.

[00320] The pharmaceutical compositions of the technology described herein can be administered alone or in combination with other therapies, including without limitation anti-inflammatories, or other therapies which can be beneficial to patients with autoimmune diseases or combinations thereof. It is contemplated that the therapeutic agents of the technology described herein can be administered together with any other therapy effective against one of the autoimmune diseases described herein. When two or more therapeutic agents are administered together, they can be administered simultaneously or with some delay between administrations thereof (i.e., according to an optimized delivery schedule). In further embodiments, the pharmaceutical compositions of the technology described herein can comprise at least one DSB repair inhibitor and at least one additional pharmaceutical agent.

[00321] Agents for treatment of lupus erythematosus include, but are not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials (e.g. chloroquinine; hydroxychloroquine; and quinacrine), immunosuppressants (e.g. azathioprine, cyclosporine A, alkylating agents, nitrogen mustards, chlorambucil or cyclophosphamide), heparin, aspirin, danazol (Danocrine), dehydroepiandrosterone (DHEA), vincristine (Oncovin), warfarin, methylprednisolone pulse therapy, dapsone, thalidomide (Synovir); methylprednisolone sodium succinate (A-Methapred, Solu-Medrol), methotrexate (Rheumatrex), hydroxychloroquine (Plaquenil), triamcinolone (Aristospan), retinoids (e.g. istretinoin and etretinate). Non-limiting examples of anti-inflammatory drugs (NSAIDs) include such as aspirin, salisylates, ibuprofen, naproxen, clinoril, oxaprozin and tolmetin.

[00322] In some embodiments, the pharmaceutical compositions of the technology described herein can be administered after or before other therapies, including without limitation, anti-inflammatories or immunosuppressants or other therapies which can be beneficial to patients with autoimmune diseases or combinations thereof.

[00323] **Sensitizing Cells to Death**

[00324] In some embodiments, there is provided herein a method of sensitizing cells to death and/or inducing or causing cell death. In some embodiments, there is provided herein a

method of causing cell death comprising: administering to a cell an effective amount of a DNA editing enzyme; and thereafter contacting the cells with an inhibitor of double strand break repair; thereby causing cell death. In some embodiments, there is provided herein a method of sensitizing a cell to cell death comprising: administering to a subject a therapeutically effective amount of a DNA editing enzyme; and thereafter administering to the subject an inhibitor of double strand break repair; thereby sensitizing a cell in the subject to cell death. In some embodiments, the DNA editing enzyme can be a member of the APOBEC family, or AID, Rag1 or Rag2 or SPO11.

[00325] In some embodiments, the DNA editing enzyme can be a member of the APOBEC family. Non-limiting examples of APOBEC family members include APOBEC1 (e.g. SEQ ID NO:138); APOBEC2 (e.g. SEQ ID NO:139), APOBEC3A (e.g. SEQ ID NO:140); APOBEC3C (e.g. SEQ ID NO:141); APOBEC3E (e.g. SEQ ID NO:142); APOBEC3F (e.g. SEQ ID NO:143); APOBEC3G (e.g. SEQ ID NO:144); APOBEC3H (e.g. SEQ ID NO:145); and APOBEC4 (e.g. SEQ ID NO:146).

[00326] In some embodiments, the DNA editing enzyme can be administered in the form of a polypeptide, a nucleic acid encoding a DNA editing enzyme, or a vector comprising a nucleic acid encoding a DNA editing enzyme. In some embodiments, the DNA editing enzyme can be AID. In some embodiments, the DNA editing enzyme administered to the cell is a polypeptide comprising the sequence of SEQ ID NO:099 or a variant, functional fragment, or homolog thereof. In some embodiments, the DNA editing enzyme administered to the cell is a nucleic acid encoding an AID polypeptide, e.g. a nucleic acid comprising the nucleotide sequence of SEQ ID NO:100, such that AID or a variant, functional fragment, or homolog thereof will be expressed in the cell administered the nucleic acid.

[00327] Gene therapy compositions and methods are also contemplated for use with the methods described herein. Such methods allow clinicians to introduce DNA encoding a polypeptide or RNA molecule of interest directly into a patient (*in vivo* gene therapy) or into cells isolated from a patient or a donor (*ex vivo* gene therapy). Therapeutic proteins produced by transduced cells after gene therapy can be maintained at a relatively constant level in, for example, in cancerous cells, e.g. a tumor of a subject, as compared to a protein that is administered directly. Such sustained production of a therapeutic agent, such as AID and/or an inhibitor of DNA double strand break repair, is particularly appropriate in the treatment of chronic diseases, such as cancers.

[00328] Further, regulatable genetic constructs using small molecule inducers have been developed that can be included in vectors to be used in some embodiments of the present

invention described herein. (Rivera et al. (1996) Nat. Med. 2:1028-32; No et al. (1996) Proc. Natl. Acad. Sci. USA, 93:3346-51; Gossen and Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-51; the GeneSwitch® system (Valentis, Inc., Burlingame, Calif.)). These systems are based on the use of engineered transcription factors the activity of which is controlled by a small molecule drug, and a transgene, the expression of which is driven by the regulated transcription factor (Rivera et al. (1996) Nat. Med. 2:1028-32; Pollock et al. (2000) Proc. Natl. Acad. Sci. USA 97:13221-26; U.S. Pat. Nos. 6,043,082 and 6,649,595; Rivera et al. (1999) Proc. Natl. Acad. Sci. USA 96:8657-62).

[00329] Vectors useful in the methods described herein can include, but are not limited to, plasmids, retroviral vectors, adenoviral vectors, adeno-associated viral vectors, herpes virus and pox virus vectors.

[00330] The term "transduction" as used herein refers to the use of viral particles or viruses to introduce exogenous nucleic acids into a cell.

[00331] The term "transfection" as used herein in reference to methods, such as chemical methods, to introduce exogenous nucleic acids, such as the nucleic acid sequences encoding an agent which increases the activity and/or level of AID as described herein, into a cell. As used herein, the term transfection does not encompass viral-based methods of introducing exogenous nucleic acids into a cell. Methods of transfection include physical treatments (electroporation, nanoparticles, magnetofection), and chemical-based transfection methods. Chemical-based transfection methods include, but are not limited to those that use cyclodextrin, polymers, liposomes, nanoparticles, cationic lipids or mixtures thereof (e.g., DOPA, Lipofectamine and UptiFectin), and cationic polymers, such as DEAE-dextran or polyethylenimine.

[00332] An inhibitor of double strand break repair can be as described above herein, e.g. a small molecule, polypeptide, protein, RNAi agent, stilbene derivative, antibody, or polypeptide comprising an epitope-binding fragment of an antibody as described above herein.

[00333] In some embodiments, the cell can be an *in vitro* cell, a cell in cell culture, or a cell in a sample obtained from a subject. In some embodiments, the DNA editing enzyme, and/or the inhibitor of double strand break repair can, for example, be added to the cell culture media in which the cell is being maintained. In some embodiments, the DNA editing enzyme, and/or the inhibitor of double strand break repair can, for example, be comprised by compositions which mediate or enhance their entry into the cell. Suitable compositions for delivering agents to cells, either *in vivo* or *in vitro* are described below herein, e.g. liposomes.

[00334] In some embodiments, the cell can be a cell *in vivo*, e.g. a cell in a subject.

[00335] In some embodiments, it is desirable to target specific cells or tissues of interest (targeted cells or tissues), e.g. to enhance effectiveness of vectors, minimize the effective dose, and/or minimize side effects or off-target effects. Methods of targeting agents to particular cell types are well known in the art. For reviews, see Peng et al., "Viral Vector Targeting", Curr. Opin. Biotechnol. 10:454-457,1999; Gunzburg et al., "Retroviral Vector Targeting for Gene Therapy", Cytokines Mol. Ther. 2:177-184, 1996.; Wickham, "Targeting Adenovirus", Gene Ther. 7:110-114, 2000; Dachs et al., "Targeting Gene Therapy to Cancer: A Review", Oncol. Res. 9:313-325, 1997; Curiel, "Strategies to Adapt Adenoviral Vectors for Targeted Delivery", Ann NY Acad. Sci. 886:158171, 1999; Findeis et al., "Targeted Delivery of DNA for Gene Therapy via Receptors", Trends Biotechnol. 11:202205, 1993; all of which are incorporated by reference herein in their entirety.

[00336] Some targeting strategies make use of cellular receptors and their natural ligands in whole or in part. See, for example, Cristiano et al., "Strategies to Accomplish Gene Delivery Via the Receptor-Mediated Endocytosis Pathway", Cancer Gene Ther., Vol. 3, No. 1, pp. 49-57, January-February 1996.; S. C. Philips, "Receptor-Mediated DNA Delivery Approaches to Human Gene Therapy", Biologicals, Vol. 23, No. 1, pp. 13-6, March 1995; Michael et al., "Strategies to Achieve Targeted Gene Delivery Via the Receptor-Mediated Endocytosis Pathway", Gene Ther., Vol. 1, No. 4, pp. 223-32, July 1994; Lin et al., "Antiangiogenic Gene Therapy Targeting The Endothelium-Specific Receptor Tyrosine Kinase Tie2", Proc. Natl. Acad. Sci., USA, Vol. 95, pp. 8829-8834, 1998. Sudimack et al, "Targeted Drug Delivery Via the Folate Receptor", Adv. Drug Deliv., pp. 147-62, March 2000; Fan et al., "Therapeutic Application of Anti-Growth Factor Receptor Antibodies", Curr. Opin. Oncol., Vol. 10, No. 1, pp. 67-73, January 1998; Wadhwa et al., "Receptor Mediated Glycotargeting", J. Drug Target, Vol. 3, No. 2, pp. 111-27, 1995; Perales et al, "An Evaluation of Receptor-Mediated Gene Transfer Using Synthetic DNA-Ligand Complexes", Eur. J. Biochem, Vol. 1, No 2, pp. 226, 255-66, December 1994; Smith et al., "Hepatocyte Directed Gene Delivery by Receptor-Mediated Endocytosis", Semin Liver Dis., Vol. 19, No. 1, pp. 83-92, 1999; which are all incorporated by reference herein in their entireties.

[00337] Antibodies, particularly single-chain antibodies, to surface antigens specific for a particular cell type may also be used as targeting elements. See, for example, Kuroki et al., "Specific Targeting Strategies of Cancer Gene Therapy Using a Single-Chain Variable Fragment (scFv) with a High Affinity for CEA", Anticancer Res., pp. 4067-71, 2000; U.S. Pat. No. 6,146,885, to Dornburg, entitled "Cell-Type Specific Gene Transfer Using

Retroviral Vectors Containing Antibody-Envelope Fusion Proteins"; Jiang et al., "In Vivo Cell Type-Specific Gene Delivery With Retroviral Vectors That Display Single Chain Antibodies", Gene Ther. 1999, 6:1982-7; Engelstadter et al., "Targeting Human T Cells By Retroviral Vectors Displaying Antibody Domains Selected From A Phage Display Library", Hum. Gene Ther. 2000, 11:293-303; Jiang et al., "Cell-Type-Specific Gene Transfer Into Human Cells With Retroviral Vectors That Display Single-Chain Antibodies", J. Virol 1998,72:10148-56; Chu et al., "Toward Highly Efficient Cell-Type-Specific Gene Transfer With Retroviral Vectors Displaying Single-Chain Antibodies", J. Virol 1997, 71:720-5; Chu et al., Retroviral Vector Particles Displaying The Antigen-Binding Site Of An Antibody Enable Cell-Type-Specific Gene Transfer, J. Virol 1995, 69:2659-63; and Chu et al, "Cell Targeting With Retroviral Vector Particles Containing Antibody-Envelope Fusion Proteins", Gene Ther. 1994, 1:292-9; which are all incorporated by reference herein in their entireties.

[00338] Administration and Dosages

[00339] The inhibitor of DSB repair and a second pharmaceutically active agent can be administrated to the subject in the same pharmaceutical composition or in different pharmaceutical compositions (at the same time or at different times). When administrated at different times, the inhibitor of DSB repair and the pharmaceutically active agent can be administered within 5 minutes, 10 minutes, 20 minutes, 60 minutes, 2 hours, 3 hours, 4, hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, one week, two weeks, three weeks or more of administration of the other. When the DSB repair inhibitor and the pharmaceutically active agent are administered in different pharmaceutical compositions, routes of administration can be different. For example, the inhibitor of DSB repair is administered by any appropriate route known in the art including, but not limited to oral or parenteral routes, including intravenous, intramuscular, intratumor, intralesional, intradermal, intraperitoneal, subcutaneous, transdermal, airway (aerosol), pulmonary, nasal, rectal, and topical (including buccal and sublingual) administration, and pharmaceutically active agent is administration by a different route, e.g. a route commonly used in the art for administration of said pharmaceutically active agent. In a non-limiting example, an inhibitor of DSB repair can be administered orally, while a pharmaceutically active agent can be administrated subcutaneously.

[00340] The dosage ranges for the administration of a inhibitor of DSB repair depend upon the form of the compound, its potency, and the extent to which symptoms, markers, or indicators of the cancer are desired to be reduced, for example the percentage reduction desired for symptoms, nausea, tumor size, etc. In certain embodiments, the dosage should not

be so large as to cause adverse side effects. Generally, the dosage will vary with the age, condition, and sex of the patient and can be determined by one of skill in the art. The dosage can also be adjusted by the individual physician in the event of any complication.

[00341] In certain embodiments, the effective dose of an inhibitor of DSB repair is administered to a patient once. In certain embodiments, the effective dose of an inhibitor of DSB repair is administered to a patient repeatedly. Patients can be administered a therapeutic amount of an inhibitor of DSB repair, such as 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 40 mg/kg or 50 mg/kg. The inhibitor of DSB repair can be administered by intravenous infusion over a period of time, such as over a 5 minute, 10 minute, 15 minute, 20 minute, or 25 minute period. The administration is repeated, for example, on a regular basis, such as hourly for 3 hours, 6 hours, 12 hours or longer or such as biweekly (*i.e.*, every two weeks) for one month, two months, three months, four months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration biweekly for three months, administration can be repeated once per month, for six months or a year or longer. Administration of the inhibitor of DSB repair can reduce levels of a marker or symptom of cancer, e.g., tumor size by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80 % or at least 90% or more.

[00342] Before administration of a full dose of the inhibitor of DSB repair, patients can be administered a smaller dose, such as a 5% infusion, and monitored for adverse effects, such as an allergic reaction.

[00343] Owing to the effects on a cancer or autoimmunity, an inhibitor of DSB repair or a pharmaceutical composition prepared there from can enhance the quality of life.

Efficacy measurement

[00344] Efficacy of treatment or prevention of disease can be assessed, for example by measuring a marker, indicator, or symptom of cancer or any other measurable parameter appropriate. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters.

[00345] A treatment is evident when there is a statistically significant improvement in one or more parameters of cancer, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of cancer, and preferably at least 20%, 30%, 40%, 50% or more can be

indicative of effective treatment. Efficacy for a given inhibitor of DSB repair or formulation of that drug can also be judged using an experimental animal model for cancer as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant increase in a marker is observed.

[00346] The efficacy of a given RAD51- strand exchange repair inhibitor can be determined by the skilled clinician. However, a treatment is considered "effective treatment", as the term is used herein, if any one or all of the signs, symptoms or makers of a cancer are altered in a beneficial manner, other clinically accepted symptoms are improved, or even ameliorated, e.g., by at least 10% following treatment with a compound as described herein. Efficacy can also be measured by a failure of an individual to worsen as assessed by hospitalization, or need for medical interventions (i.e., progression of the disease is halted). Methods of measuring these indicators are known to those of skill in the art and/or are described herein. For example, treatment of leukemia includes any treatment of a leukemia in an individual or an animal (some non-limiting examples include a human, or a mammal) and includes: (1) inhibiting the disease, e.g., arresting, or slowing the pathogenic growth of new blood vessels; or (2) relieving the disease, e.g., causing regression of symptoms, reducing the number of leukemia initiating cells; and (3) preventing or reducing the likelihood of the development of a leukemia. An effective amount for the treatment of a disease means that amount which, when administered to a mammal in need thereof, is sufficient to result in effective treatment as that term is defined herein, for that disease. Efficacy of an agent can be determined by assessing physical indicators of, for example leukemia, such as e.g., high white blood cell count, impaired immune response to infection, presence of leukemia initiating cells, etc. Efficacy can be assessed in animal models of cancer, for example a mouse transplanted with human cancer cells, and any treatment or administration of the compositions or formulations that leads to a decrease of at least one symptom, marker, or parameter of a cancer.

[00347] Efficacy can be measured by a reduction in any of the symptoms of the cancers described herein, for example, a reduction in bruising, bleeding, petechiae, infections, dyspnea, pallor, nausea, fever, chills, night sweats, flu-like symptoms, fatigue, a feeling of fullness, and/or an increase in blood platelets, white blood cells, and/or red blood cells

[00348] Efficacy can also be measured by a failure of an individual to worsen as assessed by hospitalization or need for medical interventions (i.e., progression of the disease is halted or at least slowed).

[00349] Another marker of the efficacy of treatment as described herein is survival. Statistical survival rates for specific cancers are well established – when an individual or group of individuals treated according to the methods described herein survives beyond the expected time or at a greater than expected rate, the treatment can be considered effective.

[00350] Efficacy testing can be performed during the course of treatment using the methods described herein. Measurements of the degree of severity of a number of symptoms associated with a particular ailment are noted prior to the start of a treatment and then at later specific time period after the start of the treatment. For example, leukemia is initiated in the bone marrow and can spread to other organs before it is detected, thus traditional staging of a tumor, performed routinely with other cancer types, is not useful in the staging of leukemia. Instead, physicians rely upon cytological (cellular) classification systems to identify the type and subtype of leukemia. The prognosis or outcome of specific leukemias, and also the likely response to treatment can be determined using such cell classification systems. In one embodiment, the classification method for acute leukemia is the French-American-British (FAB) system. According to FAB classification, acute leukemia is divided into eight subtypes of acute myelogenous leukemia (AML) and three subtypes of acute lymphocytic leukemia (ALL). One of skill in the art is aware of such methods for determining disease severity in a variety of different leukemias and can easily diagnose the severity of the leukemia based on such a classification scheme.

[00351] The efficacy of treatment according to the methods described herein can be evaluated by following surrogate or indirect markers of cancer. Without intending to be limiting, such markers that indicate efficacy of treatment of a cancer can include an increase in red blood cell or platelet counts, a normalization of white blood cell counts, improvements in liver and kidney function tests, a decrease in lactate dehydrogenase levels, improved scores on the follicular lymphoma international prognostic Index (FLIPI) (Lopez-Guillermo, A. et al., J Clin Oncol 1994; 12:1343-1348; Solal-Céligny et al., Blood 2004 104:1258-1265), a decrease in CD11b+ and Gr-1+ cells, improve bone marrow morphology as determined by bone marrow biopsy, decreased in cells with abnormal DNA as determined by cytogenic testing, and decreased presence of cancer cells in cerebrospinal fluid. Tests specific to each type of cancer are known to those of skill in the art. By way of non-limiting example, Burkitt's lymphoma can be diagnosed and monitored by detecting of cells with an immunophenotype that is $CD20^+$, $CD10^+$, Bcl-6^+, Bcl-2^-, TdT^-, and monotypic sIg^+, with virtually all cells $Ki67^+$ (proliferation), and a translocation involving c-*myc* and *IgH* or *IgL*, without rearrangements involving the *bcl-2* or *bcl-6* genes.

[00352] The skilled artisan will appreciate that there are many ways to use the measurements of two or more markers in order to improve the diagnostic question under investigation. In a quite simple, but nonetheless often effective approach, a positive result is assumed if a sample is positive for at least one of the markers investigated. This can e.g. be the case when diagnosing a cancer, Burkitt's lymphoma, by either detecting cells with an immunophenotype that is $CD20^+$, $CD10^+$, Bcl-6^+, Bcl-2^-, TdT^-, and monotypic sIg^+, with virtually all cells $Ki67^+$ (proliferation), and a translocation involving c-*myc* and *IgH* or *IgL*, without rearrangements involving the *bcl-2* or *bcl-6* genes. Frequently, however, the combination of markers is mathematically/statistically evaluated. Preferably the values measured for markers of a marker panel, e.g. the immunophenotype for Burkitt's lymphoma and blood panel counts, are mathematically combined and the combined value is correlated to the underlying diagnostic question. Preferably the diagnostic question is the effectiveness of an inhibitor of DSB repair in treating a cancer. Preferably the relative risk is given in comparison to controls not receiving an inhibitor of DSB repair. Preferably controls are matched for age and other covariates.

[00353] Marker values can be combined by any appropriate state of the art mathematical method. Well-known mathematical methods for correlating a marker combination to a disease or to the risk of developing a disease employ methods like, Discriminant analysis (DA) (i.e. linear-, quadratic-, regularized-DA), Kernel Methods (i.e. SVM), Nonparametric Methods (i.e. k-Nearest-Neighbor Classifiers), PLS (Partial Least Squares), Tree-Based Methods (i.e. Logic Regression, CART, Random Forest Methods, Boosting/Bagging Methods), Generalized Linear Models (i.e. Logistic Regression), Principal Components based Methods (i.e. SIMCA), Generalized Additive Models, Fuzzy Logic based Methods, Neural Networks and Genetic Algorithms based Methods. The skilled artisan will have no problem in selecting an appropriate method to evaluate a marker combination of the technology described herein. Preferably the method used in correlating the marker e.g. to the absence or presence of cancer is selected from DA (i.e. Linear-, Quadratic-, Regularized Discriminant Analysis), Kernel Methods (i.e. SVM), Nonparametric Methods (i.e. k-Nearest-Neighbor Classifiers), PLS (Partial Least Squares), Tree-Based Methods (i.e. Logic Regression, CART, Random Forest Methods, Boosting Methods), or Generalized Linear Models (i.e. Logistic Regression). Details relating to these statistical methods are found in the following references: Ruczinski, I., J. of Computational and Graphical Statistics, 12 (2003) 475-511; Friedman, J. H., Regularized Discriminant Analysis, JASA 84 (1989) 165-175; Hastie, T., Tibshirani, R., Friedman, J., The Elements of Statistical Learning, Springer Series in

Statistics, 2001; Breiman, L., Friedman, J. H., Olshen, R. A., Stone, C. J., (1984) Classification and regression trees, California: Wadsworth; Breiman, L. Random Forests, Machine Learning, 45 (2001) 5-32; Pepe, M. S., The Statistical Evaluation of Medical Tests for Classification and Prediction, Oxford Statistical Science Series, 28 (2003) and Duda, R. O., Hart, P. E., Stork, D. G., Pattern Classification, Wiley Interscience, 2nd Edition (2001).

[00354] In some embodiments, an optimized multivariate cut-off for the underlying combination of biological markers can be used to e.g. discriminate patients with low, intermediate and high risk of developing cancer. In this type of multivariate analysis the markers are no longer independent but form a marker panel.

[00355] Accuracy of a diagnostic method is best described by its receiver-operating characteristics (ROC) (see especially Zweig, M. H., and Campbell, G., Clin. Chem. 39 (1993) 561-577). The ROC graph is a plot of all of the sensitivity/specificity pairs resulting from continuously varying the decision thresh-hold over the entire range of data observed.

[00356] The clinical performance of a laboratory test depends on its diagnostic accuracy, or the ability to correctly classify subjects into clinically relevant subgroups. Diagnostic accuracy measures the test's ability to correctly distinguish two different conditions of the subjects investigated. Such conditions are for example health and disease or benign versus malignant disease, respectively.

[00357] In each case, the ROC plot depicts the overlap between the two distributions by plotting the sensitivity versus 1-specificity for the complete range of decision thresholds. On the y-axis is sensitivity, or the true-positive fraction [defined as (number of true-positive test results)/(number of true-positive+number of false-negative test results)]. This has also been referred to as positivity in the presence of a disease or condition. It is calculated solely from the affected subgroup. On the x-axis is the false-positive fraction, or 1-specificity [defined as (number of false-positive results)/(number of true-negative +number of false-positive results)]. It is an index of specificity and is calculated entirely from the unaffected subgroup. Because the true- and false-positive fractions are calculated entirely separately, by using the test results from two different subgroups, the ROC plot is independent of the prevalence of disease in the sample. Each point on the ROC plot represents a sensitivity/1-specificity pair corresponding to a particular decision threshold. A test with perfect discrimination (no overlap in the two distributions of results) has an ROC plot that passes through the upper left corner, where the true-positive fraction is 1.0, or 100% (perfect sensitivity), and the false-positive fraction is 0 (perfect specificity). The theoretical plot for a test with no discrimination (identical distributions of results for the two groups) is a 45 degree diagonal

line from the lower left corner to the upper right corner. Most plots fall in between these two extremes. (If the ROC plot falls completely below the 45degree diagonal, this is easily remedied by reversing the criterion for "positivity" from "greater than" to "less than" or vice versa.) Qualitatively, the closer the plot is to the upper left corner, the higher the overall accuracy of the test.

[00358] One convenient goal to quantify the diagnostic accuracy of a laboratory test is to express its performance by a single number. The most common global measure is the area under the ROC plot. By convention, this area is always >0.5 (if it is not, one can reverse the decision rule to make it so). Values range between 1.0 (perfect separation of the test values of the two groups) and 0.5 (no apparent distributional difference between the two groups of test values). The area does not depend only on a particular portion of the plot such as the point closest to the diagonal or the sensitivity at 90% specificity, but on the entire plot. This is a quantitative, descriptive expression of how close the ROC plot is to the perfect one (area=1.0).

Definition of Dose-Limiting Toxicity (DLT)

[00359] The determination of DLT for purposes of assessing dose escalation is defined as follows using the NCI CTC version 3.0 criteria with consideration of known and accepted toxicities of certain drugs. Toxicities reached without pre-medication are not considered DLT. Criteria for DLT include: any nausea, vomiting at or above Grade 3 with maximum anti-emetic pre-medication; all other drug-related non-hematologic toxicity at or above Grade 3; neutrophil count <500 cell/ul for >7 days; any febrile neutropenia (defined as T>101° F.) with a neutrophil count <500 cells/ul after drug administration; platelet count <10,000 cell/ul OR Grade 3 with evidence of bleeding necessitating blood product or platelet transfusion; hemoglobin at or above Grade 4 toxicity with erythropoietin co-administration. The response is measured by standard criteria. Patients are reevaluated after every two cycles of treatment. In addition to a baseline/screening scan, confirmatory scans are obtained 4 weeks following initial documentation of an objective response.

Pharmaceutical Compositions

[00360] For administration to a subject, the compounds can be provided in pharmaceutically acceptable compositions. These pharmaceutically acceptable compositions comprise a therapeutically effective amount of at least one DSB repair inhibitor as described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the technology described herein can be specially formulated for administration in solid or liquid

form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), lozenges, dragees, capsules, pills, tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, lotion, gel, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream, suppository or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) transmucosally; or (9) nasally. Additionally, compounds can be implanted into a patient or injected using a drug delivery system. Coated delivery devices can also be useful. See, for example, Urquhart, et al., Ann. Rev. Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; U.S. Pat. No. 6,747,014; and U.S. Pat. No. 35 3,270,960.

[00361] Many organized surfactant structures have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition to be delivered. Liposomes can be cationic (Wang et al., Biochem. Biophys. Res. Commun., 1987, 147, 980-985), anionic (Zhou et al., Journal of Controlled Release, 1992, 19, 269-274), or nonionic (Hu et al. S.T.P.Pharma. Sci., 1994, 4, 6, 466). Liposomes can comprise a number of different phospholipids, lipids, glycolipids, and/or polymers which can impart specific properties useful in certain applications and which have been described in the art (Allen et al., FEBS Letters, 1987, 223, 42; Wu et al., Cancer Research, 1993, 53, 3765; Papahadjopoulos et al., Ann. N.Y. Acad. Sci., 1987, 507, 64; Gabizon et al., PNAS, 1988, 85, 6949; Klibanov et al. FEBS Lett., 1990, 268, 235; Sunamoto et al., Bull. Chem. Soc. Jpn., 1980, 53, 2778; Illum et al., FEBS Lett., 1984, 167, 79; Blume et al., Biochimica et Biophysica Acta, 1990, 1029, 91; Hughes et al., Methods Mol Biol. 2010;605:445-59; US Patent Nos. 4,837,028; 5,543,152; 4,426,330; 4,534,899; 5,013,556; 5,356,633; 5,213,804; 5,225,212; 5,540,935; 5,556,948; 5,264,221; 5,665,710; European Patents EP 0 445 131 B1; EP 0 496 813 B1; and European Patent Publications WO 88/04924; WO 97/13499; WO 90/04384; WO 91/05545; WO 94/20073; WO 96/10391; WO 96/40062; WO 97/0478).

[00362] The compositions of the technology described herein can be prepared and formulated as emulsions or microemulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter and have been described in the art. Microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution and can comprise surfactants and cosurfactants. Both of these drug delivery means have been described in the art (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 199, 245, & 335; Higuchi et al., in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301; Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215; Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271; Constantinides et al., Pharmaceutical Research, 1994, 11, 1385-1390; Ritschel, Meth. Find. Exp. Clin. Pharmacol., 1993, 13, 205; Ho et al., J. Pharm. Sci., 1996, 85, 138-143; Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 92; U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099).

[00363] In one embodiment, the liposome or emulsion formulation comprises a surfactant. Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in Pharmaceutical Dosage Forms, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285). Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. In some embodiments, the surfactant can be anionic, cationic, or nonionic. The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in Pharmaceutical Dosage Forms, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

[00364] In one embodiment, the technology described herein employs various penetration enhancers to affect the efficient delivery of DSB repair inhibitors across cell membranes. Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*,

surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants all of which have been described elsewhere (see e.g., Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Takahashi et al., J. Pharm. Pharmacol., 1988, 40, 252; Touitou, E., et al. Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri et al., J. Pharm. Pharmacol., 1992, 44, 651-654; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman et al., Eds., McGraw-Hill, New York, 1996, pp. 934-935; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Yamamoto et al., J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita et al., J. Pharm. Sci., 1990, 79, 579-583; Jarrett, J. Chromatogr., 1993, 618, 315-339; Katdare, A. et al., Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Buur et al., J. Control Rel., 1990, 14, 43-51)

[00365] Oral formulations and their preparation are described in detail in U.S. Patent 6,887,906, US Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference. Compositions and formulations for parenteral, intraparenchymal, intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

[00366] The compositions of the technology described herein can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the technology described herein, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the technology described herein. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for

influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with DSB repair inhibitor(s) of the formulation.

[00367] Suitable emulsifiers include synthetic non-ionic emulsifiers, such as, for example, ethoxylated ethers, ethoxylated esters, polyoxypropylene-polyoxyethylene block co-polymers and phospholipids. Naturally-occurring phospholipids, such as egg or soya phospholipids, and modified or artificially manipulated phospholipids or mixtures thereof can also be used. In some embodiments, emulsifiers are egg phospholipids and soya phospholipids. Egg yolk phospholipids include phosphatidylcholine, lecithin and phosphatidylethanolamine.

[00368] The compositions of the technology described herein may also include stabilizing agents. Anionic stabilizers include, for example, phosphatidylethanolamines, conjugated with polyethylene glycol, (PEG-PE) and phosphatidylglycerols, a specific example of which is dimyristolphosphatidylgylcerol (DMPG). Additional stabilizers include, but are not limited to, oleic acid and its sodium salt, cholic acid and deoxycholic acid and respective salts thereof, cationic lipids such as stearylamine and oleylamine, and 3|3-[N-(N′,N′-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol).

[00369] The compositions of the technology described herein can be made isotonic with blood by the incorporation of a suitable tonicity modifier. Glycerol is most frequently used as a tonicity modifier. Alternative tonicity modifying agents include xylitol, mannitol and sorbitol. The pharmaceutical compositions are typically formulated to be at physiologically neutral pH, typically in the range 6.0-8.5. The pH can be adjusted by the addition of base, for example, NaOH or NaHCO3, or in some cases acid, such as HCl.

[00370] The compositions of the technology can be formulated with pharmaceutically safe oil-water emulsions comprising a vegetable oil, a phosphatide emulsifier, typically egg lecithin or soybean lecithin, and a tonicity modifier such as, for example, Liposyn® II and Liposyn® III (Abbott Laboratories, North Chicago, Ill.) and Intralipid® (Fresenius Kabi AB, Uppsala, Sweden) or other similar oil-water emulsions.

[00371] Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 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. Compositions that exhibit large therapeutic indices, are preferred. Murine genetics have generated a number of mouse models for the study of DSB repair inhibitors. Such models can be used for *in vivo* testing of DSB repair inhibitor , as well as for determining a therapeutically effective dose. A suitable mouse model

is, for example, the *AICDA*$^{-/-}$ mouse described herein or model developed using patient derived tissue xenografting (PDX). In certain embodiments of this technique that would be useful in the study DSB repair inhibitors, a immunocompromised mouse strain, such as Nod-scid, NSG (NOD-scid Il2ry-null; NOD.Cg-Prkdc-scid<Il2rg>/Wjl/SzJ) or NRG (NOD-RagIl2ry-null; NOD-Rag1<null> IL2rg<null>/Wjl/SzJ) is engrafted with primary human cancer cells, such as leukemias.

[00372] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized.

[00373] The therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the therapeutic which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Levels of a compound in plasma can be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay.

[00374] The amount of a DSB repair inhibitor which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally out of one hundred percent, this amount will range from about 0.1% to 99% of compound, preferably from about 5% to about 70%, most preferably from 10% to about 30%.

[00375] The dosage can be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment. Generally, the compositions are administered so that the DSB repair inhibitor is given at a dose from 1 μg/kg to 150 mg/kg, 1 μg/kg to 100 mg/kg, 1 μg/kg to 50 mg/kg, 1 μg/kg to 20 mg/kg, 1 μg/kg to 10 mg/kg, 1μg/kg to 1mg/kg, 100 μg/kg to 100 mg/kg, 100 μg/kg to 50 mg/kg, 100 μg/kg to 20 mg/kg, 100 μg/kg to 10 mg/kg, 100μg/kg to 1mg/kg, 1 mg/kg to 100 mg/kg, 1 mg/kg to 50 mg/kg, 1 mg/kg to 20 mg/kg, 1 mg/kg to 10 mg/kg, 10 mg/kg to 100 mg/kg, 10 mg/kg to 50 mg/kg, or 10 mg/kg to 20 mg/kg. It is to be understood that ranges given here include all intermediate ranges, for example, the range 1 mg/kg to 10 mg/kg includes 1mg/kg to 2 mg/kg, 1mg/kg to 3 mg/kg, 1mg/kg to 4 mg/kg, 1mg/kg to 5 mg/kg, 1mg/kg to 6 mg/kg, 1mg/kg to 7 mg/kg, 1mg/kg to 8 mg/kg, 1mg/kg to 9 mg/kg, 2mg/kg to 10mg/kg, 3mg/kg to 10mg/kg, 4mg/kg to 10mg/kg,

5mg/kg to 10mg/kg, 6mg/kg to 10mg/kg, 7mg/kg to 10mg/kg, 8mg/kg to 10mg/kg, 9mg/kg to 10mg/kg etc. It is to be further understood that the ranges intermediate to the given above are also within the scope of this technology described herein, for example, in the range 1mg/kg to 10 mg/kg, dose ranges such as 2mg/kg to 8 mg/kg, 3mg/kg to 7 mg/kg, 4mg/kg to 6mg/kg etc.

[00376] With respect to duration and frequency of treatment, it is typical for skilled clinicians to monitor subjects in order to determine when the treatment is providing therapeutic benefit, and to determine whether to increase or decrease dosage, increase or decrease administration frequency, discontinue treatment, resume treatment or make other alteration to treatment regimen. The dosing schedule can vary from once a week to daily depending on a number of clinical factors, such as the subject's sensitivity to the DSB repair inhibitor. The desired dose can be administered at one time or divided into subdoses, e.g., 2-4 subdoses and administered over a period of time, e.g., at appropriate intervals through the day or other appropriate schedule. Such sub-doses can be administered as unit dosage forms. In some embodiments, administration is chronic, e.g., one or more doses daily over a period of weeks or months. Examples of dosing schedules are administration daily, twice daily, three times daily or four or more times daily over a period of 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months or more. The desired dose can be administered using continuous infusion or delivery through a controlled release formulation. In that case, the Inhibitor of DSB repair contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, *e.g.*, using a conventional sustained release formulation which provides sustained release of the DSB repair inhibitor over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the technology described herein. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

[00377] The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the DSB repair inhibitors described herein can be

made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model, as described elsewhere herein.

[00378] In some embodiments, pharmaceutical compositions can include (a) one or more DSB repair inhibitor and (b) one or more pharmaceutically effective compounds as described herein.

[00379] **Screening Assays**

[00380] In some embodiments, the technology described herein relates to methods of determining if an agent is an inhibitor of DNA double strand break repair, e.g. screening agents to determine if one or more of them is an inhibitor of DNA double strand break repair.

[00381] In some embodiments, the method of determining if a test agent is an inhibitor of DNA double strand break repair comprises (a) contacting a cell expressing a DNA editing enzyme with a test agent; and (b) determining cell viability; wherein decreased cell viability indicates the test agent is an inhibitor of DNA double strand break repair.

[00382] In some embodiments, the method of determining if a test agent is an inhibitor of DNA double strand break repair comprises (a) contacting a cell expressing a DNA editing enzyme with a test agent; and (b) determining cell viability of the cells of step (a); (c) contacting a cell not expressing a DNA editing enzyme with the test agent; (d) determining cell viability of the cells of step c); and (e) determining the ratio by dividing the fraction of live cells of step c by the fraction of live cells in step d; wherein a ratio below 0.8 indicates the test agent is an inhibitor of DNA double strand break repair.

[00383] In the context of the screening methods described herein, "a cell expressing a DNA editing enzyme" is a cell which expresses a DNA editing enzyme at a level which is higher than the level in a control reference cell. In some embodiments, a control reference cell can be an unactivated, untransformed, healthy B cell. In some embodiments, "a cell expressing a DNA editing enzyme" can be a cell which has a higher overall mutation rate than the overall mutation rate observed in an unactivated, untransformed, healthy human B cell. In some embodiments, the cell expressing a DNA editing enzyme is a cell expressing elevated levels of AID.

[00384] In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least one copy of a DNA editing enzyme mRNA per cell, e.g. 1 or more copies per cell, 10 or more copies per cell, or 100 or more copies per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 5 copies of a DNA editing enzyme per cell. In some embodiments the cells expressing a DNA editing enzyme which are

contacted with a test agent can be cells expressing at least 10 copies of a DNA editing enzyme per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 100 copies of a DNA editing enzyme per cell.

[00385] In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 100 copies of a DNA editing enzyme polypeptide per cell, e.g. 100 or more copies per cell, 200 or more copies per cell, 300 or more copies per cell, 400 or more copies per cell, 500 or more copies per cell, 600 or more copies per cell, 1000 or more copies per cell, 5000 or more copies per cell, or 10,000 or more copies per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 200 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 300 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 400 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 500 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 600 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 1,000 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 5,000 copies of a DNA editing enzyme polypeptide per cell. In some embodiments the cells expressing a DNA editing enzyme which are contacted with a test agent can be cells expressing at least 10,000 copies of a DNA editing enzyme polypeptide per cell.

[00386] In some embodiments, the cell contacted with a test agent can be a cell selected from the group consisting of: a stimulated B cell, a splenic B cell, a cancerous cell, or an autoimmune cell. In some embodiments, a cancerous cell can be a B cell from a subject having a disease selected from the group consisting of: lymphoma; leukemia; Burkitt's lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous

leukemia (AML); chronic myelogenous leukemia (CML); and Epstein-Barr virus transformed peripheral human B-lymphocytes derived cell lines GM05881, GM07323, and GM13689.

[00387] In some embodiments, the cell contacted with a test agent can be a stably transfected cell line where the cell line has been transfected with a vector encoding a DNA editing enzyme. Cell lines suitable for transfection include but are not limited to 3T3, CH12F3, Caco-2, CCRF-CEM, CHO, CH12-F3, COS-7, HCT 116, HEK 293, HL-60, HepG2, Jurkat, KG-1, K-562, MCF-7, MDCK, MG-63, Mo-B, MOLT-4, Ramos (RA 1) and U2-OS. Further cell lines established from primary cells, embryonic stem cells and induced pluripotent cells (iPS) can be useful for screening.

[00388] In some embodiments, the cell can be a cell which has been manipulated to cause it to express higher levels of a DNA editing enzyme, e.g. a B cell which has been stimulated or a cell which contains an exogenous polypeptide comprising a DNA editing enzyme and/or exogenous nucleic acid encoding a DNA editing enzyme.

[00389] In the context of the screening methods described herein, a "test agent" or "test compound" can be a nucleic acid (DNA or RNA), small molecule, aptamer, protein, peptide, antibody, polypeptide comprising an epitope-binding fragment of an antibody, antibody fragment, peptide-nucleic acid (PNA), locked nucleic acid (LNA), small organic or inorganic molecules; saccharide; oligosaccharides; polysaccharides; biological macromolecules, e.g., peptides, proteins, and peptide analogs and derivatives; peptidomimetics; nucleic acids; nucleic acid analogs and derivatives; extracts made from biological materials such as bacteria, plants, fungi, or mammalian cells or tissues; naturally occurring or synthetic compositions; peptides; aptamers; and antibodies, or fragments thereof. In some embodiments, a test agent can be a stilbene, stilbene derivative, or stilbenoid as described above herein. Examples of stilbenes, stilbene derivatives, stilbenoids, and other inhibitors of DNA double strand break repair are described above herein. Test agents and compounds are also described above herein.

[00390] In the context of the screening methods described herein, "determining cell viability" refers to measuring or detecting any aspect of cell metabolism, growth, structure, and/or propagation which is indicative of either a healthy, viable cell or a dead and/or nonviable cell. Colorimetric, luminescent, radiometric, and/or fluorometric assays known in the art can be used. In some embodiments, determining cell viability can comprise manual counting of cells using a hemacytometer. In some embodiments, determining cell viability can comprise the use of a live-dead cell stain, e.g. a stain which will stain either a live cell or a dead cell.

[00391] Colorimetric techniques for determining cell viability include, by way of non-limiting example, Trypan Blue exclusion. In brief, cells are stained with Trypan Blue and counted using a hemocytometer. Viable cells exclude the dye whereas dead and dying cells take up the blue dye and are easily distinguished under a light microscope. Neutral Red is adsorbed by viable cells and concentrates in cell lysosomes; viable cells can be determined with a light microscope by quantitating numbers of Neutral Red stained cells.

[00392] Fluorometric techniques for determining cell viability include, by way of non-limiting example, propidium iodide, a fluorescent DNA intercalating agent. Propidium iodide is excluded from viable cells but stains the nucleus of dead cells. Flow cytometry of propidium iodide labeled cells can then be used to quantitate viable and dead cells. Release of lactate dehydrogenase (LDH) indicates structural damage and death of cells, and can be measured by a spectrophotometric enzyme assay. Bromodeoxyuridine (BrdU) is incorporated into newly synthesized DNA and can be detected with a fluorochromelabeled antibody. The fluorescent dye Hoechst 33258 labels DNA and can be used to quantitate proliferation of cells (e.g., flow cytometry). Quantitative incorporation of the fluorescent dye carboxyfluorescein diacetate succinimidyl ester (CFSE or CFDA-SE) can provide cell division analysis (e.g., flow cytometry). This technique can be used either in vitro or in vivo. 7-aminoactinomycin D (7-AAD) is a fluorescent intercalator that undergoes a spectral shift upon association with DNA, and can provide cell division analysis (e.g., flow cytometry).

[00393] Radiometric techniques for determining cell proliferation include, by way of non-limiting example, [3H]-Thymidine, which is incorporated into newly synthesized DNA of living cells and frequently used to determine proliferation of cells. Chromium (51Cr)-release from dead cells can be quantitated by scintillation counting in order to quantitate cell viability

[00394] Luminescent techniques for determining cell viability include, by way of non-limiting example, the CellTiter-Glo luminescent cell viability assay (Promega Madison Wis.). This technique quantifies the amount of ATP present to determine the number of viable cells.

[00395] Kits for determining cell viability are commercially available, e.g. the MUTLITOX-FLOUR™ Multiplex Cytotoxicity Assay (Cat. No. G9200; Promega, Inc.; Madison, WI).

[00396] In some embodiments, the means of determining cell viability can comprise a high-throughput method, e.g. live-dead cell stains can be detected using a fluorescence-capable multiplate reader. In some embodiments, imaging analysis can be performed via automated image acquisition and analysis.

[00397] Some embodiments of the technology described herein can be defined as any of the following numbered paragraphs.

1. A method of treatment comprising;

   (a) obtaining a biological sample derived from a subject;

   (b) measuring a level of a DNA editing enzyme; and

   (c) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to a subject with a detectable level of a DNA editing enzyme.

2. A method of treatment comprising;

   administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to a subject determined to have a detectable level of a DNA editing enzyme.

3. A method of treatment comprising;

   (a) selecting a subject having cells that express an elevated level of a DNA editing enzyme; and

   (b) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to the subject;

   wherein the elevated level of the DNA editing enzyme is a level of DNA editing enzyme that is higher than the level of DNA editing enzyme in cells of the same type from a healthy individual.

4. The method of paragraph 1, wherein the biological sample comprises blood cells.

5. The method of paragraph 1, wherein the biological sample comprises B cells.

6. The method of any of paragraphs 1-5, wherein the level of DNA editing enzyme in the cells expressing a detectable or elevated level of a DNA editing enzyme is statistically significantly higher than in normal cells from a healthy subject.

7. The method of paragraphs 1-6, wherein the DNA editing enzyme is selected from the group consisting of:

   recombination activating gene 1 (RAG1); recombination activating gene 2 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA

editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

8. The method of paragraph 7, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

9. The method of paragraph 8, wherein the level of activation-induced cytidine deaminase (AID) in B cells expressing an elevated level of AID is significantly higher than the level of AID expressed in unactivated B cells from a healthy subject

10. The method of any of paragraphs 1-9, wherein the subject is a human subject.

11. The method of any of paragraphs 1-10, wherein the biological sample or cells that express a detectable or elevated level of a DNA editing enzyme are cancerous cells.

12. The method of any of paragraphs 1-11, wherein the subject has cancer.

13. The method of any of paragraphs 1-11, wherein the biological sample or cells that express detectable or elevated level of a DNA editing enzyme are autoimmune cells.

14. The method of any of paragraphs 1-13, wherein the subject has a condition selected from the group consisting of:

lymphoma, leukemia, and a plasma cell neoplasm.

15. The method of paragraph 14, wherein the lymphoma is selected from the group consisting of:

Non-Hodgkin's lymphoma; Burkitt's lymphoma, small lymphocytic lymphoma; lymphoplasmacytic lymphoma; MALT lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; and T-cell lymphoma.

16. The method of paragraph 14, wherein the leukemia is selected from the group consisting of:

acute lymphoblastic leukemia (ALL), Burkitt's leukemia; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); and T-cell acute lymphoblastic leukemia (T-ALL).

17. The method of paragraph 14, wherein the plasma cell neoplasm is selected from the group consisting of:

multiple myeloma; plasma cell myeloma; plasma cell leukemia; and plasmacytoma.

18. The method of paragraph 12, wherein the subject has a cancer selected from the group consisting of:

epithelial cell cancer; colon cancer, liver cancer, gastric cancer; intestinal cancer; esophageal cancer; breast cancer; lung cancer; and thyroid cancer.

19. The method of any of paragraphs 1-10 and 13, wherein the subject has an autoimmune disease.

20. The method of paragraph 19, wherein the autoimmune disease is selected from the group consisting of:

lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, discoid lupus, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease.

21. The method of any of paragraphs 1-20, wherein the inhibitor of DNA double strand break repair decreases the expression or activity of one or more genes selected from the group consisting of:

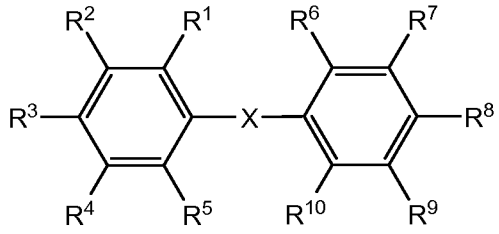
Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

22. The method of any of paragraphs 1-21, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

a small molecule; a protein; a peptide; an antibody; an antibody fragment; a protein binding protein; a ribonucleic acid; a deoxyribonucleic acid; an aptamer; a peptide nucleic acid (PNA); and a locked nucleic acid (LNA).

23. The method of any of paragraphs 1-20, wherein the inhibitor of DNA double strand break repair is stilbene, a stilbenoid, or a derivative thereof.

24. The method of paragraph 23, wherein the stilbene or stilbene derivative is a compound of Formula V:



Formula V

or a stereoisomer, enantiomer, prodrug, or pharmaceutically acceptable salt thereof;

wherein R^1 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^2 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^3 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^4 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^5 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^6 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched

C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^7 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

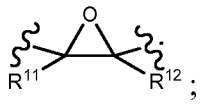
wherein R^8 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^9 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{10} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$,

optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein X can be selected from the group consisting of $C(R^{21})_2$, -C(O)N(R^{22})-, -C(O)-, -C(O)O-, -S(O)-, $-SO_2-$ $-CH(R^{11})CH(R^{12})-$, $-C(R^{11})=C(R^{12})-$, and



;

wherein R^{11} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{12} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein each R^{21} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted

heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof;

wherein each R^{22} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof.

25. The method of paragraph 21, wherein the stilbene derivative is 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS).

26. The method of paragraph 21, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))diacetamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methylpropanamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methoxyacetamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dimethanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dicyclopropanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-aminostyryl)phenyl)propane-2-sulfonamide; (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-methylthiourea); (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-isopropylthiourea); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)acetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)isobutyramide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)-2-methoxyacetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)methanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; N'-(4-{(E)-2-[4-(dimethylamino)phenyl]-1-ethenyl}phenyl)-N,N-dimethylsulfamide; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylthiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylthiourea; (E)-1-cyclopropyl-3-(4-

(4-(dimethylamino)styryl)phenyl)thiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylurea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylurea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)urea; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(methylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-cyclopropylthioureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-acetamido-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-isobutyramido-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(methylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-cyclopropylthioureido)-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-methylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-

(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-methylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N-isopropylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N,N-dimethylbenzamide); (E)-(ethene-1,2-diylbis(4,1-phenylene))bis(morpholinomethanone); (E)-5-(4-hydroxystyryl)benzene-1,3-diol(3,5,4'-trihydroxy-trans-stilbene); and resveratrol.

27. The method of paragraph 21, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; and (E)-5-

acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate.

28. The method of paragraph 20, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

4-methylquinazoline-2-carboxamide; benz[h]isoquinolin-6-amine; 5,6-dimethyl-2-mercaptomethylbenzimidazole; (E)-1-(2-hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one; N4-butyl-6-chloropyrimidine-2,4-diamine; 1-thermopsine; 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one; and 4-(2-amino-4-nitrophenylamino)phenyl.

29. The method of paragraph 20, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

7-azaindole-3-carboxaldehyde; 2-amino-4-phenylphenol; 3-(1-methyl-3-pyrrolidinyl)indole; 1-methyl-[1,2,4]Triazolo[4,3-a]quinolone; 2-amino-5-nitro-1H-benzimidazole; 2-(5-nitro-2-furfurylidene)aminoethanol-N-oxide; Nifuratrone; alpha-mercapto-N,2-naphthylacetamide; 1-thermospine; N4-butyl-6-chloro-2,4-pyrimidinediamine; 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid; 6-amino-5-nitroso-2-phenyl-1H-pyrimidin-4-one; 4-amino-2-hydroxyphenyl)arsonic acid; spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione; N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-diamine; 2-amino-9-pentyl-3H-purine-6-thione; 2-(4-methoxyphenyl)-3-(pyridin-3-yl)prop-2-enenitrile; 2-chloropyrimidine-4,6-dicarboxamide; 2-amino-3H-phenoxazin-3-one; 2-methyl-N-benzyl-7H-pyrrolo[2,3-d]pyrimidine-4-amine; 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-1-naphthalenesulfonic acid; N-sec-butyl-3-methylbenzamide; Benz[h]isoquinolin-6-amine; and 2-(2-methylcyclohexylidene) hydrazinecarboxamide.

30. The method of any of paragraphs 1-20, wherein the inhibitor of DNA double strand break repair is an antibody or polypeptide comprising an antigen-binding fragment of an antibody or a protein binding protein.

31. The method of any of paragraphs 1-20, wherein the inhibitor of DNA double strand break repair is an RNAi agent selected from the group consisting of:

miRNA; shRNA; siRNA; amiRNA; dsRNA, antisense RNA or ribozyme.

32. The method of any of paragraphs 1-31, wherein the inhibitor of DNA double strand break repair further comprises a pharmaceutically acceptable carrier.

33. The method of any of paragraphs 1-32, further comprising administration of a therapeutic agent.

34. The method of any of paragraphs 1-33, wherein the subject having cells that express an a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having detectable or elevated levels.

35. The method of any of paragraphs 1-34, wherein the subject having cells that express a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having elevated levels and comparing that level to the level of DNA editing enzyme polypeptide, mRNA, or activity found in a biological sample obtained from a healthy subject, wherein an increased amount of DNA editing enzyme polypeptide, mRNA, or activity in the test sample is indicative of a subject in need of treatment with an inhibitor of DNA double strand break repair.

36. The method of any of paragraphs 34-35, wherein measuring the level of a DNA editing enzyme polypeptide comprises using one or more assays selected from the group consisting of:

Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay; protein in situ array; immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; *in situ* immunoassay; precipitation reaction; immunofluorescence assay; quantitative in situ protein analyses (AQUA); mass spectroscopy and immunoelectrophoresis assay.

37. The method of any of paragraphs 34-36, wherein measuring the level of a DNA editing enzyme polypeptide comprises using an assay that uses an antibody, an antibody fragment, a protein binding protein, or a peptide which binds to the DNA editing enzyme polypeptide.

38. The method of any of paragraphs 34-37, wherein the antibody or antibody fragment is a monoclonal antibody.

39. The method of any of paragraphs 34-38, wherein the antibody, antibody fragment, protein binding protein or peptide which binds to the DNA editing enzyme polypeptide is labeled with a detectable label.

40. The method of any of paragraphs 34-35, wherein measuring the level of a DNA editing enzyme mRNA comprises using one or more assays selected from the group consisting of:

RT-PCR; quantitative RT-PCR; hybridization assay; Northern blot; microarray based expression analysis; transcription amplification; self-sustained sequence replication; high throughput sequencing; and RNA-Seq.

41. The method of any of paragraphs 1-40, wherein measuring the activity of a DNA editing enzyme activity comprises determining the overall mutation status of the genome or a portion thereof using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing;

wherein a mutation status 2% or greater than the normal mutation status indicates activity of a DNA editing enzyme.

42. The method of any of paragraphs 35-36 or 41, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises determining the status of hypermutations in the target genes IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing.

43. The method of any of paragraphs 35-36, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises using a phospho-H2AX assay, a 53BP1 assay, or a RAD51 assay.

44. A method of causing cell death comprising:

(a) administering to a cell an effective amount of a DNA editing enzyme; and

(b) thereafter contacting the cell of step (a) with an inhibitor of DNA double strand break repair,

thereby causing cell death.

45. A method of sensitizing a cell to cell death comprising:

(c) administering to a subject, a therapeutically effective amount of a DNA editing enzyme to sensitize a cell to cell death by use of an inhibitor of DNA double strand break repair: and

(d) thereafter administering to the subject an inhibitor of DNA double strand break repair.

46. The method of any of paragraphs 44-44, wherein the DNA editing enzyme is administered in a form selected from the group consisting of:

a polypeptide; a nucleic acid encoding a DNA editing enzyme; and a vector comprising a nucleic acid encoding a DNA editing enzyme.

47. The method of any of paragraphs 44-46, wherein the DNA editing enzyme is selected from the group consisting of:

recombination activating gene 1 (RAG1); recombination activating gene 1 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

48. The method of any of paragraphs 44-47, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

49. A method of determining if a test agent is an inhibitor of DNA double strand break repair comprising;

a) contacting a cell expressing a DNA editing enzyme with a test agent; and

b) determining cell viability of the cells of step a);

wherein decreased cell viability indicates the test agent is an inhibitor of DNA double strand break repair.

50. The method of paragraph 49, further comprising;

c) contacting a cell not expressing a DNA editing enzyme with the test agent;

d) determining cell viability of the cells of step c); and

e) determining the ratio by dividing the fraction of live cells of step b) of by the fraction of live cells in step d;

wherein a ratio below 0.8 indicates the test agent is an inhibitor of DNA double strand break repair.

51. The method of any of paragraphs 49-50, wherein the cell expressing a DNA editing enzyme is a cell expressing AID.

52. The method of paragraph 51, wherein the cell expressing AID is a stimulated B cell.

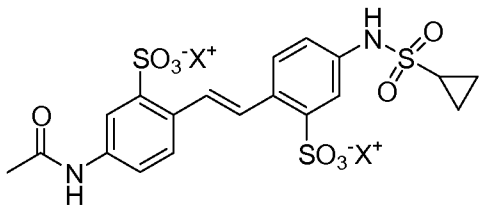
53. The method of any of paragraphs 49-52, wherein the cell is a cancerous cell.

54. The method of any of paragraphs 49-53, wherein the cells are transfected with a nucleic acid vector encoding a DNA editing enzyme.

55. The method of any of paragraphs 49-54, wherein the cell is a cell line selected from the group consisting of CH12-F3, 3T3, CH12F3, Caco-2, CCRF-CEM, CHO, CH12-F3, COS-7, HCT 116, HEK 293, HL-60, HepG2, Jurkat, KG-1, K-562, MCF-7, MDCK, MG-63, Mo-B, MOLT-4, Ramos (RA 1) and U2-OS,

56. The method of any of paragraphs 49-55, wherein the cell is an autoimmune cell.

57. A compound of Formula XXIV:



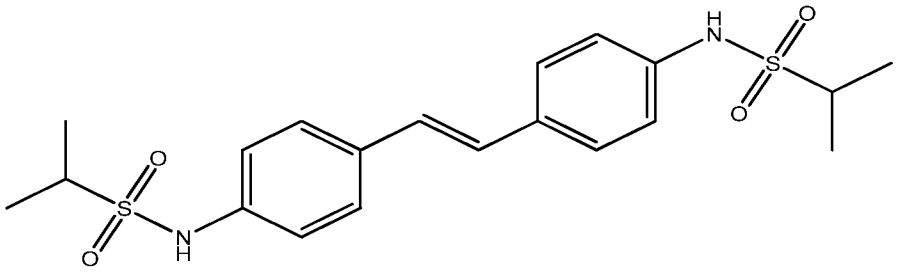
XXIV

a stereoisomer or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

58. The compound of paragraph 57, wherein X is sodium.

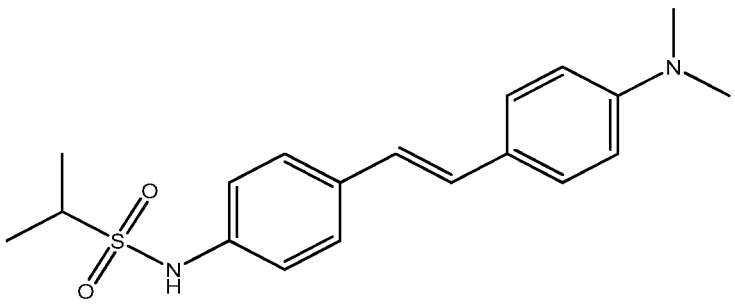
59. A compound of Formula VIII:



VIII

a stereoisomer, prodrug, or pharmaceutically acceptable salt thereof.

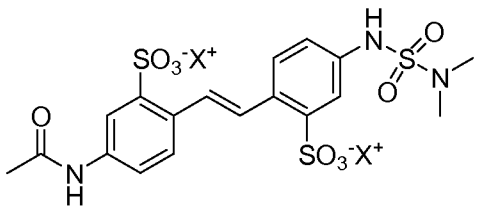
60. A compound of Formula X;



X

a stereoisomer, prodrug, or pharmaceutically acceptable salt thereof.

61. A compound of Formula XXV;



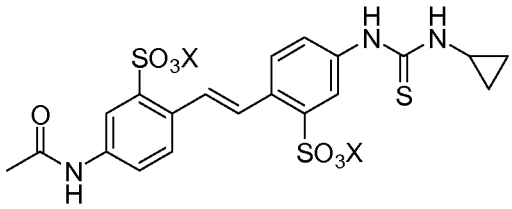
XXV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

62. The compound of paragraph 61, wherein X is sodium.

63. A compound of Formula XXXI;



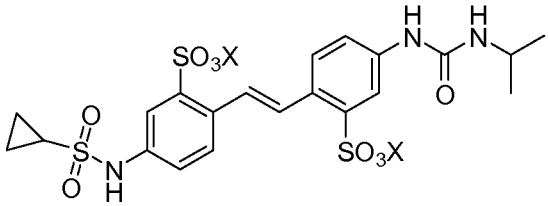
XXXI

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

64. The compound of paragraph 63, wherein X is sodium.

65. A compound of Formula XXXII;



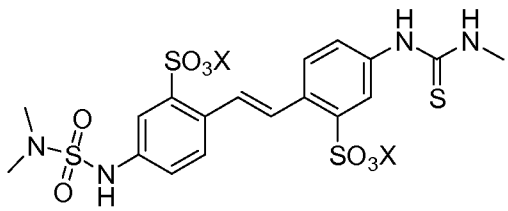
XXXII

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

66. The compound of paragraph 65, wherein X is sodium.

67. A compound of Formula XXXIII;



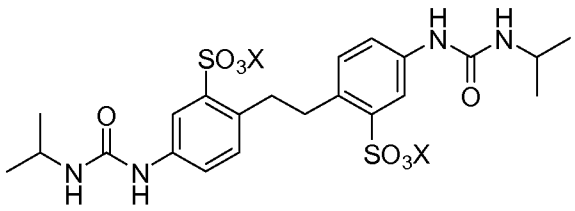
XXXIII

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

68. The compound of paragraph 67, wherein X is sodium.

69. A compound of Formula XXXIV;



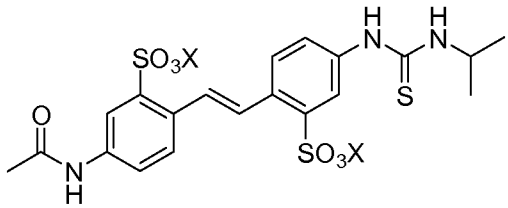
XXXIV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

70. The compound of paragraph 69, wherein X is sodium.

71. A compound of Formula XXXV;



XXXV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

72. The compound of paragraph 71, wherein X is sodium.

73. The use of an inhibitor of DNA double strand break repair to treat a subject determined to have a detectable level of a DNA editing enzyme.

74. The use of paragraph 73, wherein the subject is determined to have a detectable level of DNA editing enzyme by;

(a) obtaining a biological sample derived from a subject; and

(b) measuring a level of a DNA editing enzyme.

75. The use of an inhibitor of DNA double strand break repair to treat a subject, the method comprising;

(a) selecting a subject having cells that express an elevated level of a DNA editing enzyme; and

(b) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to the subject;

wherein the elevated level of the DNA editing enzyme is a level of DNA editing enzyme that is higher than the level of DNA editing enzyme in cells of the same type from a healthy individual.

76. The use of paragraph 73, wherein the biological sample comprises blood cells.

77. The use of paragraph 73, wherein the biological sample comprises B cells.

78. The use of any of paragraphs 73-77, wherein the level of DNA editing enzyme in the cells expressing a detectable or elevated level of a DNA editing enzyme is statistically significantly higher than in normal cells from a healthy subject.

79. The use of paragraphs 73-78, wherein the DNA editing enzyme is selected from the group consisting of:

recombination activating gene 1 (RAG1); recombination activating gene 2 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

80. The use of paragraph 79, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

81. The use of paragraph 80, wherein the level of activation-induced cytidine deaminase (AID) in B cells expressing an elevated level of AID is significantly higher than the level of AID expressed in unactivated B cells from a healthy subject

82. The use of any of paragraphs 73-81, wherein the subject is a human subject.

83. The use of any of paragraphs 73-82, wherein the biological sample or cells that express a detectable or elevated level of a DNA editing enzyme are cancerous cells.

84. The use of any of paragraphs 73-83, wherein the subject has cancer.

85. The use of any of paragraphs 73-84, wherein the biological sample or cells that express detectable or elevated level of a DNA editing enzyme are autoimmune cells.

86. The use of any of paragraphs 73-85, wherein the subject has a condition selected from the group consisting of:

lymphoma, leukemia, and a plasma cell neoplasm.

87. The use of paragraph 86, wherein the lymphoma is selected from the group consisting of:

Non-Hodgkin's lymphoma; Burkitt's lymphoma, small lymphocytic lymphoma; lymphoplasmacytic lymphoma; MALT lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; and T-cell lymphoma.

88. The use of paragraph 86, wherein the leukemia is selected from the group consisting of:

acute lymphoblastic leukemia (ALL), Burkitt's leukemia; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); and T-cell acute lymphoblastic leukemia (T-ALL).

89. The use of paragraph 86, wherein the plasma cell neoplasm is selected from the group consisting of:

multiple myeloma; plasma cell myeloma; plasma cell leukemia; and plasmacytoma.

90. The use of paragraph 86, wherein the subject has a cancer selected from the group consisting of:

epithelial cell cancer; colon cancer; liver cancer, gastric cancer; intestinal cancer; esophageal cancer; breast cancer; lung cancer; and thyroid cancer.

91. The use of any of paragraphs 73-82 and 85, wherein the subject has an autoimmune disease.

92. The use of paragraph 91, wherein the autoimmune disease is selected from the group consisting of:

lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, discoid lupus, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis,

autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease.

93. The use of any of paragraphs 73-92, wherein the inhibitor of DNA double strand break repair decreases the expression or activity of one or more genes selected from the group consisting of:

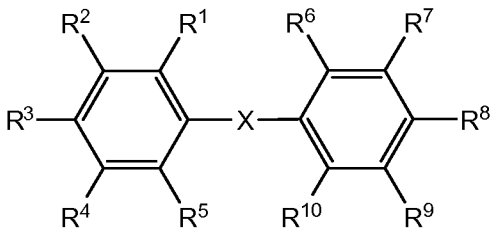
Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

94. The use of any of paragraphs 73-93, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

a small molecule; a protein; a peptide; an antibody; an antibody fragment; a protein binding protein; a ribonucleic acid; a deoxyribonucleic acid; an aptamer; a peptide nucleic acid (PNA); and a locked nucleic acid (LNA).

95. The use of any of paragraphs 73-93, wherein the inhibitor of DNA double strand break repair is stilbene, a stilbenoid, or a derivative thereof.

96. The use of paragraph 95, wherein the stilbene or stilbene derivative is a compound of Formula V:



Formula V

or a stereoisomer, enantiomer, prodrug, or pharmaceutically acceptable salt thereof;

wherein R^1 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$,

optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^2 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^3 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^4 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^5 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S,

$NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^6 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

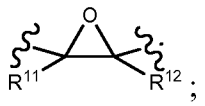
wherein R^7 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^8 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^9 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{10} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein X can be selected from the group consisting of $C(R^{21})_2$, $-C(O)N(R^{22})-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-SO_2-$ $-CH(R^{11})CH(R^{12})-$, $-C(R^{11})=C(R^{12})-$, and



;

wherein R^{11} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{12} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein each R^{21} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof;

wherein each R^{22} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof.

97. The use of paragraph 95, wherein the stilbene derivative is 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS).

98. The use of paragraph 95, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))diacetamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methylpropanamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methoxyacetamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dimethanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dicyclopropanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N,N'-(ethene-1,2-

diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-aminostyryl)phenyl)propane-2-sulfonamide; (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-methylthiourea); (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-isopropylthiourea); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)acetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)isobutyramide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)-2-methoxyacetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)methanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; N'-(4-{(E)-2-[4-(dimethylamino)phenyl]-1-ethenyl}phenyl)-N,N-dimethylsulfamide; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylthiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylthiourea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)thiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylurea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylurea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)urea; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(methylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-cyclopropylthioureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-acetamido-2-

(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-

isobutyramido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(methylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(methylsulfonamido)-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-methylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-methylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N-isopropylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N,N-dimethylbenzamide); (E)-(ethene-1,2-diylbis(4,1-phenylene))bis(morpholinomethanone); (E)-5-(4-hydroxystyryl)benzene-1,3-diol(3,5,4'-trihydroxy-trans-stilbene); and resveratrol.

99. The use of paragraph 95, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide); (E)-N-(4-(4-

(dimethylamino)styryl)phenyl)propane-2-sulfonamide; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; and (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate.

100. The use of paragraph 94, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

4-methylquinazoline-2-carboxamide; benz[h]isoquinolin-6-amine; 5,6-dimethyl-2-mercaptomethylbenzimidazole; (E)-1-(2-hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one; N4-butyl-6-chloropyrimidine-2,4-diamine; 1-thermopsine; 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one; and 4-(2-amino-4-nitrophenylamino)phenyl.

101. The use of paragraph 94, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

7-azaindole-3-carboxaldehyde; 2-amino-4-phenylphenol; 3-(1-methyl-3-pyrrolidinyl)indole; 1-methyl-[1,2,4]Triazolo[4,3-a]quinolone; 2-amino-5-nitro-1H-benzimidazole; 2-(5-nitro-2-furfurylidene)aminoethanol-N-oxide; Nifuratrone; alpha-mercapto-N,2-naphthylacetamide; 1-thermospine; N4-butyl-6-chloro-2,4-pyrimidinediamine; 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid; 6-amino-5-nitroso-2-phenyl-1H-pyrimidin-4-one; 4-amino-2-hydroxyphenyl)arsonic acid; spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione; N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-

diamine; 2-amino-9-pentyl-3H-purine-6-thione; 2-(4-methoxyphenyl)-3-(pyridin-3-yl)prop-2-enenitrile; 2-chloropyrimidine-4,6-dicarboxamide; 2-amino-3H-phenoxazin-3-one; 2-methyl-N-benzyl-7H-pyrrolo[2,3-d]pyrimidine-4-amine; 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-1-naphthalenesulfonic acid; N-sec-butyl-3-methylbenzamide; Benz[h]isoquinolin-6-amine; and 2-(2-methylcyclohexylidene) hydrazinecarboxamide.

102. The use of any of paragraphs 73-94, wherein the inhibitor of DNA double strand break repair is an antibody or polypeptide comprising an antigen-binding fragment of an antibody or a protein binding protein.

103. The use of any of paragraphs 73-94, wherein the inhibitor of DNA double strand break repair is an RNAi agent selected from the group consisting of:

miRNA; shRNA; siRNA; amiRNA; dsRNA; antisense RNA or ribozyme.

104. The use of any of paragraphs 73-103, wherein the inhibitor of DNA double strand break repair further comprises a pharmaceutically acceptable carrier.

105. The use of any of paragraphs 73-104, further comprising administration of a therapeutic agent.

106. The use of any of paragraphs 73-105, wherein the subject having cells that express an a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having detectable or elevated levels.

107. The use of any of paragraphs 73-106, wherein the subject having cells that express a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having elevated levels and comparing that level to the level of DNA editing enzyme polypeptide, mRNA, or activity found in a biological sample obtained from a healthy subject, wherein an increased amount of DNA editing enzyme polypeptide, mRNA, or activity in the test sample is indicative of a subject in need of treatment with an inhibitor of DNA double strand break repair.

108. The use of any of paragraphs 106-107, wherein measuring the level of a DNA editing enzyme polypeptide comprises using one or more assays selected from the group consisting of:

Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay; protein in situ array; immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; *in situ* immunoassay; precipitation reaction; immunofluorescence assay; quantitative in situ protein analyses (AQUA); mass spectroscopy and immunoelectrophoresis assay.

109. The use of any of paragraphs 106-107, wherein measuring the level of a DNA editing enzyme polypeptide comprises using an assay that uses an antibody, an antibody fragment, a protein binding protein, or a peptide which binds to the DNA editing enzyme polypeptide.

110. The use of any of paragraphs 106-109, wherein the antibody or antibody fragment is a monoclonal antibody.

111. The use of any of paragraphs 106-110, wherein the antibody, antibody fragment, protein binding protein or peptide which binds to the DNA editing enzyme polypeptide is labeled with a detectable label.

112. The use of any of paragraphs 106-107, wherein measuring the level of a DNA editing enzyme mRNA comprises using one or more assays selected from the group consisting of:

RT-PCR; quantitative RT-PCR; hybridization assay; Northern blot; microarray based expression analysis; transcription amplification; self-sustained sequence replication; high throughput sequencing; and RNA-Seq.

113. The use of any of paragraphs 106-107, wherein measuring the activity of a DNA editing enzyme comprises determining the overall mutation status of the genome or a portion thereof using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing;

wherein a mutation status 2% or greater than the normal mutation status indicates activity of a DNA editing enzyme.

114. The use of any of paragraphs 106-107 and 113, wherein measuring the activity of activation-induced cytidine deaminase (AID) activity comprises determining the status of hypermutations in the target genes IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing.

115. The use of any of paragraphs 106-107, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises using a phospho-H2AX assay, a 53BP1 assay, or a RAD51 assay.

EXAMPLES

Example 1: Inhibition of XRCC2 in splenocytes

[00398] Adult splenocytes were isolated from 4 to 6-month-old C57BL6/J mice. A single cell suspension was prepared by mechanical disruption, dispersing the spleens through fine, sterile mesh in RPMI-1640 medium with 2-10 mM L-glutamine (Gibco) with 10% (vol/vol) heat-inactivated fetal bovine serum (FBS, Gibco). Red blood cells were removed by hypotonic lysis using 8.3 g/L of ammonium chloride in 0.01M Tris-HCl buffer at a pH of 7.5. The remaining splenocytes were cultured in supplemented RPMI-1640 with 2-10 mM L-glutamine supplemented with 10 % fetal bovine serum (FBS) in a 5% CO_2 humidified atmosphere at 37 °C. The cells were transduced with lentiviral shRNA vectors targeting Xrcc2 (TRCN0000071023, TRCN0000071024 and TRCN0000071027; from Sigma). CH12-F3-derivative lines stably expressing Xrcc2-specific short hairpin RNA (shRNA) or control shRNA (with a scrambled sequence) were generated by direct transduction with individual shRNA vectors, followed by selection for puromycin resistance. For transduction of primary splenocytes, the original vectors were modified by replacement of the puromycin-resistance cassette with sequence encoding enhanced Green Fluorescent Protein (eGFP) (Clontech). As

a control, e*mpty* pLKO.1-eGFP vector or vector expressing scrambled shRNA was used. Vectors were packaged into pseudotyped viruses and were used to transduce primary cells as described in Hasham, and Tsygankov, 2004, Virology 320, 313–329. The cells transduced with the *Xrcc2*-specific shRNA were called XKD cells and the controls labeled Ctrl. One subset was cultured as non-activated (Non) with 1 μg/ml antibody to CD40 (anti-CD40; HM40-3; Pharmingen) alone to induce proliferation without class switching, and the other set as activated (Act) with 1 μg/ml anti-CD40 plus 25 ng/ml interleukin 4 (IL-4; Peprotech, Cat. No. 214-14) to induce proliferation and class-switch recombination. Media and cytokines were replenished after 2 days. After 3 days of stimulation cells were assessed for viability using the expression of eGFP. Figure 1 shows that all non-activated cells behave the same. In activated cells the knockdown of *Xrcc2* results in a greatly reduced cell number. Figure 1 further shows that the lack of p53 (Trp53-/-) can partially rescue the cytotoxicity observed in the group expressing *Xrcc2* shRNA.

Example 2: Comparison of AID expressing cells with AID-deficient cells

[00399] Splenocytes were isolated and cultured as described in Example 1 from either wild type mice ($AID^{+/+}$) or AID-deficient (*AID-/-)* mice (Muramatsu et al. et al., 2000, Cell 102: 553-63) and transduced with Xrcc2 shRNA (XKD) or control shRNA as described in Example 1. Knockdown of XRCC2 in $AID^{+/+}$ B cells compromised survival after activation (Figure 2). In contrast, activation of XKD B cells from $AID^{-/-}$ mice produced no detectable change in cell viability or survival. When XKD cells were enriched specifically for $B220^{+}IgM^{+}$ B cells by depletion of CD43-expressing cells via magnetic bead-based cell sorting (120-000-302; Miltenyi) and assayed at various time points after activation for cell viability or survival, no change was observed in $AID^{-/-}$ cells (Figure 3). In B-cells expressing AID (WT), an increase in cell death was observed on day 2 and day 3.

[00400] $AID^{+/+}$ or $AID^{-/-}$ XKD B cell cultures were cultured with either 1 μg/ml anti-CD40 (nonactivated, Non) or 1 μg/ml anti-CD40 plus 25 ng/ml IL-4 (activated, Act) and the cells then stained for foci of γ-H2AX, a marker of unrepaired double strand breaks (DSBs) (Rogakou et al., J Biol Chem 1998, 273:5858-5868) using a polyclonal antibody to phosphorylated γ-H2AX (1:400 dilution; A300-018A; Bethyl Laboratories, Montgomery, TX). Both control and XKD B cell cultures showed an AID-dependent larger fraction of γ-$H2AX^{+}$ cells (cells containing one γ-H2AX focus or more γ-H2AX foci) after activation (Figure 4). $AID^{-/-}$ cultures transduced with control shRNA or $AID^{-/-}$ XKD cultures showed no change in γ-H2AX positivity after activation (Figure 5). However, when foci per cell were quantified in the γ-$H2AX^{+}$ fraction, XKD cells were found to have had a specific and

significant increase in the number of γ-H2AX foci per cell (from approximately two foci per cell before activation to more than four foci per cell after activation; Figure 5). This effect was not seen in *AID*$^{-/-}$ cells suggesting that it is dependent on AID.

[00401] A similar γ-H2AX response was observed in the class-switch-competent mouse B cell line CH12-F3 (Nakamura, M. et al. 1996, Int. Immunol. 8, 193–201) containing the same *Xrcc2*-knockdown construct used in primary cells (CH12-XKD cells) (Figure 6). CH12-F3 cells were maintained in RPMI-1640 medium supplemented with 2-10 mM L-glutamine (Gibco) 10% (vol/vol) heat-inactivated fetal bovine serum (FBS) (Omega Scientific) and 5% (vol/vol) NCTC 109 media (Gibco). CH12-F3-derivative lines stably expressing Xrcc2-specific shRNA or control shRNA (with a scrambled sequence) were generated by direct transduction with individual shRNA vectors, followed by selection for puromycin resistance. Accumulation of activation-induced foci was observed specifically in XKD cells but not in control cells using the DNA damage–response factor 53BP1, another marker of DNA DSBs.

[00402] In summary, it is demonstrated herein that AID can promiscuously attack the B cell genome, producing widespread DSBs. It has been further demonstrated herein that the homologous recombination factor XRCC2 is critical in the resistance to AID-induced collateral damage, ensuring B cell viability and genome stability. Specifically, these findings indicate that the same mechanisms that introduce developmentally programmed DSBs can carry an inherent and simultaneous risk for the genome at large. This suggests that homologous recombination is important not only for normal lymphocyte development but also for the prevention of lymphoid pathologies such as immunodeficiency or cancer.

Example 3: DIDS reduces cell viability of receptive cells

[00403] To validate DIDS as a potential agent, and to confirm its DSB repair inhibitory activity, radiosensitivity of primary wild-type mouse splenocytes was measured after exposure to DIDS. A total of $2x10^6$ splenocytes were suspended in medium with 0, 300 μM, 600 μM or 1000 μM DIDS, or in vehicle-only control, and immediately given 2.5 Gy ionizing irradiation using a ^{137}Cs irradiator (Shepard). Cells were then cultured in medium containing the same DIDS concentration, and cell counts were determined after 36 hours recovery time. DIDS treatment resulted in hypersensitivity to 2.5 Gy irradiation, relative to vehicle-control, in a dose-dependent manner. At 0 and 300 μM DIDS, cell counts were similar to vehicle-only. But cells cultured in 600 μM DIDS showed approximately 25% reduction in viability, and cells cultured in 1000 μM DIDS showed 87% reduction in

viability. These data show that DIDS treatment confers the expected radiosensitivity on primary splenocytes, consistent with its known role in RAD51 inhibition.

[00404] Primary mouse B-cells were isolated from spleens of adult C57BL/6J mice (AID+/+) and from AID knockout mice (AID-/-) (see Example 1 and 2). 1x10^6 primary B-cells were seeded into tissue culture plates, stimulated with 1 μg/ml anti-CD40 antibodies (anti-CD40; BD Pharmingen; Cat. No.553721) and 25 ng/ml IL-4 or with anti-CD40 alone on day 0 and day 2. 0, 50 μM, 100 μM or 150 μM of DIDS was added at time 0 and 2 days after culture initiation, when culture volumes were adjusted to accommodate cell growth. The cells were cultured over 6 days. The number of viable cells were counted after staining with Trypan blue using a hemacytometer on days 1, 2, 3, 4 and 6. In Figure 7 the number of viable primary B-cells from C57BL/6J mice (*AID*+/+) and *AID*-knockout mice (*AID*-/-) after treatment with DIDS is shown. In *AID*+/+ B-cells 150 μM DIDS greatly reduces the cell viability from day 3 on. A decrease of B-cell viability is also observed at concentration of 100 μM DIDS. When AID+/+ B-cells are not stimulated with anti-CD40 + IL-4, DIDS does not influence the cell viability. Further AID-/- cells are not affected by DIDS and show no significant change in cell viability.

[00405] Cells were isolated from the spleens of wild type or AID knockout (-/-) mice, cultured and stimulated with anti-CD40 antibodies and IL-4 on day 0 and day 2. DIDS was added on day 0 and day 2 at concentrations of 0 or 150 μM. The total number of viable cells was determined every other day using Guava EasyCyte Flow Cytometer Assay. Stimulated cells treated with 150 μM DIDS showed lower viability (Figure 9).

Example 4: AID Gene Expression Profiling

[00406] The expression of AID was profiled in the NCI-60 set of 59 human cancer cell lines derived from diverse tissues; brain, blood and bone marrow, breast, colon, kidney, lung, ovary, prostate and skin. As shown in Figure 8A high AID expression was detected in lymphoma and leukemia cell lines. Expression was further characterized in primary human cells/tissues and high expression was detected in leukemia and lymphoma samples (Fig. 8 B).

Example 5: Screening of new bioactive compounds

[00407] To identify bioactive derivatives of DIDS, a library of 10^5 chemical variants of DIDS was generated by replacing the sulfonate or isothiocyanate group with other chemical entities, or by altering the double bond joining the two rings in the stilbene backbone. All compounds were resuspended in dimethyl sulfoxide (DMSO) at a stock concentration of 100 micromolar, and used by serial dilution to generate working concentrations of 10, 50, or 150 μM. These were individually pipetted into 96-well microtiter culture dishes in duplicate,

generating two plates of 10 μM , two plates of 50 μM, and two plates of 150 μM compounds. In each set, one plate was seeded with 100,000 normal C57BL/6J splenic B-cells (AID+/+) isolated by magnetic bead based sorting to enrich for B220+ IgM+ B-cells; and one plate was seeded with 100,000 splenic B-cells from AID -/- mice identically isolated. Each culture was stimulated on day 0 by addition of 1 μg/ml anti-CD40 plus 25 ng/ml IL-4 to induce proliferation and class-switch recombination. After two days, each culture was re-stimulated by an additional 1 μg/ml anti-CD40 plus 25 ng/ml IL-4. After two additional days in culture, for a total of 4 days of stimulation, viable cell counts were determined in each well of each plate using the MultiTox-Fluor Multiplex Cytotoxicity Assay (Promega, Inc.). For viability measurements, 100 microliters of the 2X MultiTox-Fluor Multiplex Cytotoxicity Reagent was added to each well and mixed before incubating at 37 °C for 30 min. Plates were then transferred to a fluorescence-capable multiplate reader and analyzed using 400 nm excitation and detection of 505 nm emission to measure the fraction of remaining live cells. As controls, wells containing either vehicle alone (DMSO) or 150 μM DIDS were included on each plate. Viability scores for each compound were determined as the fraction of live cells in the normal B-cell plate divided by the fraction of live cells in the corresponding AID knockout plate. Compounds that produce normal/AID knockout ratios at or below the level of the DIDS ratio were considered candidate compounds for further validation and testing. In the absence of DIDS compounds that result in a reduced cell viability selectively in the AID+/+ cell relative to the AID-/- cells leading to an AID+/+ : AID-/- ratio of less than 1 are scored as a initial positive hit. The initial screen identified 10 derivatives, BB5-6, BB1-6, BB1-7, BB2-6, BB2-5, BB5-39, BB4B-2, BB5-4, BB5-47, and BB8-1 (Figure 10).

Example 6: Effect of DIDS on human CLL cells

[00408] Blood samples (8-16 mL) from patients were collected via peripheral bleed into BD Vacutainer CPT tubes (BD, Franklin Lakes, NJ), centrifuged to sequester red blood cells below the separation gel according to manufacturer instructions, and transported within 24 hours to the Jackson Laboratory. Upon receipt, peripheral blood mononuclear cells (PBMC) were isolated from samples according to manufacturer specifications. White blood cell (WBC) counts from 14 primary chronic lymphocytic leukemia (CLL) samples from human patients were calculated from complete blood count (CBC) with differentials. Calculated values were compared with empirical cell counts following cell separation and overnight shipping. This reveals remarkably consistent efficiency of isolation. The primary CLL samples (WBC) were diluted to standard concentration and 3.0x10^6 cells were seeded in cultures. Replicate cultures were supplemented with 0 μM (n=5), 150 μM DIDS (n=4), or

600 μM DIDS (n=2). Viable cell counts were determined by manual counting using a hemacytometer on days 2, 4, 6, and 8 of culture. DIDS-treated cultures showed a significant decline in viable cell counts, relative to untreated control (Figure 11).

Example 7: Effects of 4'-Bromo-3'-nitropropiophenone on splenocytes

[00409] Primary mouse B-cells were isolated from spleens of adult AID-/- mice as described in Example 1. Cultures were established at a concentration of 1x10^6 cells per ml in RPMI-1640 medium with 10% FBS. Cultures were activated with anti-CD40 antibody plus IL-4, and treated with 4'-Bromo-3'nitropropiophenone (NS-123) (purchased from Calbiochem; CAS No. 101860-83-7) at concentrations of 0.5, 5, 50, or 500 μM. Cells were re-activated by anti-CD40 plus IL-4 after two days in culture. Cell counts were determined after 1, 2, 3, and 4 days in culture by Trypan blue staining. At the concentration of 50 μM and 500 μM of NS-123 AID-null splenocytes were not viable. At the concentration of 5 μM of NS-123 the viability of the splenocytes is reduced when compared to untreated splenocytes (Figure 12).

[00410] Primary AID-knockout mouse splenocytes were seeded in cultures at day 0 at a concentration of 1x10^6 cells/ml in RPMI-1640 medium supplemented with anti-CD40 plus IL-4 to activate B-cells. Individual cultures were supplemented with 0, 5, 10, 20, 30, 40, or 50 μM NS-123 and viable cells were counted after Trypan blue staining on days 1, 2, 3, and 4 (Figure 13). The LD50 for NS-123 in AID-null splenocytes was determined to be 14 μM. To demonstrate the effectiveness of NS-123 splenocytes isolated from wild type mice (expressing AID) and compared to the splenocytes from AID -/- mice, activated and non-activated can be tested.

Example 8: In vivo testing of DSB inhibitors

[00411] Mice overexpressing AID ubiquitously or tissue-specific are treated with a DSB inhibitor. One such suitable mouse model is B6.Cg-Tg(Igk-Aicda)14Mnz/J where AID is overexpressed in B lymphocytes (B cells) or C57BL/6-Tg(CAG-Aicda)B1Hon/HonRbrc where AID is ubiquitously expressed using the CAG (chicken beta-actin promoter, rabbit beta-globin poly A, CMV-IE enhancer) promoter (Okazaki et al., J Exp Med. 2003, 197(9):1173-81). It has been reported that such mouse models do develop lymphomas and other cancerous lesions. The DSB inhibitor, (e.g. stilbene, DIDS, NS-123, or resveratrol) can be administered to the mice. Administration can be done by intravenous (i.v.), intraperitoneal (i.p.), intramuscular (i.m.) or subcutaneous (s.c.) injection, or using osmotic pumps for continuous treatment or via the drinking water.

[00412] In the case of C57BL/6-Tg(CAG-Aicda) mice it has been reported that these mice develop T cell lymphoma and die between 40 and 80 weeks depending on transgene insertion (Okazaki et al., J Exp Med. 2003, 197(9):1173-81). Treatment with DSB inhibitors can result in a decrease of the lymphomas and extension of lifespan.

Example 9: Xenograft mouse model

[00413] 5×10^6 primary white blood cells (WBC) from primary chronic lymphocytic leukemia (CLL) patients with AID activity can be suspended in 0.1 mL of PBS and then injected i.v. or administered by osmotic pump into immunodeficient mice, e.g. NOD-scid or NOD-scid IL2Rgamma (NSG). After tumors formed flow on peripheral blood mice can be randomly assigned into one of four groups: vehicle control, 5 mg/kg DIDS, 25 mg/kg DIDS and 50 mg/kg DIDS is mixed in DMSO with 30% propylene glycol and injected i.v. at 1-week intervals for 4-8 weeks. Groups not receiving DIDS can be treated with the same volume of DMSO alone dissolved in 30% propylene glycol. Peripheral blood can be analyzed by flow in 1-week intervals. At the end of the study the mice can be sacrificed and histological analysis performed.

Example 10: Xenograft mouse model with AID+ or AID- human tumor samples.

[00414] NOD-scid IL2Rgamma (NSG mice) can be engrafted with AID+ and AID- human tumor samples to generate multiple, replicate *in vivo* models that as closely as possible reflect the patient disease. These can then be used to test *in vivo* efficacy of genetic chemotherapy, to relate efficacy to AID expression level, and to evaluate potential genetic chemotherapy side effects.

[00415] To generate multiple recipients (up to 15) from each patient sample, 1x10^6 peripheral blood mononuclear cells (PBMC) from each patient sample can be introduced into 6 week old male NSG mice by intravenous, intrasplenic, or if necessary intra-bone marrow, injection. Previous studies have indicated that B-lymphoid cancers have a successful rate of engrafting NSG mice of greater than 60% (Immunol, 2005, 174(10), 6477-89; Leukemia. 24(11), 1859-66; Ann NY Acad Sci, 2007. 1103: p. 90-3). Following engraftment each group of recipients can be subdivided divided into treatment subgroups of up to 5 mice each. Between one week and month after injection, mice (in groups of up to 5) can be treated with DIDS (using empirically determined concentrations), vehicle control, or remain untreated. As a starting regimen, mice can be treated with DIDS or other compounds by i.v. injection at 1 week intervals for 4 to 8 weeks, and can be monitored for human lymphoid cells in circulation by flow cytometry, collecting peripheral blood at 1 week intervals between drug

injections. After 4-8 weeks of treatment, all recipient mice can be euthanized, and tumor development, burden,
regression, and survival time can be subsequently be determined for all mice in each treatment group.

[00416] **Tumor burden**: At sacrifice, peripheral blood and lymphoid organ tissue will be analyzed for human leukemia cells by flow cytometry or immunofluorescence. To detect human cells, and distinguish them from mouse cells, co-stain for human leukemia diagnostic markers hCD19, hCD22, and hCD79a, as well as mouse markers, such as mCD19 can be performed. The number of human cells can be compared in untreated, vehicle-treated, and DIDS-treated recipients. If DIDS elicits a genetic chemotherapy response then fewer human leukemia cells would be expected in treated versus controls.

[00417] **Apoptosis** can be measured by staining with fluorescently labeled Annexin V, and counterstaining with the DNA binding dye 7-amino-actinomycin D (7-AAD). Human cells can be distinguished from mouse as above. The percentage of apoptotic cells can be determined by flow cytometry. Alternatively, apoptosis can be measured by immunofluorescence microscopy to detect AC3.

[00418] **Post-treatment histopathology analysis**. To evaluate response or resistance of patient derived xenograft mice to genetic chemotherapy all drug treated and control mice can be subjected to exhaustive histopathology analysis. Prior studies have suggested that leukemia cells in bone marrow microenvironments can survive otherwise cytotoxic chemotherapy. Thus analysis of bone marrow, other lymphoid niches, and potential sanctuary sites such as CNS for tumor cell occupancy, as well as staining for human B-cell markers such as CD5, CD19, CD22, CD23, or CD79a can be performed. The effects of drug treatment on the niche itself can be examined by performing parallel mouse histopathology using appropriate mouse tissue stains and markers. All tissues collected for histopathology (bone marrow, spleen, other tissues showing evidence of abnormality) can be fixed in formalin, trimmed, and paraffin embedded. All fixed, tissues can be stained with hematoxylin and eosin (H&E). For these analyses, the presence of human leukemia in the mice, and anatomical abnormalities caused by the drug treatment regimen can be sought. Formalin-fixed, paraffin embedded sections of femurs and spleens from xenograft mice can be specifically immunostained for human CD19, CD22, and CD79a (B-cell leukemia markers) as well as a panel of other lineage markers as negative controls (e.g. CD33, CD34 myeloid markers) to pinpoint human cell components of bone marrow and secondary hematopoietic organs. The

goal of these analyses will be to measure residual human cells, and to identify the microenvironments they inhabit.

Example 11: AID expression analysis and genotyping

[00419] For RNA and DNA preparation, between 1x10^6 cells and 5X10^7 cells, can be extracted using standard molecular biology protocols. AID mRNA expression can be measured in each sample by quantitative reverse transcription PCR (qRT-PCR). Oligonucleotide primer sequences to detect human AID transcript are: hAID fwd 5'-TCCTTTTCACTGGACTTTGG-3' (SEQ ID NO:101); and hAID rev 5'-GACTGAGGTTGGGGTTCC-3' (SEQ ID NO:102). RT-PCR with these primers produces a 196 bp reaction product specific for human AID. Primer sequences for human GAPDH transcript (on type of loading control) are: hGAPDH fwd 5'-GAGTCAACGGATTTGGTCGT-3' (SEQ ID NO:103); and hGAPDH rev 5'-TTGATTTTGGAGGGATCTCG-3' (SEQ ID NO:104). RT-PCR with these primers produces a reaction product of 238 bp specific for the human GAPDH gene. Expression levels are quantified using a multiple normalization protocol according to Woo et al., Oncogene 2007, 26(41), 6010-20, ensuring the highest-level of confidence in sample-to-sample comparisons across the tumor cell collection. In each qRT-PCR assay, an AID-negative control can be included, such as normal human fibroblast (NHF). Tumors that show AID mRNA levels above the baseline level in negative controls can be classified as AID expressing (+); samples with AID mRNA levels at or below control levels can be classified as AID negative (-) categories. AID expression data can be integrated with clinical diagnostic information, especially the surface Ig and somatic hypermutation status. Within the AID+ category samples can be ranked according to AID mRNA expression level, and the presence or absence of somatic hypermutation in Ig loci, determined by standard clinical surrogate markers or by direct sequencing following sample collection.

Example 12: Sequencing to measure AID activity

[00420] The basis for genetic chemotherapy is AID activity in tumor cells. Therefore genome sequence analysis can be carried out to measure AID mutational activity. It is known that AID acts at Igh (the major physiological target), and at a host of non-Ig genes including Myc, Bcl6, Bcl11a (all frequently targeted oncogenes), CD93, and many others varying frequencies. A robotic capture system can be used to isolate genomic DNA flanking promoter elements (1-2 kb per gene) for all known human protein coding genes – approximately 26,000 genes. In this way, both known and unknown AID targets, as well as non-targeted (negative control) genes can be analyzed. All captured sequences can be bar-coded and

multiplexed (2-4 samples per lane) for sequencing using a HiSeq instrument (Illumina, San Diego, CA). Because a standard HiSeq lane currently gives more than 20 billion nucleotides of sequence, 4X multiplexing can provide sufficient coverage to detect mutations occurring in any single gene at less than 2% frequency (see analytic strategy, below). The known AID targets (IGH (NCBI Gene ID 3492), BCL6 (NCBI Gene ID 604), MYC (NCBI Gene ID 4609), BCL11A (NCBI Gene ID 53335), CD93 (NCBI Gene ID 22918), PIM1 (NCBI Gene ID 5292) and/or PAX5) as well as MEF2B CD93 (NCBI Gene ID 100271849) and LTB (NCBI Gene ID 4050), two genes very rarely targeted by AID for either point mutations or DNA breaks (negative controls) can be analyzed. This is approach is ideal for detecting non-selected somatic mutations in heterogeneous cell populations containing a mix of tumor and non-tumor cells. After alignment of sequences to the human reference genome sequence using Burrows-Wheeler Aligner (BWA), spontaneously occurring somatic mutations can be identified as sequence differences that: (1) occur in at least two independent reads per sample, and are thus unlikely to be sequencing error; and (2) occur with a frequency of less than 50%, and thus are non-clonal somatic events, rather than germ-line polymorphisms (Bioinformatics 2009, 25(14): 1754-60). For most samples non-CLL cells can be sorted from the blood of many patients to use as an internal, patient-specific sample against which AID-dependent tumor mutation rates can be measured.

Table 1: Chromosomal damage in XKD cells. Karyotypes of CH12-F3 cells, a mouse lymphoma cell line, transduced with control shRNA (CH12-Ctrl) and CH12-XKD cells left untreated (no culture supplement) or cultured under non-activating conditions (anti-CD40) or activating conditions (anti-CD40 plus IL-4 plus TGF-β):

	CH12-Ctrl			CH12-XKD		
	Untreated	Nonactivated	Activated	Untreated	Nonactivated	Activated
Cells with breaks (%)	13	9	21	29	29	76
Chromosomes (average)	40	41	40	40	41	39
Metaphases	23	22	24	21	21	21

Example 13: DIDS radiosensitizes primary mouse B

[00421] Primary mouse splenic B-cells were isolated from normal, wild-type C57BL/6J mice as described in Example 1 and sorted with magnetic beads (Miltenyi) to enrich B220+ IgM+ B-cells. Purified B-cells were cultured in complete RPMI-1640 medium with 10% FBS with 0, 50, 100, or 150 micromolar DIDS. Cells were then subjected to either

0 (Fig. 14, filled circles) or 2.5 Gy (=250 rads; Fig. 14, open circles) of gamma irradiation in a Cs137 irradiator. Cell viability was subsequently scored for each condition and plotted relative to the no DIDS condition by manual cytometry using a hemacytometer and Trypan blue dye exclusion 24 hours after irradiation. The fraction of viable cells is reported normalized to the corresponding 0 μM DIDS condition. Error bars represent the standard error of the mean (S.E.M) from three independent experiments. The data show that irradiation treatment combined with DIDS reduces viability significantly starting at a concentration of 50 micromolar DIDS.

Example 14: DIDS synergizes with AID (AICDA) to inhibit growth and impair survival of transformed B-cells

[00422] The mouse B-lymphoid leukemia cell line CH12-F3 was cultured in RPMI-1640 medium supplemented with 2-10 mM L-glutamine (Gibco), 10% (vol/vol) heat-inactivated fetal bovine serum (Omega Scientific) and 5% (vol/vol) NCTC 109 media (Gibco) (complete RPMI; non-activated) or complete RPMI-1640 medium containing 1 μg/ml anti-CD40 antibody, 25 ng/ml IL-4 and 1 ng/ml transforming growth factor beta 1 (TGF-beta1) (activated). Cultures were supplemented with 0, 50, 100, or 150 micromolar DIDS, and total cell counts were determined by manual cytometry after 0, 1, 2, 3, 4, or 6 days in culture. In Figure 15A the non-activated cells treated with the various DIDS concentrations show no difference in cell viability or cell proliferation. In contrast, a strong decrease of total cell number was observed in activated CH12-F3 cells exposed to 150 micromolar DIDS (Figure 15B).

Example 15: DIDS treatment prevents repair of AID generated DNA damage

[00423] Mouse primary splenocytes isolated from 8-12 week old wild type (AID+/+) and AID-knockout (AID-/-) mice as described in Example 1 were exposed to 150 micromolar DIDS, and activated by anti-CD40 antibody plus interleukin-4, fixed and stained for the DNA break marker phospho-H2AX and for nuclear DNA using the fluorescent DNA staining dye 4',6-diamidino-2-phenylindole (DAPI). In Figure 16A the fraction of cells containing 0, 1-2, or greater than 2 phospho-H2AX positive foci was quantified for AID+/+ (filled bars) and AID-/- (open bars) cells. A significant higher fraction of cells with greater than 2 foci was observed specifically in the DIDS-treated AID+/+ cells. In Figure 16B the proportion of phospho-H2AX positive cells (filled bars) versus phospho-H2AX negative cells (open bars) was quantified for AID+/+ in comparison to AID-/- cultures. AID+/+ cells show a higher percentage of phospho-H2AX positive cells. In Figure 16C the number of foci per cell was quantified for DIDS-treated AID+/+ (filled bars) versus AID-/- (open bars) cells. Data are

expressed as the absolute number of cells (y-axis) harboring the indicated number of phosphor-H2AX foci (from 0 to >20; x-axis).

Example 16: AID (AICDA) expression status is a biomarker that identifies candidate patients for genetic chemotherapy

[00424] AID (AICDA) expression status combined with IGVH hypermutation status is a biomarker that further stratifies candidate patients for genetic chemotherapy. In standard practice, IGVH mutation-positive (greater that 2% deviation from reference sequence) CLL is associated with generally better prognosis that IGVH mutation negative (less than 2% deviation from reference sequence). Genomic DNA was isolated from primary human chronic lymphocytic leukemia (CLL) cells, specific IGVH segments amplified by PCR, and sequenced using standard Sanger sequencing. Primer sequences for amplification of IGVH gene segments are:

VH1-FR1 5'-GGCCTCAGTGAAGGTCTCCTGCAAG-3' (SEQ ID NO:107);

VH2-FR1 5'-GTCTGGTCCTACGCTGGTGAAACCC-3' (SEQ ID NO:108);

VH3-FR1 5'-CTGGGGGGTCCCTGAGACTCTCCTG-3'(SEQ ID NO:109);

VH4-FR1 5'-CTTCGGAGACCCTGTCCCTCACCTG-3' (SEQ ID NO:110);

VH5-FR1 5'-CGGGGAGTCTCTGAAGATCTCCTGT-3'(SEQ ID NO:111);

VH6-FR1 5'-TCGCAGACCCTCTCACTCACCTGTG-3' (SEQ ID NO:112);

JH consensus 5'-CTTACCTGAGGAGACGGTGACC (SEQ ID NO:113).

Mutations were identified as nucleotide differences relative to the reference genome sequence, and quantified as a percentage of total nucleotides. Mutation-positive samples were identified, per clinical diagnostic standards, as samples with greater than 2% deviation from reference. Mutation positive samples in Table 2 are JE1010, JE1014, JE1015, JE1021, JE1030, JE1048 and JE1061. The sample JE1050 shows no mutations. The samples JE1010, JE1014, JE1048 and JE1050 were also positive for AID expression.

Table 2: IgVH Hypermutation Analysis

CDR2 (IGVH4-34)		SEQ ID NO
Germline	GAAATCAATCATAGTGGAAGCACCAACTACAACCCGTCCCTCAAGAGT	147
JE1010(AID+)	GATATCAGTCATAGTGGCATCCCCAAGTACAACCCGTCCCTCAAGAGT	148

JE1014(AID+)	GAAATCAATCATGGTGGAAATCCCAACTACAACCCGTCTCTCAGGAGC	149
JE1015(AID-)	GAAATCAATCATGTTGGAAGTACCACCTACAACCCCTCCCTCAAGAGT	150
JE1021(AID-)	GCAATCAATAATAGTGGAAACACCTTGTTCACCCCATCCCTCACGAGT	151
JE1030(AID-)	GAAATCAATCACAGTGGAAGAACCAACCACAACCCGTCCCTCAGGAGT	152
JE1048(AID+)	GAAACCTATCATAGTGCATACACCAAGTACAGCCCGTCCCTCCAGGGT	153
JE1061(AID-)	GAGATCGATTATAGTGGAAACGCCAACTACAACCCGTCCCTCAAGAGT	154
JE1050(AID+)	GAAATCAATCATAGTGGAAGCACCAACTACAACCCGTCCCTCAAGAGT	155

Example 17: DIDS synergizes with AID (AICDA) to reduce survival of CLL cells

[00425] AID-expressing (AID+) or AID-negative (AID-) primary human CLL cells were cultured as described in Example 4. Cells were cultured in basic RPMI-1640 medium without supplementation (untreated; triangle in Figure 17) or with 30 micromolar DIDS. Open circles represent the data for AID-negative cells treated with 30 micromolar DIDS and filled boxes represent the data for AID-positive cells treated with 30 micromolar DIDS. The cell survival was scored by manual cytometry for viable cells after 2, 4, or 8 days of exposure. The untreated and the DIDS-treated AID- cells cultures were indistinguishable, whereas the DIDS-treated AID+ cultures showed reduced cell viability.

Example 18: Use of AID expression as a biomarker identifies CLL patients that respond to genetic chemotherapy by DIDS

[00426] Four individual AID-expressing (AID+) human CLL samples (JE1010, JE1036, JE1070, JE1075) and four individual AID-negative (AID-) human CLL samples (JE1015, JE1019, JE1031, JE1057) were identified using reverse-transcription (RT)-PCR with oligonucleotide primers specific to either human AID or human GAPDH (loading control). RT-PCR was done with the One-Step RT-PCR kit according to manufacturer's protocols (Qiagen). The oligonucleotide primers and PCR conditions used to detect *Xrcc2* and *GAPDH* have been described (Deans et al., EMBO J 2000 19:6675-6685). As a specificity control for knockdown studies, the related gene *Rad51* was detected by RT-PCR. Oligonucleotides to detect AID transcripts were hAID fwd 5'-TCCTTTTCACTGGACTTTGG-3' (SEQ ID NO:101); and hAID rev 5'-GACTGAGGTTGGGGTTCC-3' (SEQ ID NO:102). RT-PCR with these primers produces a

196bp reaction product specific for human AID. Oligonucleotides to detect human *GAPDH* were 5'-ACCACAGTCCATGCCATCAC-3' (SEQ ID NO:105) and 5'-TCCACCACCCTGTGGCTGTA-3' (SEQ ID NO:106) producing a 238 bp reaction product. Reverse transcription and PCR conditions were Step 1. 50 °C, 30 min; Step 2. 95 °C, 15 min; Step 3. 94 °C, 1 min; Step 4. 55 °C, 30 sec; Step 5. °C, 1 min; Step 6. Cycle steps 3-5, 35 times; Step 7. 72 °C, 10 min; Step 8. 4 °C, and hold indefinitely.

[00427] The RT-PCR products were separated by electrophoresis on a 1.0% agarose gel (with ethidium bromide) and were visualized with a Bio-Rad Gel Doc system.

[00428] This assay rapidly and sensitively identifies AID+ and AID- patient samples as shown in Figure 18A, where 8 representative samples are shown. Eight AID+ and eight AID- CLL samples were cultured in basic RPMI-1640 medium plus 30 micromolar DIDS, and survival was scored by manual cytometry for viable cells after 2, 4, 6, or 8 days. This analysis revealed that DIDS more strongly reduces cell viability in AID-positive than in AID-negative primary human CLL cells. This also reveals that AID expression, as a single marker, effectively identifies DIDS-responsive samples. When CLL cells expressing AID were treated with 10 μM DIDS significant effects on cell viability have been determined. A total of 117 lymphoma or leukemia patients were studies, of which 106 were CLL patients. In 47 % AID expression was determined by RT-PCR.

Example 16: Effect of DIDS on mouse systemic lupus erythematosus (SLE) model

[00429] BXSB.Yaa Cd8/IL15-/- mice are an established model for SLE. These mice display many characteristics of human SLE including hypergammaglobulinemia, circulating antinuclear antibodies and immune complex medicated glomerulonephritis, and ultimately succumb to disease around 24 weeks of age (Andrews et al. 1978, *J Exp Med* 148: 1198-215; Dixon et al. 1978, *Arthritis Rheum* 21: S64-7; Izui et al. 2000, *Int Rev Immunol* 19: 447-72). Genetic deletion of *Cd8a* and *IL15* from the model results in a similar clinical phenotype which appears much early with survival averaging 14 weeks of age (McPhee et al. 2011, *J Immunol* 187:4695-4704)

[00430] Six week old male BXSB.Cg-Cd8a<tm1Mak> IL15<tm1Imx>/Dcr (abbreviated as BXSB.Yaa Cd8/IL15-/-) mice were retro-orbitally bled into heparin primed tubes to collect serum. 25mg/kg (n=5) or 50 mg/kg DIDS (n=6) in 4% potassium bicarbonate with PBS or an equivalent volume of 4% potassium bicarbonate (n=2 and n=4) was administered intraperitoneally on day 0, and every seven days for five weeks. Mice were weighed weekly and serum was collected at 14 day intervals for a 5-week period. These mice were then aged for survival. The serum was analyzed by ELISA for IgG1 and IgG2b content.

For the ELISA plates were coated with goat anti-mouse Ig (IgG1 or IgG2b) and incubated overnight at 40 °C. Plates were washed and serum samples were applied at appropriate dilutions along with mouse isotype standards and incubated for 1 hour at 37 °C. Plates were washed three times and incubated with goat anti-mouse antibody conjugated to alkaline phosphatase for 1 hour. Plates were washed three times and P-nitrophenyl Phosphate (p-NPP, AMRESCO) was applied, incubated until standards developed adequately and read on a SpectraMax ELISA plate reader using SoftmaxPro software. Data are expressed as concentration of IgG (mg/ml) based on titration of isotype-specific purified mouse standards. Figure 19A shows no weight difference between controls and treated animals. However, the analysis of IgG2b showed a striking decrease indicating being effective for lupus treatment (Figure 20B). No significant difference was observed for IgG1 (data not shown). Survival data was analyzed using Graphpad Prism software and assessed for statistical significance using both the log-rank Mantel Cox with (Fig. 20A for the 25 mg/kg group with a p value of 0.4289 and Fig. 20B for the 50 mg/kg group with a p value of 0.3698) and Gehan-Breslow-Wilcoxan tests (Fig. 21A for the 25 mg/kg group with a p value of 0.7003 and Fig. 21B for the 50 mg/kg group with a p value of 0.7505).

Example 17: DIDS disrupts RAD51 focus formation after DNA damage

[00431] Primary mouse B-cells were isolated from spleen of wild type C57BL/6J mice by magnetic bead based sorting (Miltenyi) to purify B220+ IgM+ B-cells. B-cells were then cultured in standard RPMI-1640 medium supplemented with 10% FBS in the presence of either 0 or 150 μM DIDS, exposed to 0 or 2.5 Gy ionizing radiation in a Cs137 irradiator, and then stained by immunofluorescence for foci of the homologous recombination factor RAD51. The fraction of cells in each culture showing formation of RAD51 foci within the nucleus is reported. Irradiated cells not cultured with DIDS (0 μM) show efficient focus formation. DIDS exposure (150 μM) completely inhibits radiation-induced RAD51 focus formation, reducing the fraction of Rad51 focus+ cells to baseline levels (equivalent to those in the unirradiated, 0 Gy samples) as shown in Figure 22. Error bars show the standard error of the mean (S.E.M) from three independent experiments.

Example 18: DIDS treatment leads to increased levels of phospho-H2AX foci preferentially in AID-expressing primary human chronic lymphocytic leukemia (CLL) cells.

[00432] Primary human CLL patient derived cells were obtained from peripheral bleeds collected at the time of routine clinical monitoring. Primary peripheral blood samples were collected via routine venipuncture into BD Vacutainer CPT Cell Separation Tubes

(Becton Dickinson). Samples were centrifuged to separate red blood cells (RBC) and then inverted to resuspend the monocuclear cells in their own plasma. Samples were stored overnight at the site of collection at room temperature then shipped via courier to the site of analysis. Each sample was tested for AID expression status by reverse transcription PCR (RT-PCR) to detect presence of the human AID mRNA (see Example 11). Samples were then divided into AID+ (those showing detectable levels of AID mRNA) and AID- (those showing no detectable AID mRNA above background) groups. Multiple independent cultures from different AID+ and AID- samples were initiated in standard RPMI-1640 medium containing 10% FBS plus either 0 or 30 μM DIDS. After 2 days in culture, cells from each culture/condition were fixed using paraformaldehyde, mounted on microscope coverslips, permeabilized by washing with weak detergent, and were processed for immunofluorescent detection of the DNA double strand break marker phosphor-H2AX (primary antibody: cat. No. A300-081A, Bethyl Laboratories; 1:400 dilution). After staining, cells were imaged using a Nikon 90i upright epifluorescence microscope and 100 individual nuclei were imaged for each sample. Nuclear DNA was counterstained with 4',6-diamidino-2-phenylindole (DAPI). The average percentage of cells showing 1-2 (Low), 3-10 (Mod.), or greater than 10 (High) phosphor-H2AX foci is shown in Figures 23 A and B. Error bars represent the standard error of the mean (S.E.M.) for 4 independent cultures of the AID- (open bars) samples and 5 independent cultures of the AID+ samples (filled bars). These data show that DIDS inhibits repair of AID-mediated genomic DNA double strand breaks (DSBs).

Example 19: DIDS treatment leads to apoptosis preferentially in AID+ primary human CLL cells.

[00433] Primary human CLL patient derived cells were obtained from peripheral bleeds collected at the time of routine clinical monitoring. Primary peripheral blood samples were collected via routine venipuncture into BD Vacutainer CPT Cell Separation Tubes. Samples were centrifuged to separate red blood cells (RBC) and then inverted to resuspend the mononuclear cells in their own plasma. Samples were stored overnight at the site of collection at room temperature then shipped via courier to the site of analysis. Each sample was tested for AID expression status by reverse transcription PCR (RT-PCR) to detect presence of the human AID mRNA (see Example 11). Samples were then divided into AID+ (those showing detectable levels of AID mRNA) and AID- (those showing no detectable AID mRNA above background) groups. Multiple independent cultures from different AID+ and AID- samples were initiated in standard RPMI-1640 medium containing 10%FBS plus either 0 or 30 μM DIDS. After 3 days in culture, cells from were fixed with paraformaldehyde,

mounted on microscope coverslips, permeabilized by washing with weak detergent, and processed for immunofluorescent detection of the apoptosis marker activated caspase 3 (AC3) (primary antibody: cat. No. ab13847, Abcam; 1:100 dilution). Nuclear DNA was counterstained with 4',6-diamidino-2-phenylindole (DAPI). After staining, cells were imaged using a Nikon 90i upright epifluorescence microscope. The fraction of cells showing positive staining for AC3 is shown for AID+ (Fig. 24, filled bars) and AID- samples (Fig. 24, open bars). Error bars represent standard error of the mean (S.E.M.) for 4 independent cultures of the AID- samples and 5 independent cultures of the AID+ samples. AID positive cells treated with 30 μM DIDS show a higher fraction of AC3-positive cells.

Example 20: AID expression and its association with primary human chronic lymphocytic leukemia prognosis.

[00434] AID expression is associated with worse overall disease in primary human chronic lymphocytic leukemia. Eight individual AID+ and 8 individual AID- primary human CLL samples were selected on the basis of high white blood cell (WBC) count (greater than 58,000 per microliter). These were then analyzed for mean and median age at diagnosis (Age @ Dx) and for treatment. AID+ samples showed a lower mean age (63.75 versus 68 years) and median age (62.5 versus 68.5 years) at diagnosis (Table 3). Moreover, 4/8 AID+ patients received treatment whereas 1/8 AID- patients received treatment.

Table 3: Human CLL samples analyzed AID expression

	ID	WBC	% lymph	sex	Age @ Dx	treatment
AID-	JE1015 (1)	20.4	58.1	M	86	None
	JE1019 (1,2,3)	102.5	95.8	M	76	None
	JE1031 (1)	32.6	80.7	F	47	None
	JE1056 (2,3)	68.1	91.1	M	70	None
	JE1057 (1)	31.3	81.3	F	64	None
	JE1069 (2,3)	44.1	91.7	M	53	Chloram.
	JE1088 (2,3)	135.4	93.5	M	67	None
	JE1095 (2,3)	80.7	90.0	M	81	None
					Mean 68	
					Median 68.5	
AID+	JE1010 (1)	43.6	83.2	F	51	None
	JE1036 (1)	22.6	65	M	63	None
	JE1044 (2,3)	55.3	93.7	F	57	IgG
	JE1045 (2,3)	17.1	68.7	M	62	Flud.
	JE1046 (2,3)	47.8	89.5	M	79	None
	JE1070 (1,2,3)	78.3	91.0	M	53	Chloram.
	JE1075 (1)	39.3	87.6	F	72	None
	JE1098 (2,3)	41.2	86.0	F	73	Chloram.
					Mean 63.75	
					Median 62.5	

Example 21: In vivo testing of AID in a mouse model

[00435] To test the in vivo effectiveness of DIDS, either AID+/+ (C57BL/6) or AID-/- mice (Muramatsu et al. et al., 2000 supra) were administered DIDS (10 mg/kg or 50 mg/kg) at weekly intervals, immunized at weeks 1 with dinitrophenol conjugated Keyhole limpet hemocyanin (DNP-KLH) in complete Freund's adjuvant (CFA) to stimulate lymphocyte activation, and boosted after 4 weeks with DNP-KLH (in incomplete Freund's adjuvant, IFA). After a total of 7 weeks (Fig. 25A) mice were euthanized. The group size was n=5. No animals in either the control or DIDS-treated groups showed overt signs of toxicity, relative to the untreated control groups. After 5 weeks, the AID+/+ mice showed slightly greater weight gain than the AID-/- mice, but this effect was independent of DIDS exposure, affecting the 0 mg/kg control and 50 mg/kg experimental cohorts equally (Fig. 25B). For this the mice were weighed weekly and the data represent the average fractional change in body mass for five animals, and error bars denote S.E.M.

[00436] After the 7-week trial window, tissues from treated and control animals were fixed, sectioned, and analyzed after hematoxylin and eosin (H&E) staining. Analysis of spleen sections revealed no gross anatomical defects or differences in germinal center (GC) architecture between untreated and DIDS-treated animals, and no differences between AID+/+ mice and AID-/- controls. These data suggest that DIDS, at least up to 50 mg/kg, does not induce significant toxicity or general defects in splenic physiology in either AID+/+ or AID-/- mice. To determine whether DIDS induced a B-cell specific phenotype related to AID, bone marrow, spleen, and peripheral blood, from DIDS-treated AID+/+ versus AID-/- mice, were analyzed for the presence of B220+CD19+ B-cells, by flow cytometry (Figure 26). A small (25%) reduction in B220+CD19+ B-cells was observed in the bone marrow of both 10μM and 50μM treated AID+/+ mice, but no consistent differences in the percentages of splenic B-cells in either AID+/+ or AID-/- mice. By contrast, both 10μM and 50μM DIDS induced a significant (9-11 fold) reduction in circulating B-lymphoid cells, specifically in AID+/+ but not AID-/- mice. In Figure 26 the endpoint flow cytometry dot plot analysis of bone marrow, spleen, and peripheral blood from AID-/- and AID+/+ mice immunized with DNP-KLH and treated with 0, 10, or 50 mg/kg DIDS is shown. Plots represent the population of cells in the lymphocyte gate stained for expression of B220 (y-axis) and CD19 (x-axis). The numbers in the upper right corner of each plot provide the percentage of B220+/CD19+ cells for each analysis. The progression of B-cell maturation from early/pre-GC to post-GC is indicated below.

[00437] These data suggest that in vivo, systemic DIDS treatment selectively affected mature, post-germinal center B-cells, but had a negligible effect on early or pre-GC B-cells. This is consistent with the cell culture data described herein demonstrating a synergistic cytotoxicity induced by the combined effects of AID and DIDS. Significantly, none of the DIDS treated animals, in either the AID+/+ or AID-/- cohort, showed evidence of overt non-B-cell toxicity. Taken together, these data strongly imply that in vivo administration of DIDS specifically sensitizes AID-expressing B-cells – those undergoing germinal center reactions or ectopically expressing AID.

Example 22: AID expression analysis in Epstein-Barr virus transformed peripheral human B-lymphocytes

[00438] Epstein-Barr virus transformed peripheral human B-lymphocytes derived cell lines GM05881, GM07323, and GM13689 (obtained from Corriell Institute, NIGMS Human Genetic Cell Repository) are a good representation of human non-Hodgkin's lymphoma. These cells were cultured in RPMI1640 medium supplemented with 2mM glutamine and 15 % fetal bovine serum. Total RNA was prepared from each of the cultured cell lines, or from human primary stimulated B-cells (Stim B), or from the human embryonic kidney cell line HEK293T by standard ribonucleic acid extraction methods (see Example 11). RNA was then analyzed by reverse-transcription (RT)-PCR for the AID transcript using the same primers as described in Example 11, and for the GAPDH transcript (loading control). These data show that AID is highly expressed in these transformed B-cell lines, at levels even higher than those in purified, activated primary B-cells (see Figure 27).

Table 4: SEQ ID NOs

SEQ ID NO	Description
001	BCL6 mRNA; NM_001130845
002	MYC mRNA; NM_002467
003	BCL11A mRNA;NM_018014
004	CD93 mRNA; NM_012072
005	PIM1 mRNA; NM_002648
006	PAX5 mRNA; NM_016734
007	Rad51AP1 mRNA; NM_001130862
008	Rad51B mRNA; NM_002877
009	Rad51D mRNA; NM_002878
010	XRCC2 mRNA; NM_005431
011	XRCC3 mRNA; NM_001100119
012	RAD54 mRNA; NM_000489

013	RAD52 mRNA; NM_134424
014	BRCA1 mRNA; NM_007300
015	BRCA2 mRNA; NM_000059
016	ATM mRNA; NM_000051
017	ATR mRNA; NM_001184
018	MRE11 mRNA; NM_005591
019	RAD50 mRNA; NM_005732
020	NBS1 mRNA; NM_002485
021	WRN mRNA; NM_000553
022	BLM mRNA; NM_000057
023	RECQ4 mRNA; NM_004260
024	LIG4 mRNA; NM_001098268
025	XRCC4 mRNA; NM_003401
026	PRKDC mRNA; NM_006904
027	DCLRE1C mRNA; NM_001033855
028	XRCC6 mRNA; NM_001469
029	XRCC5 mRNA; NM_021141
030	XLF mRNA; NM_024782
050	XRCC2 inhibitory RNA
051	XRCC2 inhibitory RNA
052	XRCC2 inhibitory RNA
053	XRCC2 inhibitory RNA
054	XRCC2 inhibitory RNA
055	XRCC2 inhibitory RNA
056	XRCC2 inhibitory RNA
057	XRCC2 inhibitory RNA
058	XRCC2 inhibitory RNA
059	XRCC3 inhibitory RNA
060	XRCC3 inhibitory RNA
061	XRCC3 inhibitory RNA
062	XRCC3 inhibitory RNA
063	XRCC3 inhibitory RNA
064	RAD51 inhibitory RNA
065	RAD51 inhibitory RNA
066	RAD51 inhibitory RNA
067	RAD51 inhibitory RNA
068	RAD51 inhibitory RNA
069	RAD51 inhibitory RNA
070	RAD51 inhibitory RNA
071	RAD51 inhibitory RNA
072	RAD51 inhibitory RNA
073	RAD51B inhibitory RNA
074	RAD51B inhibitory RNA
075	RAD51B inhibitory RNA
076	RAD51B inhibitory RNA
077	RAD51B inhibitory RNA
078	RAD51B inhibitory RNA

079	RAD51B inhibitory RNA
080	RAD51B inhibitory RNA
081	RAD51C inhibitory RNA
082	RAD51C inhibitory RNA
083	RAD51C inhibitory RNA
084	RAD51C inhibitory RNA
085	RAD51C inhibitory RNA
086	RAD51C inhibitory RNA
087	RAD51C inhibitory RNA
088	RAD51C inhibitory RNA
089	RAD51C inhibitory RNA
090	RAD51D inhibitory RNA
091	RAD51D inhibitory RNA
092	RAD51D inhibitory RNA
093	RAD51D inhibitory RNA
094	RAD51D inhibitory RNA
095	RAD51D inhibitory RNA
096	RAD51D inhibitory RNA
097	RAD51D inhibitory RNA
098	RAD51D inhibitory RNA
099	AID amino acid sequence; NCBI Ref Seq: NP_065712
0100	AID mRNA sequence; NCBI Ref Seq: NP_020661
0101	hAID forward primer
0102	hAID rev primer
0103	hGAPDH fwd primer
0104	hGAPDH rev primer
0105	GAPDH primer
0106	GAPDH primer
0107	VH1-FR1
0108	VH2-FR1
0109	VH3-FR1
0110	VH4-FR1
0111	VH5-FR1
0112	VH6-FR1
0113	JH consensus
0114	Rad51AP1 amino acid sequence; NCBI Ref: NP_001124334
0115	RAD51B amino acid sequence; NCBI Ref: NP_002868
0116	RAD51D amino acid sequence; NCBI Ref: NP_001136043
0117	XRCC2 amino acid sequence; NCBI Ref: NP_005422
0118	XRCC3 amino acid sequence; NCBI Ref: NP_001093588
0119	RAD54 amino acid sequence; NCBI Ref: NP_000480
0120	RAD52 amino acid sequence; NCBI Ref: NP_602296
0121	BRCA1 amino acid sequence; NCBI Ref: NP_009225
0122	BRCA2 amino acid sequence; NCBI Ref: NP_000050
0123	ATM amino acid sequence; NCBI Ref: NP_000042
0124	ATR amino acid sequence; NCBI Ref: NP_001175
0125	MRE11 amino acid sequence; NCBI Ref: NP_005582
0126	RAD50 amino acid sequence; NCBI Ref: NP_005723

0127	NBS1 amino acid sequence; NCBI Ref: NP_002476
0128	WRN amino acid sequence; NCBI Ref: NP_000544
0129	BLM amino acid sequence; NCBI Ref: NP_000048
0130	RECQ4 amino acid sequence; NCBI Ref: NP_004251
0131	LIG4 amino acid sequence; NCBI Ref: NP_001091738
0132	XRCC4 amino acid sequence; NCBI Ref: NP_071801
0133	PRKDC amino acid sequence; NCBI Ref: NP_008835
0134	DCLRE1C amino acid sequence; NCBI Ref: NP_001029027
0135	XRCC6 amino acid sequence; NCBI Ref: NP_001460
0136	XRCC5 amino acid sequence; NCBI Ref: NP_066964
0137	XLF amino acid sequence; NCBI Ref: NP_079058
0138	APOBEC1 amino acid sequence; NCBI Ref: NP_001635
0139	APOBEC2 amino acid sequence; NCBI Ref: NP_006780
0140	APOBEC3A amino acid sequence; NCBI Ref: NNP_663745
0141	APOBEC3C amino acid sequence; NCBI Ref: NP_055323
0142	APOBEC3E amino acid sequence; NCBI Ref: NP_689639
0143	APOBEC3F amino acid sequence; NCBI Ref: NP_660341
0144	APOBEC3G amino acid sequence; NCBI Ref: NP_068594
0145	APOBEC3H amino acid sequence; NCBI Ref: NP_001159475
0146	APOBEC4 amino acid sequence; NCBI Ref: NP_982279
0157	RAG1 mRNA sequence; NCBI Ref: NM_00448
0158	RAG1 amino acid sequence; NCBI Ref: NP_000439
0159	RAG2 mRNA sequence; NCBI Ref:NM_001243785
0160	RAG2 amino acid sequence; NCBI Ref: NP_001230714
0161	SPO11 mRNA sequence; NCBI Ref: NM_012444
0162	SPO11 amino acid sequence; NCBI Ref: NP_036576
0163	Rad51C isoform 1 mRNA sequence; NCBI Ref: NM_058216
0164	Rad51C isoform 1 amino acid sequence; NCBI Ref: NP_478123
0165	Rad51C isoform 2 mRNA sequence; NCBI Ref: NM_002876
0166	Rad51C isoform 2 amino acid sequence; NCBI Ref: NP_002867

What is claimed herein is:

1. A method of treatment comprising;

(d) obtaining a biological sample derived from a subject;

(e) measuring a level of a DNA editing enzyme; and

(f) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to a subject with a detectable level of a DNA editing enzyme.

2. A method of treatment comprising;

administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to a subject determined to have a detectable level of a DNA editing enzyme.

3. A method of treatment comprising;

(c) selecting a subject having cells that express an elevated level of a DNA editing enzyme; and

(d) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to the subject;

wherein the elevated level of the DNA editing enzyme is a level of DNA editing enzyme that is higher than the level of DNA editing enzyme in cells of the same type from a healthy individual.

4. The method of claim 1, wherein the biological sample comprises blood cells.

5. The method of claim 1, wherein the biological sample comprises B cells.

6. The method of any of claims 1-5, wherein the level of DNA editing enzyme in the cells expressing a detectable or elevated level of a DNA editing enzyme is statistically significantly higher than in normal cells from a healthy subject.

7. The method of claims 1-6, wherein the DNA editing enzyme is selected from the group consisting of:

recombination activating gene 1 (RAG1); recombination activating gene 2 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA

editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

8. The method of claim 7, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

9. The method of claim 8, wherein the level of activation-induced cytidine deaminase (AID) in B cells expressing an elevated level of AID is significantly higher than the level of AID expressed in unactivated B cells from a healthy subject

10. The method of any of claims 1-9, wherein the subject is a human subject.

11. The method of any of claims 1-10, wherein the biological sample or cells that express a detectable or elevated level of a DNA editing enzyme are cancerous cells.

12. The method of any of claims 1-11, wherein the subject has cancer.

13. The method of any of claims 1-11, wherein the biological sample or cells that express detectable or elevated level of a DNA editing enzyme are autoimmune cells.

14. The method of any of claims 1-13, wherein the subject has a condition selected from the group consisting of:

lymphoma, leukemia, and a plasma cell neoplasm.

15. The method of claim 14, wherein the lymphoma is selected from the group consisting of:

Non-Hodgkin's lymphoma; Burkitt's lymphoma, small lymphocytic lymphoma; lymphoplasmacytic lymphoma; MALT lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; and T-cell lymphoma.

16. The method of claim 14, wherein the leukemia is selected from the group consisting of:

acute lymphoblastic leukemia (ALL), Burkitt's leukemia; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); and T-cell acute lymphoblastic leukemia (T-ALL).

17. The method of claim 14, wherein the plasma cell neoplasm is selected from the group consisting of:

multiple myeloma; plasma cell myeloma; plasma cell leukemia; and plasmacytoma.

18. The method of claim 12, wherein the subject has a cancer selected from the group consisting of:

epithelial cell cancer; colon cancer, liver cancer, gastric cancer; intestinal cancer; esophageal cancer; breast cancer; lung cancer; and thyroid cancer.

19. The method of any of claims 1-10 and 13, wherein the subject has an autoimmune disease.

20. The method of claim 19, wherein the autoimmune disease is selected from the group consisting of:

lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, discoid lupus, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease.

21. The method of any of claims 1-20, wherein the inhibitor of DNA double strand break repair decreases the expression or activity of one or more genes selected from the group consisting of:

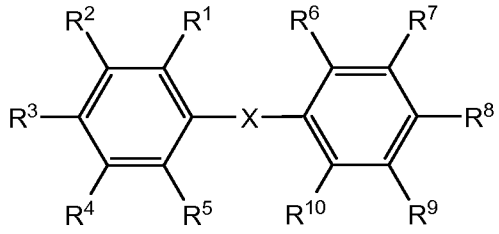
Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

22. The method of any of claims 1-21, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

a small molecule; a protein; a peptide; an antibody; an antibody fragment; a protein binding protein; a ribonucleic acid; a deoxyribonucleic acid; an aptamer; a peptide nucleic acid (PNA); and a locked nucleic acid (LNA).

23. The method of any of claims 1-20, wherein the inhibitor of DNA double strand break repair is stilbene, a stilbenoid, or a derivative thereof.

24. The method of claim 23, wherein the stilbene or stilbene derivative is a compound of Formula V:



Formula V

or a stereoisomer, enantiomer, prodrug, or pharmaceutically acceptable salt thereof;

wherein R^1 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^2 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^3 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^4 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^5 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^6 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched

C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^7 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

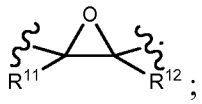
wherein R^8 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^9 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{10} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$,

optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein X can be selected from the group consisting of $C(R^{21})_2$, -C(O)N(R^{22})-, -C(O)-, -C(O)O-, -S(O)-, $-SO_2-$ $-CH(R^{11})CH(R^{12})-$, $-C(R^{11})=C(R^{12})-$, and



;

wherein R^{11} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{12} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein each R^{21} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted

heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof;

wherein each R^{22} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof.

25. The method of claim 21, wherein the stilbene derivative is 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS).

26. The method of claim 21, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))diacetamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methylpropanamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methoxyacetamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dimethanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dicyclopropanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-aminostyryl)phenyl)propane-2-sulfonamide; (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-methylthiourea); (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-isopropylthiourea); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)acetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)isobutyramide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)-2-methoxyacetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)methanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; N'-(4-{(E)-2-[4-(dimethylamino)phenyl]-1-ethenyl}phenyl)-N,N-dimethylsulfamide; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylthiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylthiourea; (E)-1-cyclopropyl-3-(4-

(4-(dimethylamino)styryl)phenyl)thiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylurea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylurea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)urea; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(methylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-cyclopropylthioureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-acetamido-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-isobutyramido-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(methylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-cyclopropylthioureido)-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-methylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-

(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-methylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N-isopropylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N,N-dimethylbenzamide); (E)-(ethene-1,2-diylbis(4,1-phenylene))bis(morpholinomethanone); (E)-5-(4-hydroxystyryl)benzene-1,3-diol(3,5,4'-trihydroxy-trans-stilbene); and resveratrol.

27. The method of claim 21, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; and (E)-5-

acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate.

28. The method of claim 20, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

4-methylquinazoline-2-carboxamide; benz[h]isoquinolin-6-amine; 5,6-dimethyl-2-mercaptomethylbenzimidazole; (E)-1-(2-hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one; N4-butyl-6-chloropyrimidine-2,4-diamine; 1-thermopsine; 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one; and 4-(2-amino-4-nitrophenylamino)phenyl.

29. The method of claim 20, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

7-azaindole-3-carboxaldehyde; 2-amino-4-phenylphenol; 3-(1-methyl-3-pyrrolidinyl)indole; 1-methyl-[1,2,4]Triazolo[4,3-a]quinolone; 2-amino-5-nitro-1H-benzimidazole; 2-(5-nitro-2-furfurylidene)aminoethanol-N-oxide; Nifuratrone; alpha-mercapto-N,2-naphthylacetamide; 1-thermospine; N4-butyl-6-chloro-2,4-pyrimidinediamine; 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid; 6-amino-5-nitroso-2-phenyl-1H-pyrimidin-4-one; 4-amino-2-hydroxyphenyl)arsonic acid; spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione; N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-diamine; 2-amino-9-pentyl-3H-purine-6-thione; 2-(4-methoxyphenyl)-3-(pyridin-3-yl)prop-2-enenitrile; 2-chloropyrimidine-4,6-dicarboxamide; 2-amino-3H-phenoxazin-3-one; 2-methyl-N-benzyl-7H-pyrrolo[2,3-d]pyrimidine-4-amine; 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-1-naphthalenesulfonic acid; N-sec-butyl-3-methylbenzamide; Benz[h]isoquinolin-6-amine; and 2-(2-methylcyclohexylidene) hydrazinecarboxamide.

30. The method of any of claims 1-20, wherein the inhibitor of DNA double strand break repair is an antibody or polypeptide comprising an antigen-binding fragment of an antibody or a protein binding protein.

31. The method of any of claims 1-20, wherein the inhibitor of DNA double strand break repair is an RNAi agent selected from the group consisting of:

miRNA; shRNA; siRNA; amiRNA; dsRNA, antisense RNA or ribozyme.

32. The method of any of claims 1-31, wherein the inhibitor of DNA double strand break repair further comprises a pharmaceutically acceptable carrier.

33. The method of any of claims 1-32, further comprising administration of a therapeutic agent.

34. The method of any of claims 1-33, wherein the subject having cells that express an a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having detectable or elevated levels.

35. The method of any of claims 1-34, wherein the subject having cells that express a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having elevated levels and comparing that level to the level of DNA editing enzyme polypeptide, mRNA, or activity found in a biological sample obtained from a healthy subject, wherein an increased amount of DNA editing enzyme polypeptide, mRNA, or activity in the test sample is indicative of a subject in need of treatment with an inhibitor of DNA double strand break repair.

36. The method of any of claims 34-35, wherein measuring the level of a DNA editing enzyme polypeptide comprises using one or more assays selected from the group consisting of:

Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay; protein in situ array; immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; *in situ* immunoassay; precipitation reaction; immunofluorescence assay; quantitative in situ protein analyses (AQUA); mass spectroscopy and immunoelectrophoresis assay.

37. The method of any of claims 34-36, wherein measuring the level of a DNA editing enzyme polypeptide comprises using an assay that uses an antibody, an antibody fragment, a protein binding protein, or a peptide which binds to the DNA editing enzyme polypeptide.

38. The method of any of claims 34-37, wherein the antibody or antibody fragment is a monoclonal antibody.

39. The method of any of claims 34-38, wherein the antibody, antibody fragment, protein binding protein or peptide which binds to the DNA editing enzyme polypeptide is labeled with a detectable label.

40. The method of any of claims 34-35, wherein measuring the level of a DNA editing enzyme mRNA comprises using one or more assays selected from the group consisting of:

RT-PCR; quantitative RT-PCR; hybridization assay; Northern blot; microarray based expression analysis; transcription amplification; self-sustained sequence replication; high throughput sequencing; and RNA-Seq.

41. The method of any of claims 1-40, wherein measuring the activity of a DNA editing enzyme activity comprises determining the overall mutation status of the genome or a portion thereof using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing;

wherein a mutation status 2% or greater than the normal mutation status indicates activity of a DNA editing enzyme.

42. The method of any of claims 35-36 or 41, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises determining the status of hypermutations in the target genes IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing.

43. The method of any of claims 35-36, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises using a phospho-H2AX assay, a 53BP1 assay, or a RAD51 assay.

44. A method of causing cell death comprising:

(e) administering to a cell an effective amount of a DNA editing enzyme; and

(f) thereafter contacting the cell of step (a) with an inhibitor of DNA double strand break repair,

thereby causing cell death.

45. A method of sensitizing a cell to cell death comprising:

(g) administering to a subject, a therapeutically effective amount of a DNA editing enzyme to sensitize a cell to cell death by use of an inhibitor of DNA double strand break repair: and

(h) thereafter administering to the subject an inhibitor of DNA double strand break repair.

46. The method of any of claims 44-44, wherein the DNA editing enzyme is administered in a form selected from the group consisting of:

a polypeptide; a nucleic acid encoding a DNA editing enzyme; and a vector comprising a nucleic acid encoding a DNA editing enzyme.

47. The method of any of claims 44-46, wherein the DNA editing enzyme is selected from the group consisting of:

recombination activating gene 1 (RAG1); recombination activating gene 1 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

48. The method of any of claims 44-47, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

49. A method of determining if a test agent is an inhibitor of DNA double strand break repair comprising;

a) contacting a cell expressing a DNA editing enzyme with a test agent; and

b) determining cell viability of the cells of step a);

wherein decreased cell viability indicates the test agent is an inhibitor of DNA double strand break repair.

50. The method of claim 49, further comprising;

c) contacting a cell not expressing a DNA editing enzyme with the test agent;

d) determining cell viability of the cells of step c); and

e) determining the ratio by dividing the fraction of live cells of step b) of by the fraction of live cells in step d;

wherein a ratio below 0.8 indicates the test agent is an inhibitor of DNA double strand break repair.

51. The method of any of claims 49-50, wherein the cell expressing a DNA editing enzyme is a cell expressing AID.

52. The method of claim 51, wherein the cell expressing AID is a stimulated B cell.

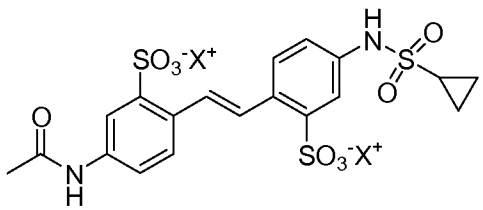
53. The method of any of claims 49-52, wherein the cell is a cancerous cell.

54. The method of any of claims 49-53, wherein the cells are transfected with a nucleic acid vector encoding a DNA editing enzyme.

55. The method of any of claims 49-54, wherein the cell is a cell line selected from the group consisting of CH12-F3, 3T3, CH12F3, Caco-2, CCRF-CEM, CHO, CH12-F3, COS-7, HCT 116, HEK 293, HL-60, HepG2, Jurkat, KG-1, K-562, MCF-7, MDCK, MG-63, Mo-B, MOLT-4, Ramos (RA 1) and U2-OS,

56. The method of any of claims 49-55, wherein the cell is an autoimmune cell.

57. A compound of Formula XXIV:



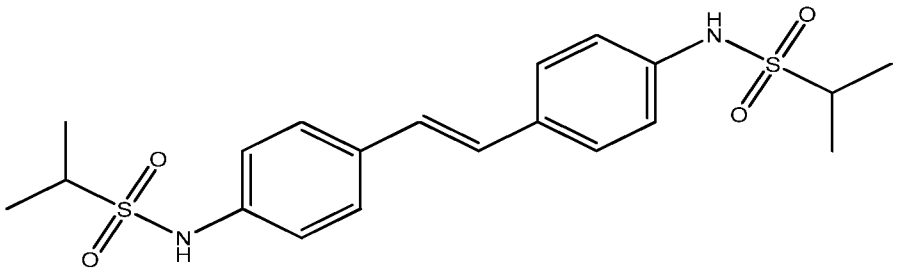
XXIV

a stereoisomer or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

58. The compound of claim 57, wherein X is sodium.

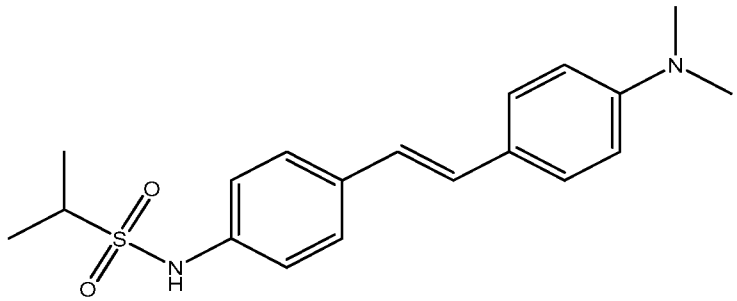
59. A compound of Formula VIII:



VIII

a stereoisomer, prodrug, or pharmaceutically acceptable salt thereof.

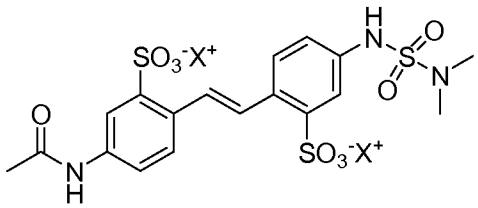
60. A compound of Formula X;



X

a stereoisomer, prodrug, or pharmaceutically acceptable salt thereof.

61. A compound of Formula XXV;



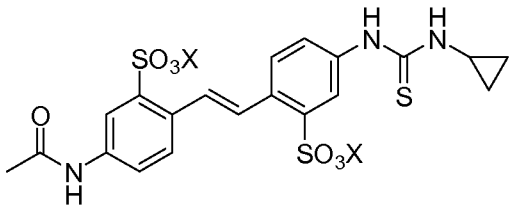
XXV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

62. The compound of claim 61, wherein X is sodium.

63. A compound of Formula XXXI;



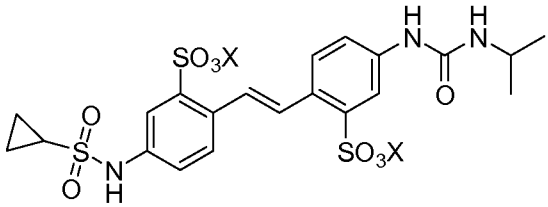
XXXI

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

64. The compound of claim 63, wherein X is sodium.

65. A compound of Formula XXXII;



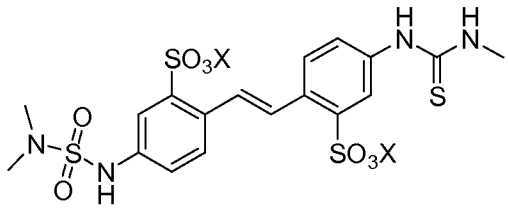
XXXII

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

66. The compound of claim 65, wherein X is sodium.

67. A compound of Formula XXXIII;



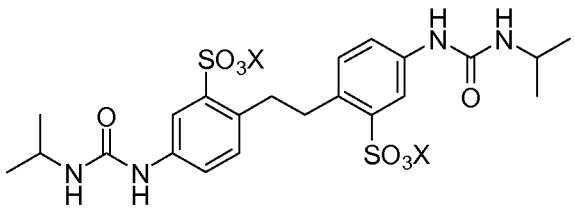
XXXIII

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

68. The compound of claim 67, wherein X is sodium.

69. A compound of Formula XXXIV;



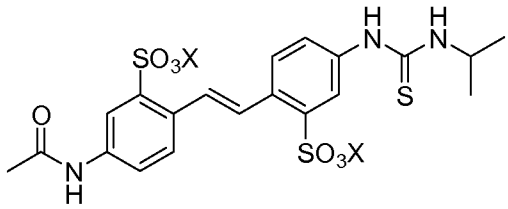
XXXIV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

70. The compound of claim 69, wherein X is sodium.

71. A compound of Formula XXXV;



XXXV

a stereoisomer, or prodrug thereof;

wherein X is sodium, potassium, aluminum, calcium, lithium, magnesium, barium, or zinc.

72. The compound of claim 71, wherein X is sodium.

73. The use of an inhibitor of DNA double strand break repair to treat a subject determined to have a detectable level of a DNA editing enzyme.

74. The use of claim 73, wherein the subject is determined to have a detectable level of DNA editing enzyme by;

(c) obtaining a biological sample derived from a subject; and

(d) measuring a level of a DNA editing enzyme.

75. The use of an inhibitor of DNA double strand break repair to treat a subject, the method comprising;

(c) selecting a subject having cells that express an elevated level of a DNA editing enzyme; and

(d) administering a therapeutically effective amount of an inhibitor of DNA double strand break repair to the subject;

wherein the elevated level of the DNA editing enzyme is a level of DNA editing enzyme that is higher than the level of DNA editing enzyme in cells of the same type from a healthy individual.

76. The use of claim 73, wherein the biological sample comprises blood cells.

77. The use of claim 73, wherein the biological sample comprises B cells.

78. The use of any of claims 73-77, wherein the level of DNA editing enzyme in the cells expressing a detectable or elevated level of a DNA editing enzyme is statistically significantly higher than in normal cells from a healthy subject.

79. The use of claims 73-78, wherein the DNA editing enzyme is selected from the group consisting of:

recombination activating gene 1 (RAG1); recombination activating gene 2 (RAG2); sporulation-specific protein 11 (SPO11); apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family member; and activation-induced cytidine deaminase (AID).

80. The use of claim 79, wherein the DNA editing enzyme is activation-induced cytidine deaminase (AID).

81. The use of claim 80, wherein the level of activation-induced cytidine deaminase (AID) in B cells expressing an elevated level of AID is significantly higher than the level of AID expressed in unactivated B cells from a healthy subject

82. The use of any of claims 73-81, wherein the subject is a human subject.

83. The use of any of claims 73-82, wherein the biological sample or cells that express a detectable or elevated level of a DNA editing enzyme are cancerous cells.

84. The use of any of claims 73-83, wherein the subject has cancer.

85. The use of any of claims 73-84, wherein the biological sample or cells that express detectable or elevated level of a DNA editing enzyme are autoimmune cells.

86. The use of any of claims 73-85, wherein the subject has a condition selected from the group consisting of:

lymphoma, leukemia, and a plasma cell neoplasm.

87. The use of claim 86, wherein the lymphoma is selected from the group consisting of:

Non-Hodgkin's lymphoma; Burkitt's lymphoma, small lymphocytic lymphoma; lymphoplasmacytic lymphoma; MALT lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; and T-cell lymphoma.

88. The use of claim 86, wherein the leukemia is selected from the group consisting of:

acute lymphoblastic leukemia (ALL), Burkitt's leukemia; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); and T-cell acute lymphoblastic leukemia (T-ALL).

89. The use of claim 86, wherein the plasma cell neoplasm is selected from the group consisting of:

multiple myeloma; plasma cell myeloma; plasma cell leukemia; and plasmacytoma.

90. The use of claim 86, wherein the subject has a cancer selected from the group consisting of:

epithelial cell cancer; colon cancer; liver cancer, gastric cancer; intestinal cancer; esophageal cancer; breast cancer; lung cancer; and thyroid cancer.

91. The use of any of claims 73-82 and 85, wherein the subject has an autoimmune disease.

92. The use of claim 91, wherein the autoimmune disease is selected from the group consisting of:

lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosis, discoid lupus, subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus including chilblain lupus erythematosus, chronic arthritis, Sjogren's syndrome, inflammatory chronic rhinosinusitis, colitis, celiac disease, inflammatory bowel disease, Barrett's esophagus, inflammatory gastritis autoimmune nephritis, autoimmune vasculitis, autoimmune hepatitis, autoimmune carditis, autoimmune encephalitis, and autoimmune mediated hematological disease.

93. The use of any of claims 73-92, wherein the inhibitor of DNA double strand break repair decreases the expression or activity of one or more genes selected from the group consisting of:

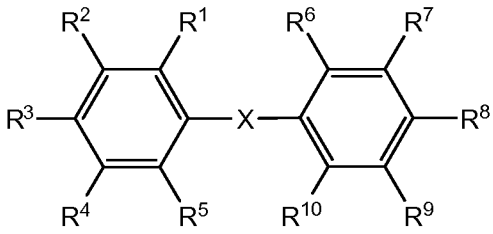
Rad51; Rad51AP1; Rad51B; Rad51C; Rad51D; XRCC2; XRCC3; RAD54; RAD52; BRCA1; BRCA2; ATM; ATR; MRE11; RAD50; NBS1; WRN; BLM; RECQ4; LIG4; XRCC4; PRKDC; DCLRE1C; XRCC6; XRCC5; and XLF.

94. The use of any of claims 73-93, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

a small molecule; a protein; a peptide; an antibody; an antibody fragment; a protein binding protein; a ribonucleic acid; a deoxyribonucleic acid; an aptamer; a peptide nucleic acid (PNA); and a locked nucleic acid (LNA).

95. The use of any of claims 73-93, wherein the inhibitor of DNA double strand break repair is stilbene, a stilbenoid, or a derivative thereof.

96. The use of claim 95, wherein the stilbene or stilbene derivative is a compound of Formula V:



Formula V

or a stereoisomer, enantiomer, prodrug, or pharmaceutically acceptable salt thereof;

wherein R^1 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched

C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^2 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^3 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^4 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^5 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$,

optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^6 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^7 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

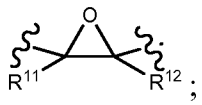
wherein R^8 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^9 can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S,

$NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{10} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$, N=C=S, $NHC(O)R^{21}$, $NHC(O)OR^{21}$, $NHC(S)R^{21}$, $NHC(S)N(R^{22})_2$, $NHSO_2R^{21}$, $NHSO_2N(R^{22})_2$, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein X can be selected from the group consisting of $C(R^{21})_2$, $-C(O)N(R^{22})-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-SO_2-$ $-CH(R^{11})CH(R^{12})-$, $-C(R^{11})=C(R^{12})-$, and



;

wherein R^{11} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21}, SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein R^{12} can be selected from the group consisting of hydrogen, halogen, CF_3, CN, $C(O)R^{21}$, CO_2R^{21}, $C(O)N(R^{22})_2$, OH, OR^{21}, $N(R^{22})_2$ $NC(O)R^{21}$, $NC(O)OR^{21}$, $NC(S)R^{21}$, $NC(S)N(R^{22})_2$, NSO_2R^{21}, NO_2, N_2-R^{22}, SOR^{21},

SO_2R^{21}, SO_3R^{21}, $OP(O)(OH)_2$, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein each R^{21} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof;

wherein each R^{22} can be selected independently from the group consisting of hydrogen, optionally substituted linear or branched C_1-C_{10} alkyl, optionally substituted linear or branched C_2-C_{10} alkenyl, optionally substituted linear or branched C_2-C_{10} alkynyl, optionally substituted cyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and any combinations thereof.

97. The use of claim 95, wherein the stilbene derivative is 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS).

98. The use of claim 95, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))diacetamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methylpropanamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(2-methoxyacetamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dimethanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))dicyclopropanesulfonamide; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-aminostyryl)phenyl)propane-2-sulfonamide; (E)-1,1'-(ethene-1,2-diylbis(4,1-phenylene))bis(3-methylthiourea); (E)-1,1'-(ethene-1,2-diylbis(4,1-

phenylene))bis(3-isopropylthiourea); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)acetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)isobutyramide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)-2-methoxyacetamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)methanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; N'-(4-{(E)-2-[4-(dimethylamino)phenyl]-1-ethenyl}phenyl)-N,N-dimethylsulfamide; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylthiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylthiourea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)thiourea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-methylurea; (E)-1-(4-(4-(dimethylamino)styryl)phenyl)-3-isopropylurea; (E)-1-cyclopropyl-3-(4-(4-(dimethylamino)styryl)phenyl)urea; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-acetamidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-isobutyramidobenzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(2-methoxyacetamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(methylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(cyclopropanesulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(1-methylethylsulfonamido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-((N,N-dimethylsulfamoyl)amino)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-cyclopropylthioureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); sodium (E)-5-acetamido-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-

isopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(methylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(1-methylethylsulfonamido)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-acetamido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-isobutyramido-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(methylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-ethylureido)-2-(4-(1-methylethylsulfonamido)-2-

sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-ethylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-isobutyramido-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(2-methoxyacetamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(cyclopropanesulfonamido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-methylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-cyclopropylthioureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-5-(3-isopropylureido)-2-(2-sulfonatostyryl)benzenesulfonate; sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-methylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylthioureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-ethylureido)benzenesulfonate); sodium (E)-6,6'-(ethene-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N-isopropylbenzamide); (E)-4,4'-(ethene-1,2-diyl)bis(N,N-dimethylbenzamide); (E)-(ethene-1,2-diylbis(4,1-phenylene))bis(morpholinomethanone); (E)-5-(4-hydroxystyryl)benzene-1,3-diol(3,5,4'-trihydroxy-trans-stilbene); and resveratrol.

99. The use of claim 95, wherein the stilbene or stilbene derivative is selected from the group consisting of:

(E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(propane-2-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)cyclopropanesulfonamide; sodium (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; (E)-N,N'-(ethene-1,2-diylbis(4,1-phenylene))bis(dimethylamino-sulfonamide); (E)-N-(4-(4-(dimethylamino)styryl)phenyl)propane-2-sulfonamide; sodium (E)-5-(3-cyclopropylthioureido)-2-(4-(1-methylethylsulfonamido)-2-sulfonatostyryl)benzenesulfonate; sodium 6,6'-(ethane-1,2-diyl)bis(3-(3-

isopropylureido)benzenesulfonate); sodium (E)-5-(3-ethylureido)-2-(4-(2-methoxyacetamido)-2-sulfonatostyryl)benzenesulfonate; (E)-4,4'-(ethene-1,2-diyl)bis(N-methylbenzamide); (E)-5-acetamido-2-(4-(3-cyclopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-(cyclopropanesulfonamido)-2-(4-(3-isopropylureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-((N,N-dimethylsulfamoyl)amino)-2-(4-(3-methylthioureido)-2-sulfonatostyryl)benzenesulfonate; 6,6'-(ethane-1,2-diyl)bis(3-(3-isopropylureido)benzenesulfonate); (E)-5-acetamido-2-(4-(3-isopropylthioureido)-2-sulfonatostyryl)benzenesulfonate; (E)-5-acetamido-2-(4-(cyclopropanesulfonamido)-2-sulfonatostyryl)benzenesulfonate; and (E)-5-acetamido-2-(4-((N,N-dimethylsulfamoyl)amino)-2-sulfonatostyryl)benzenesulfonate.

100. The use of claim 94, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

4-methylquinazoline-2-carboxamide; benz[h]isoquinolin-6-amine; 5,6-dimethyl-2-mercaptomethylbenzimidazole; (E)-1-(2-hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one; N4-butyl-6-chloropyrimidine-2,4-diamine; 1-thermopsine; 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one; and 4-(2-amino-4-nitrophenylamino)phenyl.

101. The use of claim 94, wherein the inhibitor of DNA double strand break repair is selected from the group consisting of:

7-azaindole-3-carboxaldehyde; 2-amino-4-phenylphenol; 3-(1-methyl-3-pyrrolidinyl)indole; 1-methyl-[1,2,4]Triazolo[4,3-a]quinolone; 2-amino-5-nitro-1H-benzimidazole; 2-(5-nitro-2-furfurylidene)aminoethanol-N-oxide; Nifuratrone; alpha-mercapto-N,2-naphthylacetamide; 1-thermospine; N4-butyl-6-chloro-2,4-pyrimidinediamine; 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid; 6-amino-5-nitroso-2-phenyl-1H-pyrimidin-4-one; 4-amino-2-hydroxyphenyl)arsonic acid; spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione; N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-diamine; 2-amino-9-pentyl-3H-purine-6-thione; 2-(4-methoxyphenyl)-3-(pyridin-3-yl)prop-2-enenitrile; 2-chloropyrimidine-4,6-dicarboxamide; 2-amino-3H-phenoxazin-3-one; 2-methyl-N-benzyl-7H-pyrrolo[2,3-

d]pyrimidine-4-amine; 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-1-naphthalenesulfonic acid; N-sec-butyl-3-methylbenzamide; Benz[h]isoquinolin-6-amine; and 2-(2-methylcyclohexylidene) hydrazinecarboxamide.

102. The use of any of claims 73-94, wherein the inhibitor of DNA double strand break repair is an antibody or polypeptide comprising an antigen-binding fragment of an antibody or a protein binding protein.

103. The use of any of claims 73-94, wherein the inhibitor of DNA double strand break repair is an RNAi agent selected from the group consisting of:

miRNA; shRNA; siRNA; amiRNA; dsRNA; antisense RNA or ribozyme.

104. The use of any of claims 73-103, wherein the inhibitor of DNA double strand break repair further comprises a pharmaceutically acceptable carrier.

105. The use of any of claims 73-104, further comprising administration of a therapeutic agent.

106. The use of any of claims 73-105, wherein the subject having cells that express an a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having detectable or elevated levels.

107. The use of any of claims 73-106, wherein the subject having cells that express a detectable or elevated level of DNA editing enzyme is identified by measuring the level of DNA editing enzyme polypeptide, mRNA, or activity in a biological sample obtained from the subject suspected of having elevated levels and comparing that level to the level of DNA editing enzyme polypeptide, mRNA, or activity found in a biological sample obtained from a healthy subject, wherein an increased amount of DNA editing enzyme polypeptide, mRNA, or activity in the test sample is indicative of a subject in need of treatment with an inhibitor of DNA double strand break repair.

108. The use of any of claims 106-107, wherein measuring the level of a DNA editing enzyme polypeptide comprises using one or more assays selected from the group consisting of:

Western blot; immunoprecipitation; enzyme-linked immunosorbent assay (ELISA); radioimmunological assay (RIA); sandwich assay;

protein in situ array; immunohistological staining; radioimmunometric assay; gel diffusion precipitation reaction; immunodiffusion assay; *in situ* immunoassay; precipitation reaction; immunofluorescence assay; quantitative in situ protein analyses (AQUA); mass spectroscopy and immunoelectrophoresis assay.

109. The use of any of claims 106-107, wherein measuring the level of a DNA editing enzyme polypeptide comprises using an assay that uses an antibody, an antibody fragment, a protein binding protein, or a peptide which binds to the DNA editing enzyme polypeptide.

110. The use of any of claims 106-109, wherein the antibody or antibody fragment is a monoclonal antibody.

111. The use of any of claims 106-110, wherein the antibody, antibody fragment, protein binding protein or peptide which binds to the DNA editing enzyme polypeptide is labeled with a detectable label.

112. The use of any of claims 106-107, wherein measuring the level of a DNA editing enzyme mRNA comprises using one or more assays selected from the group consisting of:

RT-PCR; quantitative RT-PCR; hybridization assay; Northern blot; microarray based expression analysis; transcription amplification; self-sustained sequence replication; high throughput sequencing; and RNA-Seq.

113. The use of any of claims 106-107, wherein measuring the activity of a DNA editing enzyme comprises determining the overall mutation status of the genome or a portion thereof using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing;

wherein a mutation status 2% or greater than the normal mutation status indicates activity of a DNA editing enzyme.

114. The use of any of claims 106-107 and 113, wherein measuring the activity of activation-induced cytidine deaminase (AID) activity comprises determining the

status of hypermutations in the target genes IGH, BCL6, MYC, BCL11A, CD93, PIM1 and/or PAX5 using one or more assays selected from the group consisting of:

hybridization; high throughput sequencing; exome sequencing; fluorescence in situ hybridization (FISH), PCR, and genome sequencing.

115. The use of any of claims 106-107, wherein measuring the activity of activation-induced cytidine deaminase (AID) comprises using a phospho-H2AX assay, a 53BP1 assay, or a RAD51 assay.

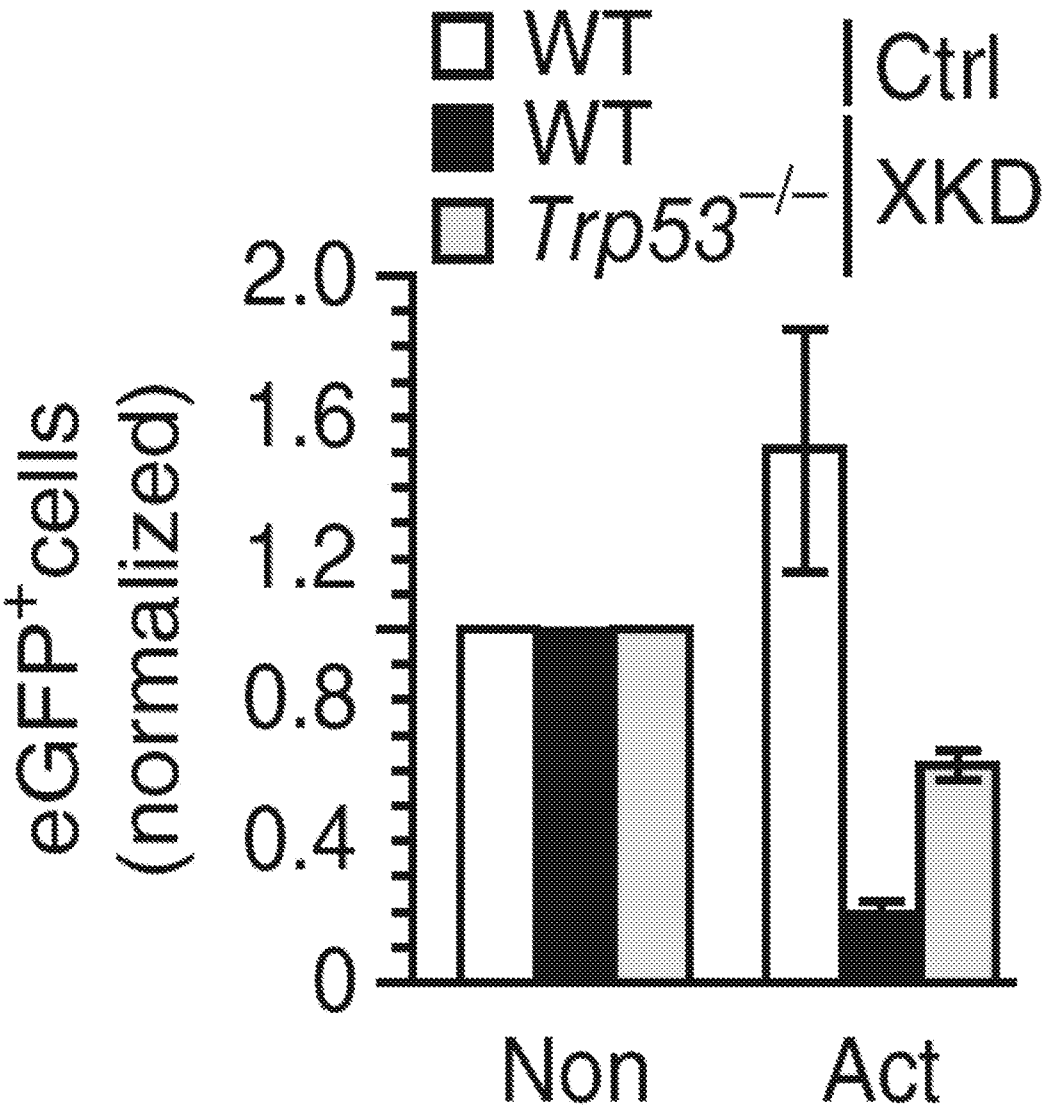

WT
WT
Trp53−/−
Ctrl
XKD
eGFP+ cells
(normalized)
2.0
1.6
1.2
0.8
0.4
0
Non
Act

FIG. 1

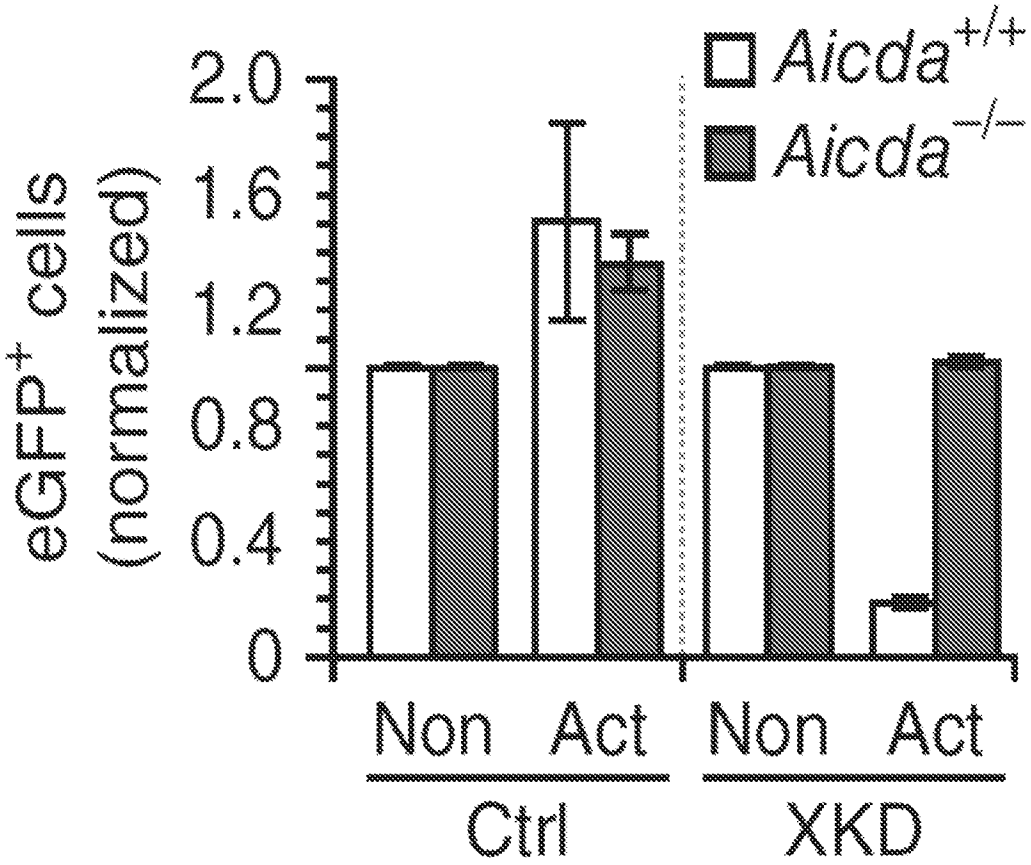

Aicda+/+
Aicda−/−
eGFP+ cells (normalized)
2.0
1.6
1.2
0.8
0.4
0
Non
Act
Non
Act
Ctrl
XKD

FIG. 2

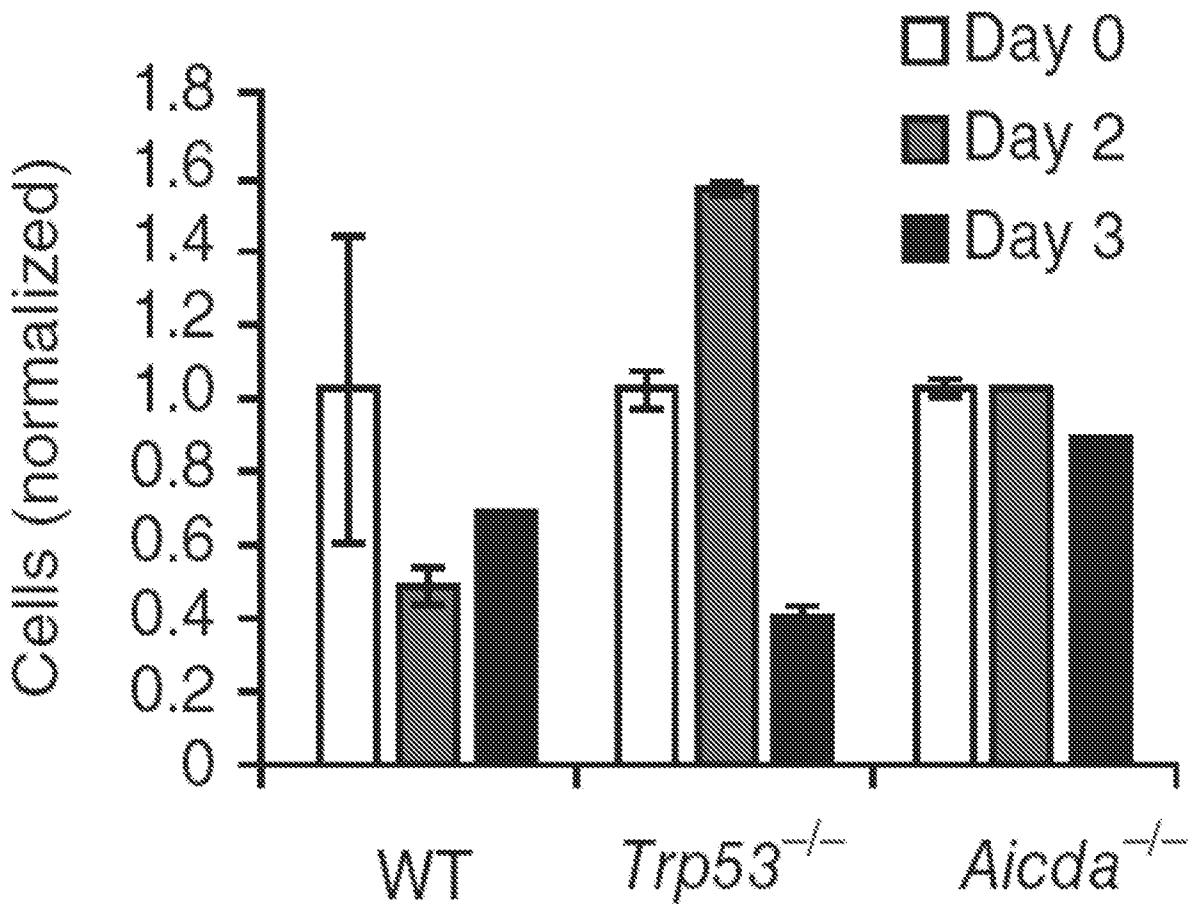

Day 0
Day 2
Day 3
Cells (normalized)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
WT
Trp53−/−
Aicda−/−

FIG. 3

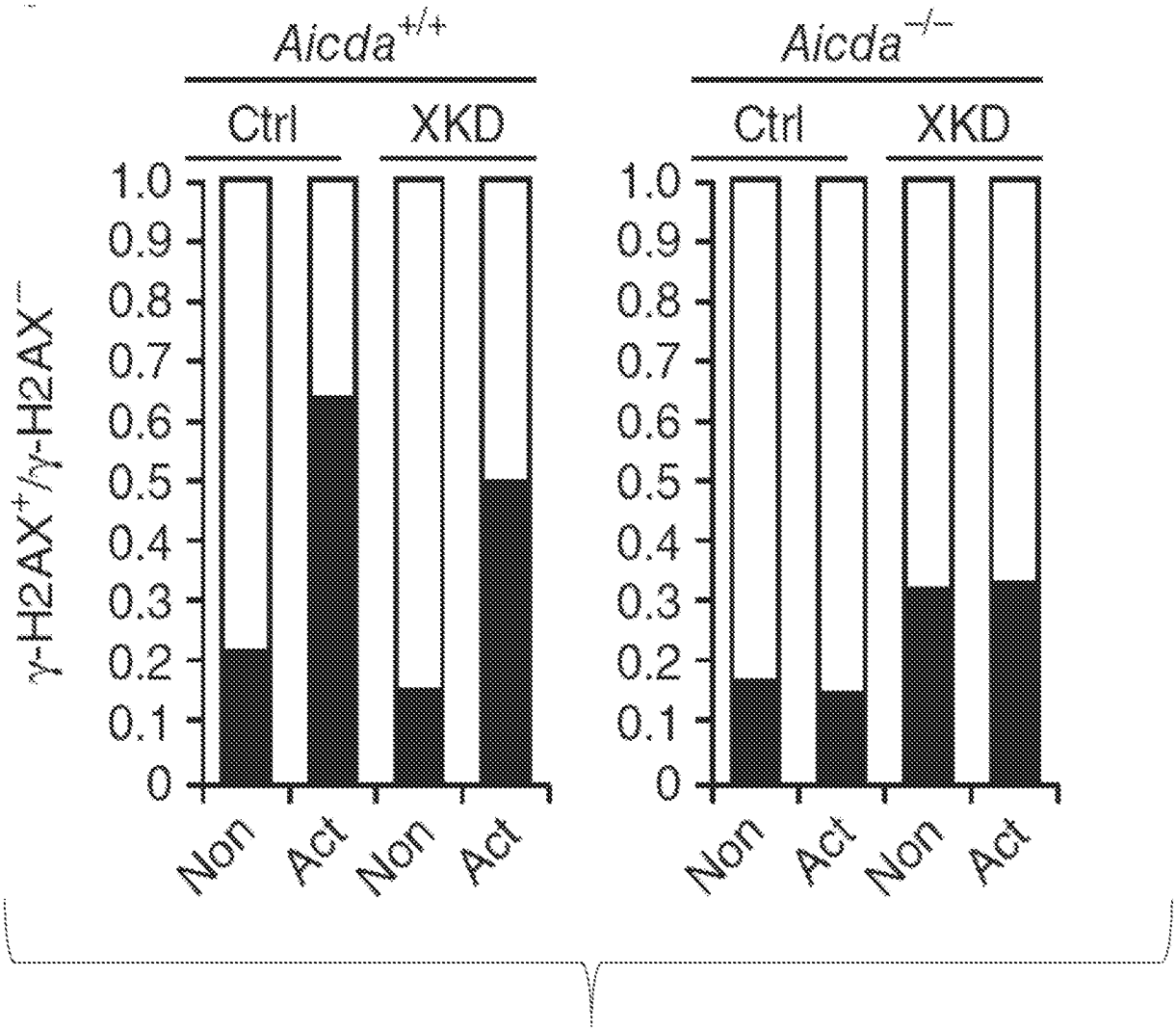

Aicda+/+
Aicda−/−
Ctrl
XKD
Ctrl
XKD
γ-H2AX+/γ-H2AX−
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Non
Act
Non
Act
Non
Act
Non
Act

FIG. 4

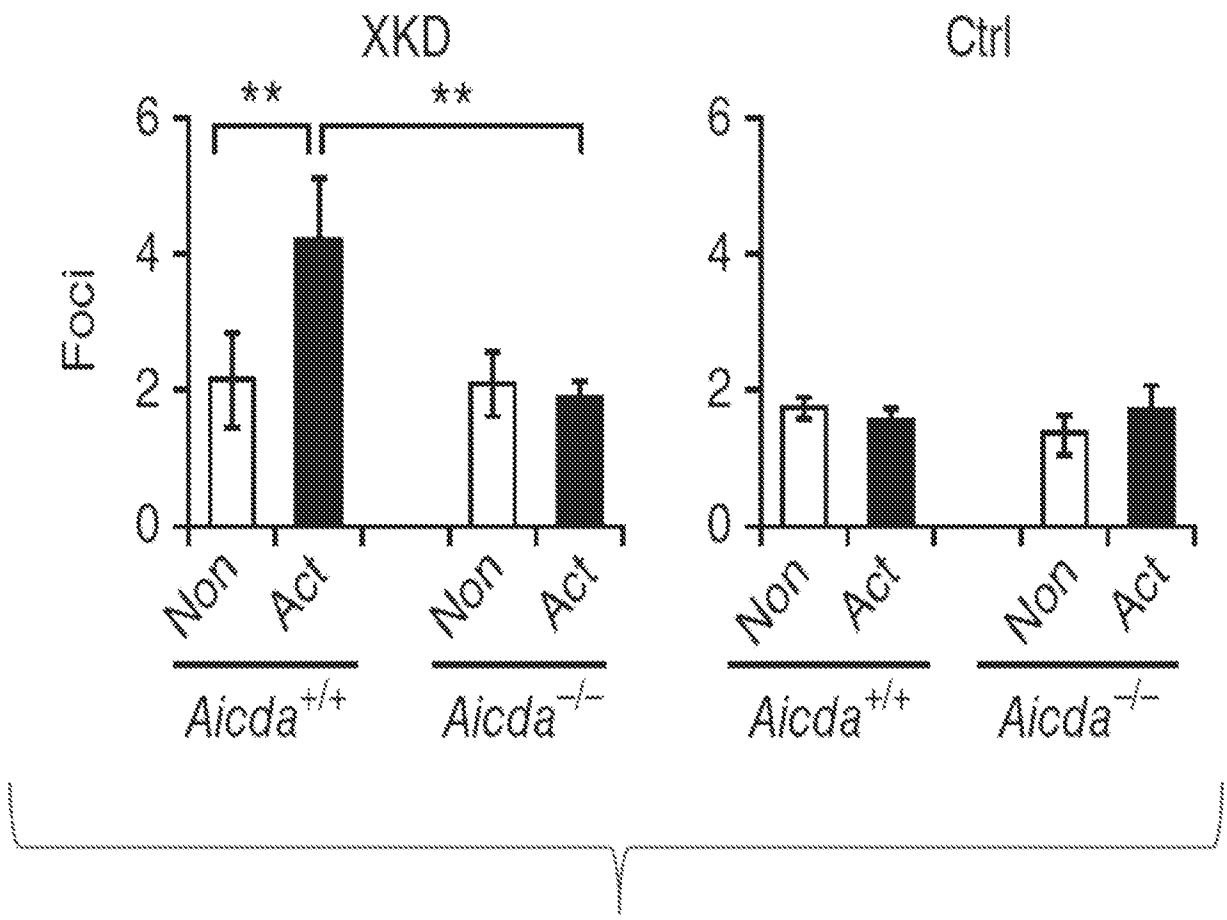

XKD
Ctrl
**
**
Foci
6
4
2
0
Non
Act
Non
Act
Non
Act
Non
Act
Aicda+/+
Aicda−/−
Aicda+/+
Aicda−/−

FIG. 5

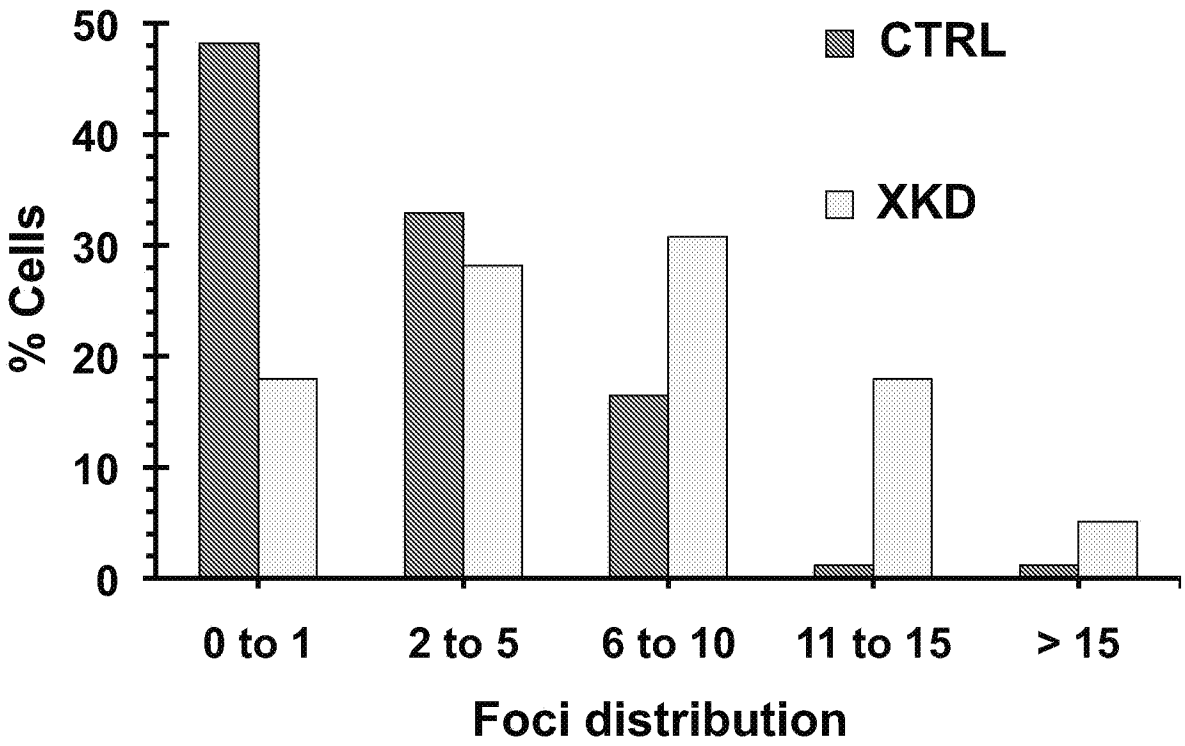

50
40
30
20
10
0
% Cells
CTRL
XKD
0 to 1
2 to 5
6 to 10
11 to 15
> 15
Foci distribution

FIG. 6

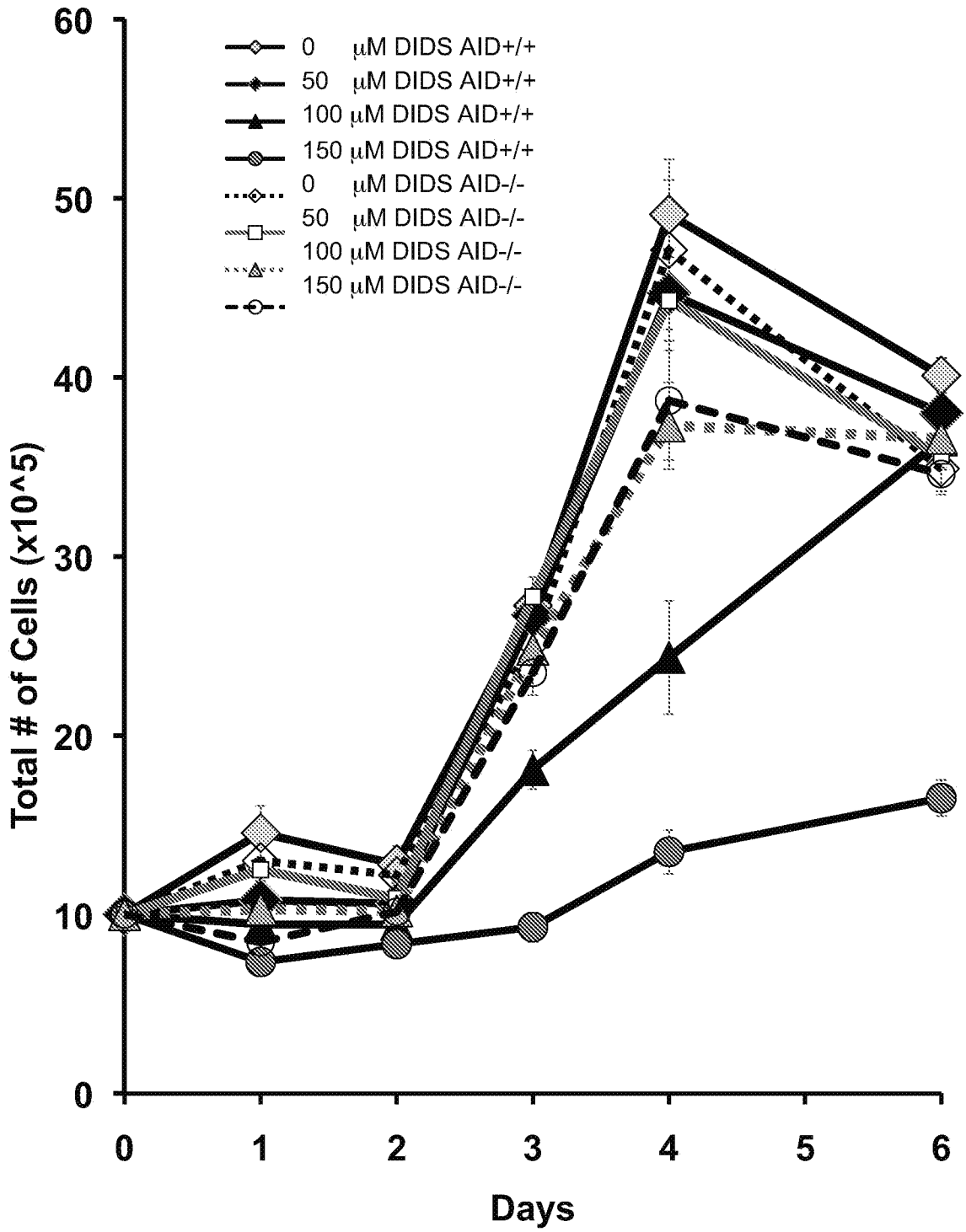

0 μM DIDS AID+/+
50 μM DIDS AID+/+
100 μM DIDS AID+/+
150 μM DIDS AID+/+
0 μM DIDS AID-/-
50 μM DIDS AID-/-
100 μM DIDS AID-/-
150 μM DIDS AID-/-
Total # of Cells (x10^5)
0
10
20
30
40
50
60
0
1
2
3
4
5
6
Days

FIG. 7

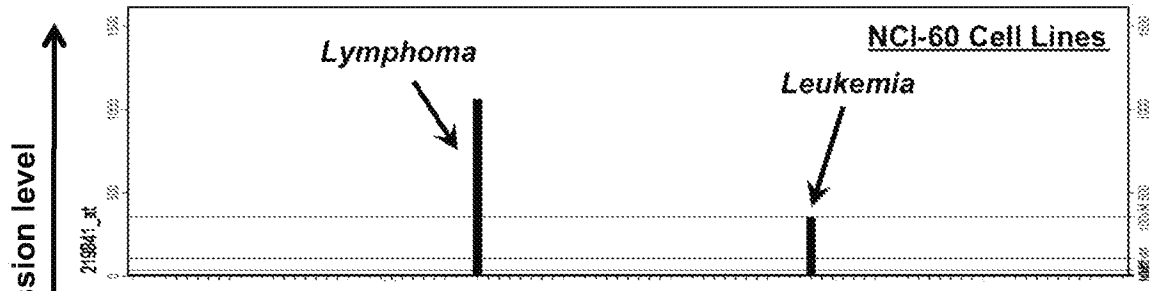

Lymphoma
Leukemia
NCI-60 Cell Lines

FIG. 8A

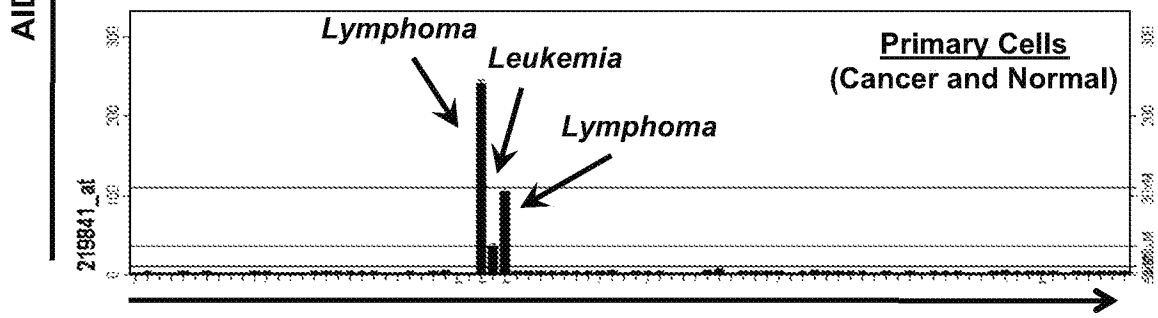

AID Expression level
Lymphoma
Leukemia
Lymphoma
Primary Cells
(Cancer and Normal)

FIG. 8B

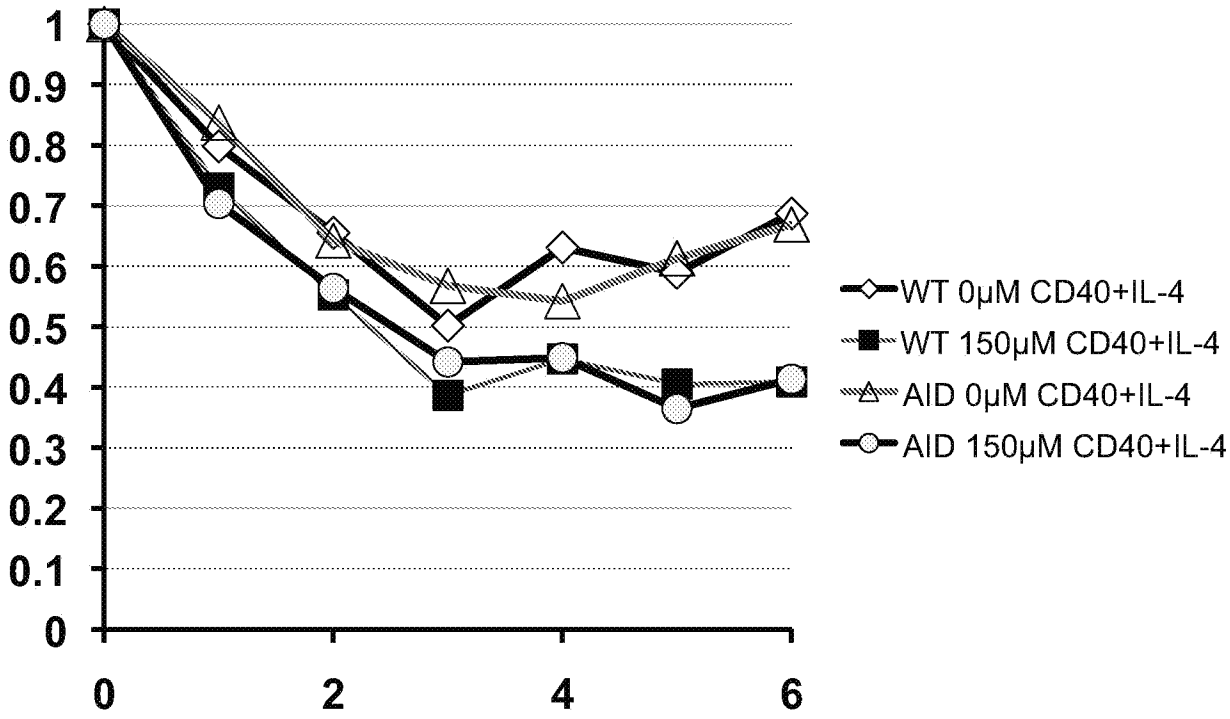

1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
WT 0μM CD40+IL-4
WT 150μM CD40+IL-4
AID 0μM CD40+IL-4
AID 150μM CD40+IL-4

FIG. 9

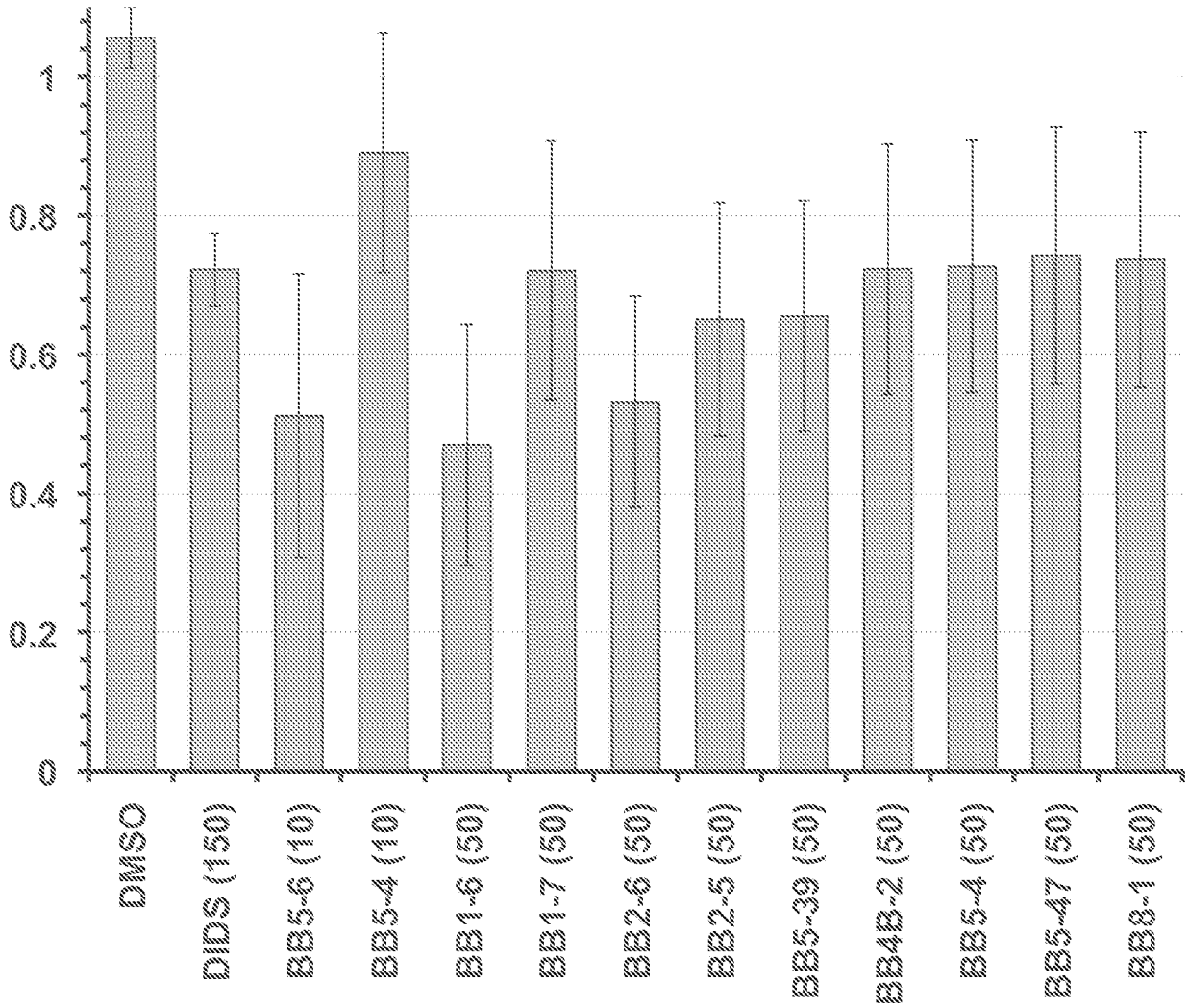

0
0.2
0.4
0.6
0.8
1
DMSO
DIDS (150)
BB5-6 (10)
BB5-4 (10)
BB1-6 (50)
BB1-7 (50)
BB2-6 (50)
BB2-5 (50)
BB5-39 (50)
BB48-2 (50)
BB5-4 (50)
BB5-47 (50)
BB8-1 (50)

FIG. 10

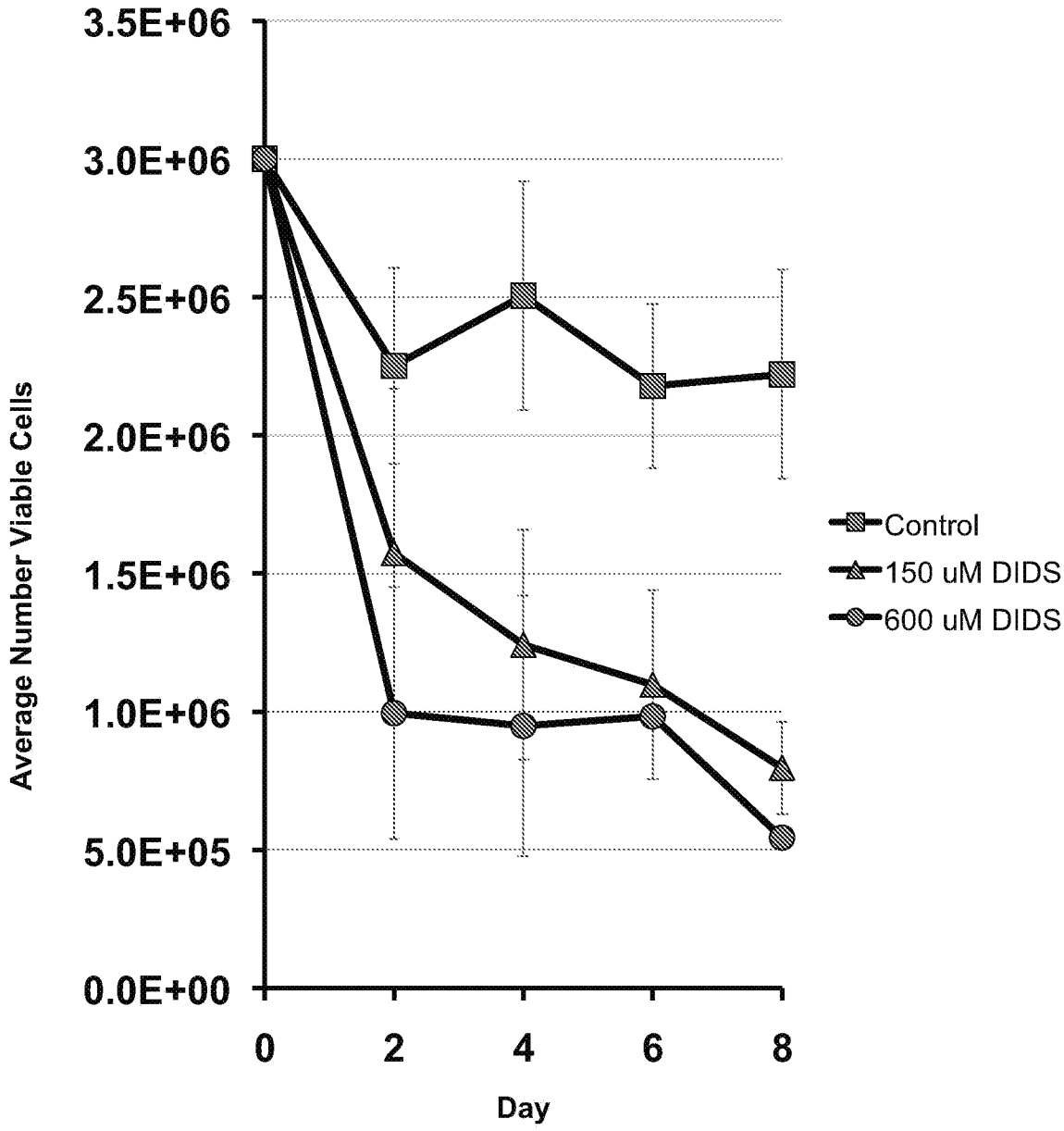

3.5E+06
3.0E+06
2.5E+06
2.0E+06
1.5E+06
1.0E+06
5.0E+05
0.0E+00
Average Number Viable Cells
0
2
4
6
8
Day
Control
150 uM DIDS
600 uM DIDS

FIG. 11

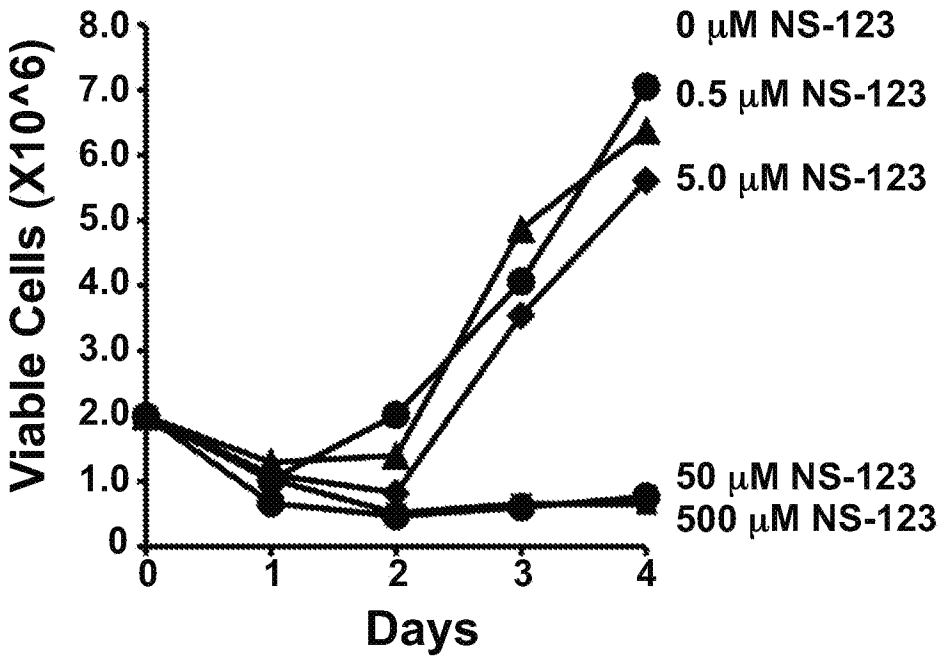

Viable Cells (X10^6)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
0
1
2
3
4
Days
0 μM NS-123
0.5 μM NS-123
5.0 μM NS-123
50 μM NS-123
500 μM NS-123

FIG. 12

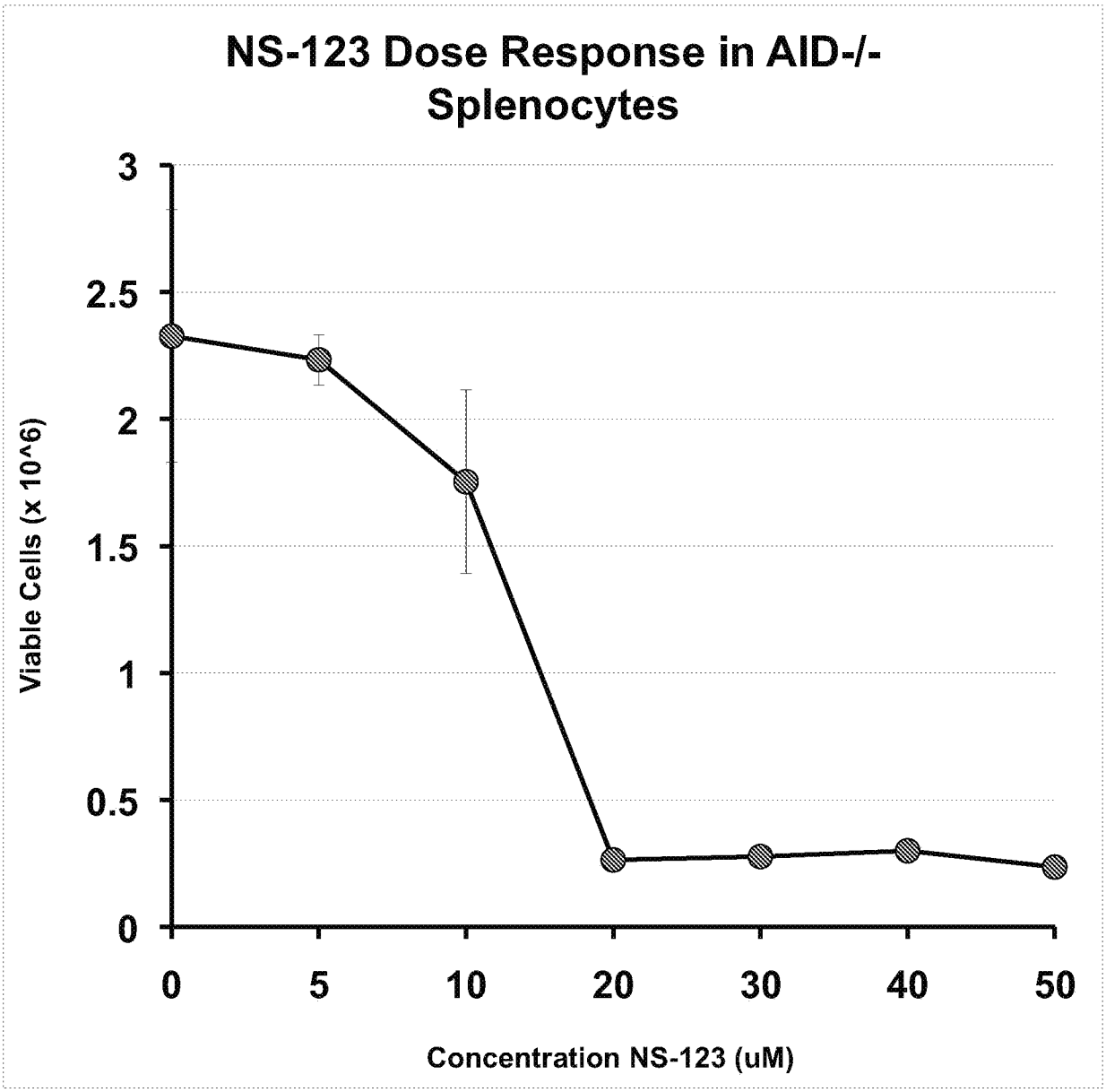

NS-123 Dose Response in AID-/- Splenocytes
Viable Cells (x 10^6)
3
2.5
2
1.5
1
0.5
0
0
5
10
20
30
40
50
Concentration NS-123 (uM)

FIG. 13

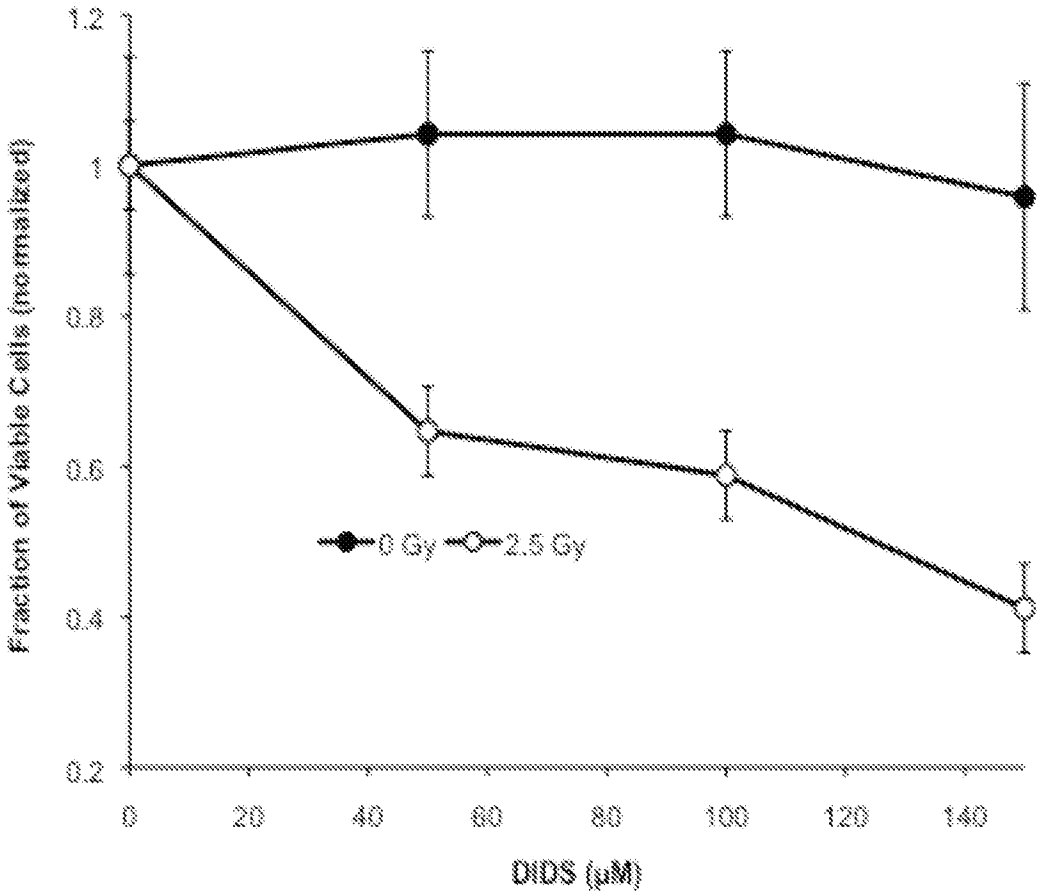

Fraction of Viable Cells (normalized)
1.2
1
0.8
0.6
0.4
0.2
0
20
40
60
80
100
120
140
DIDS (μM)
0 Gy
2.5 Gy

FIG. 14

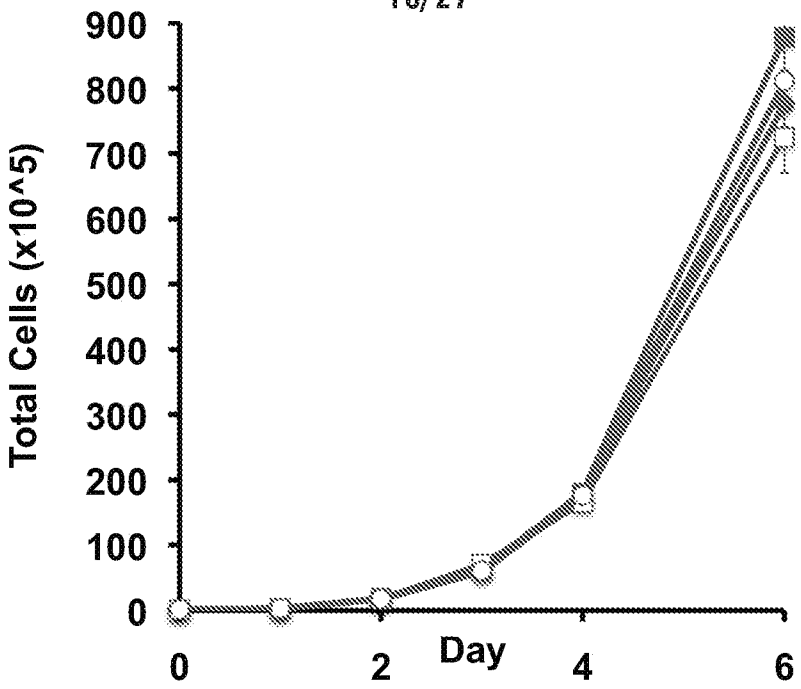


FIG. 15A

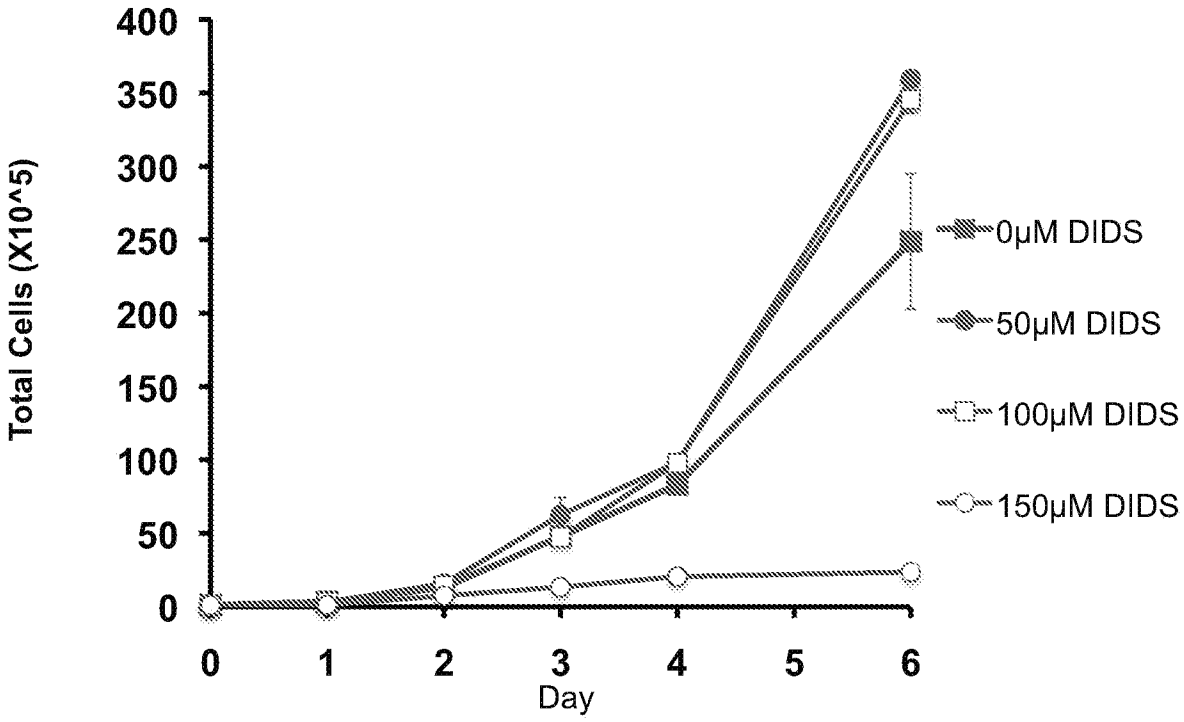


FIG. 15B

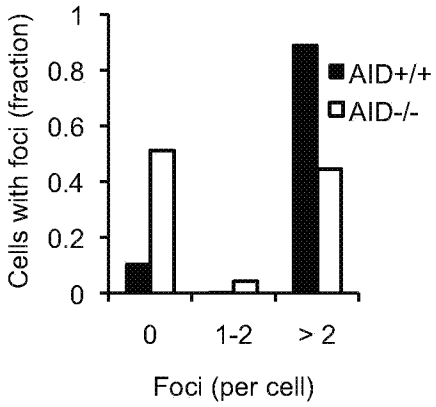


FIG. 16A

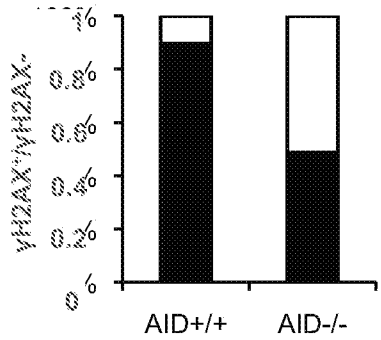


FIG. 16B

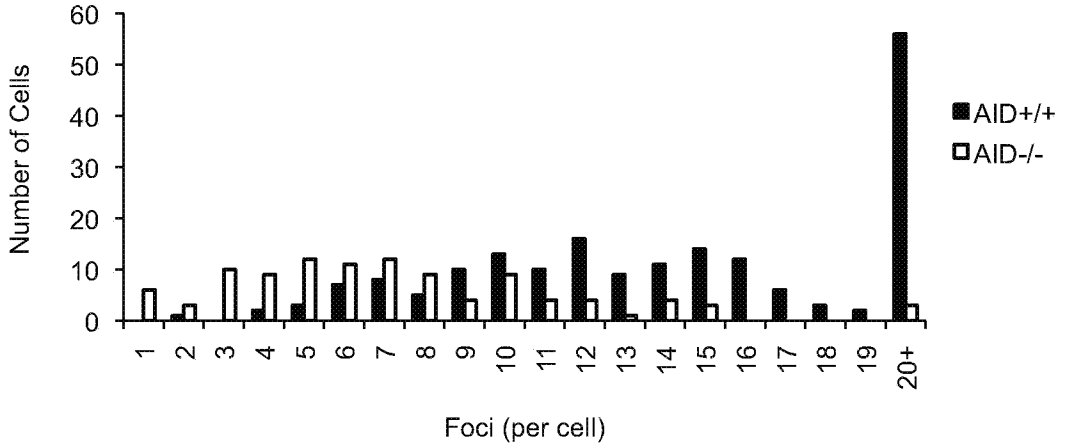


FIG. 16C

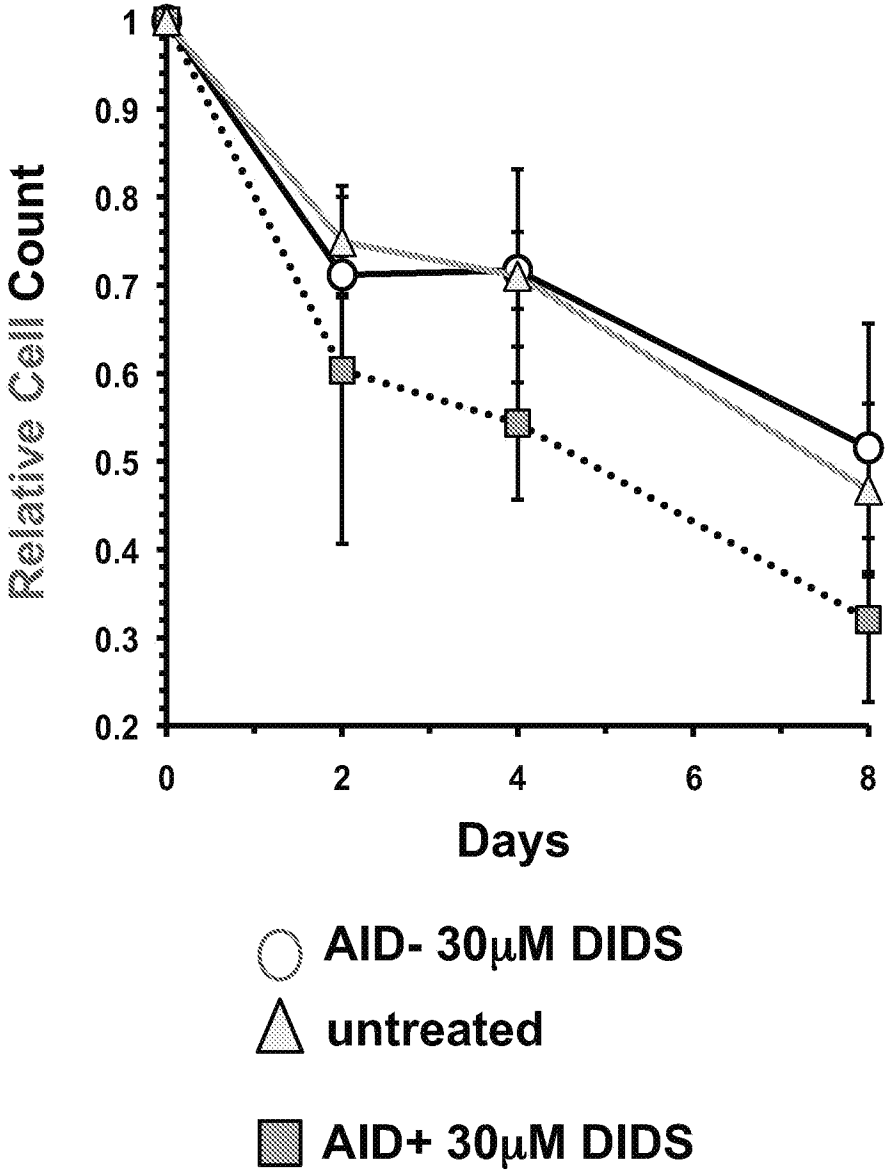

Relative Cell Count
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
2
4
6
8
Days
AID- 30μM DIDS
untreated
AID+ 30μM DIDS

FIG. 17

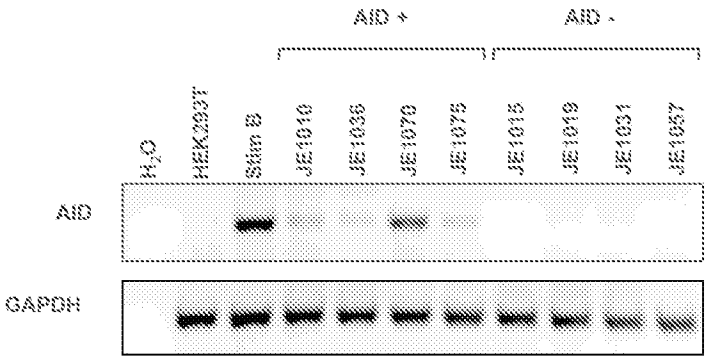


FIG. 18A

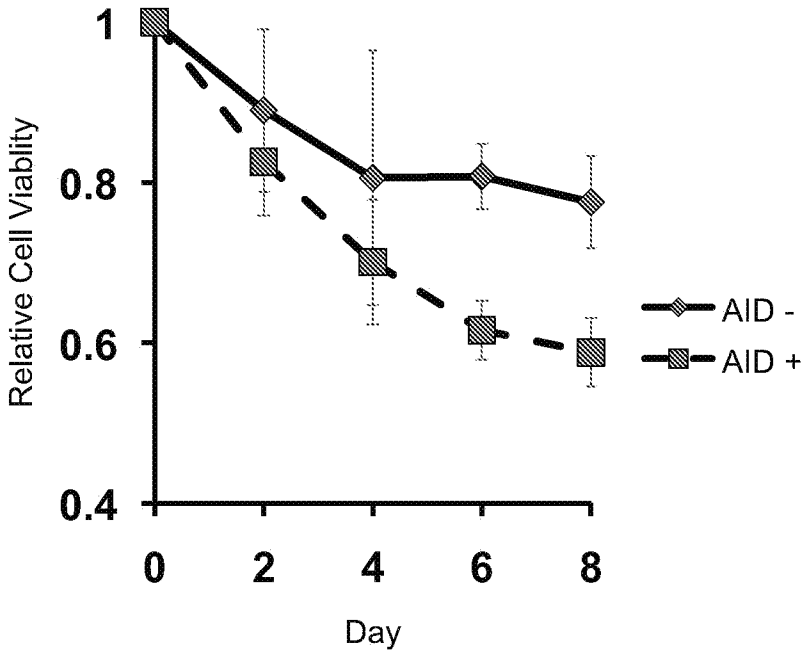


FIG. 18B

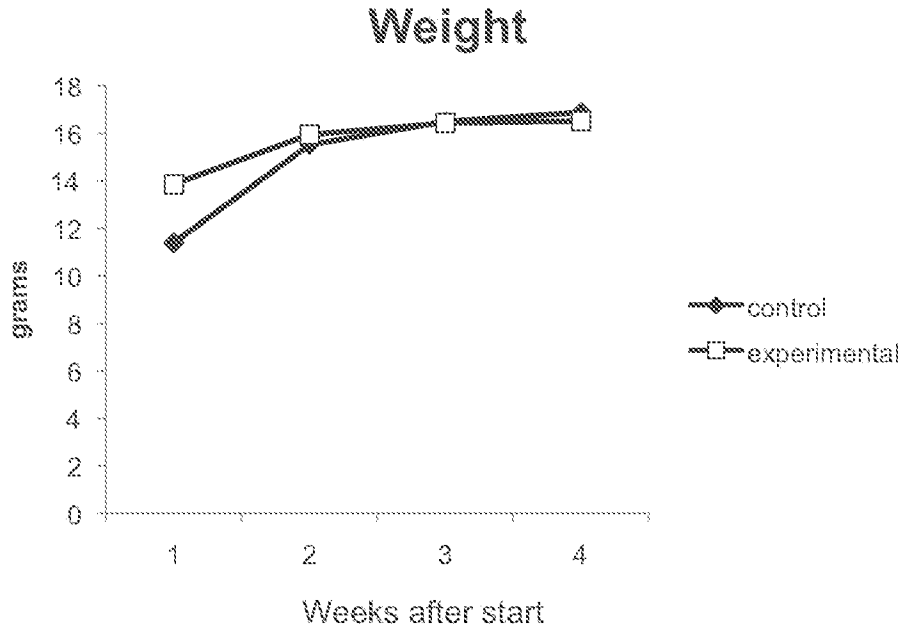


FIG. 19A

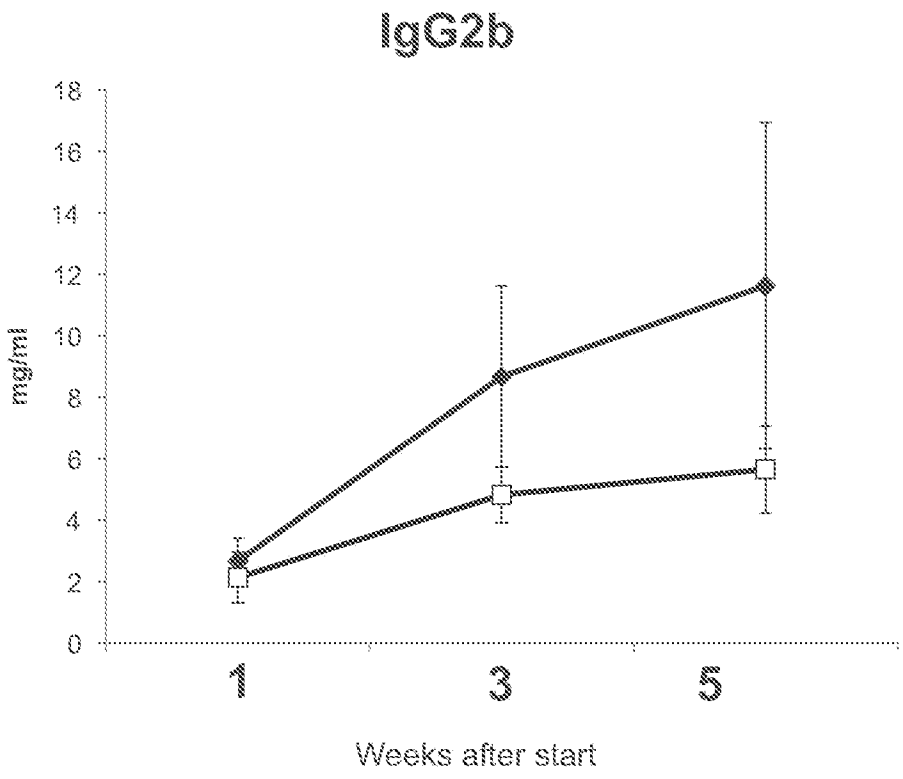


FIG. 19B

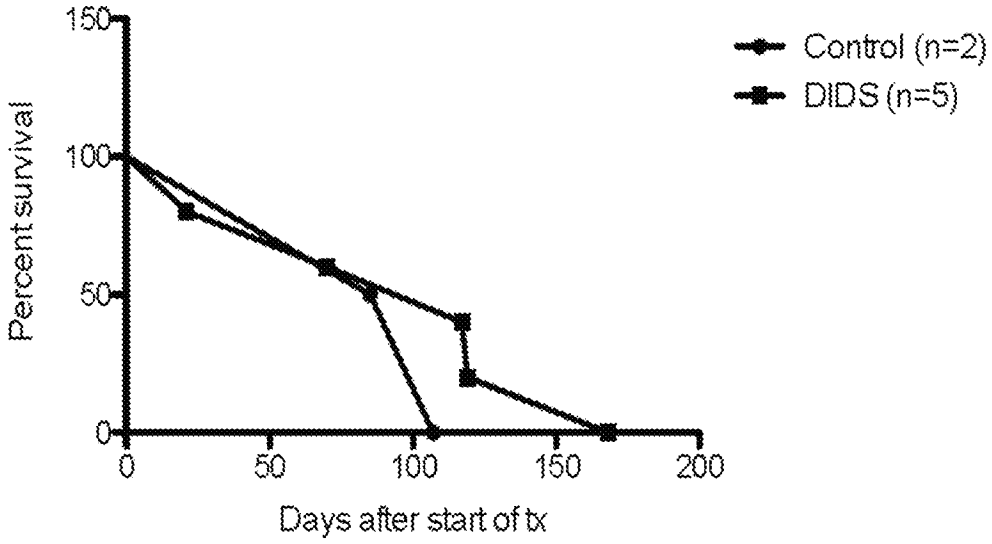


FIG. 20A

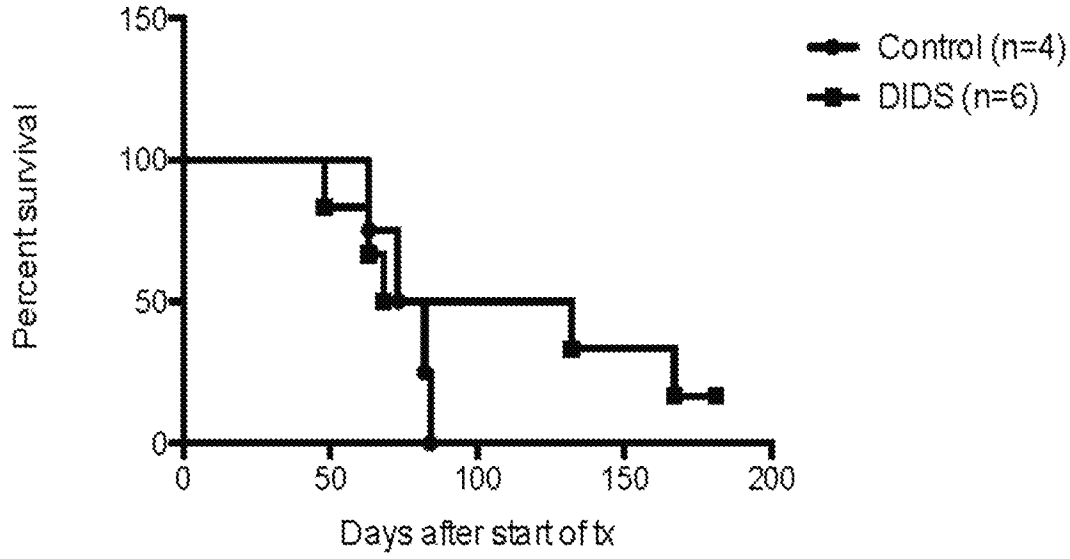


FIG. 20B

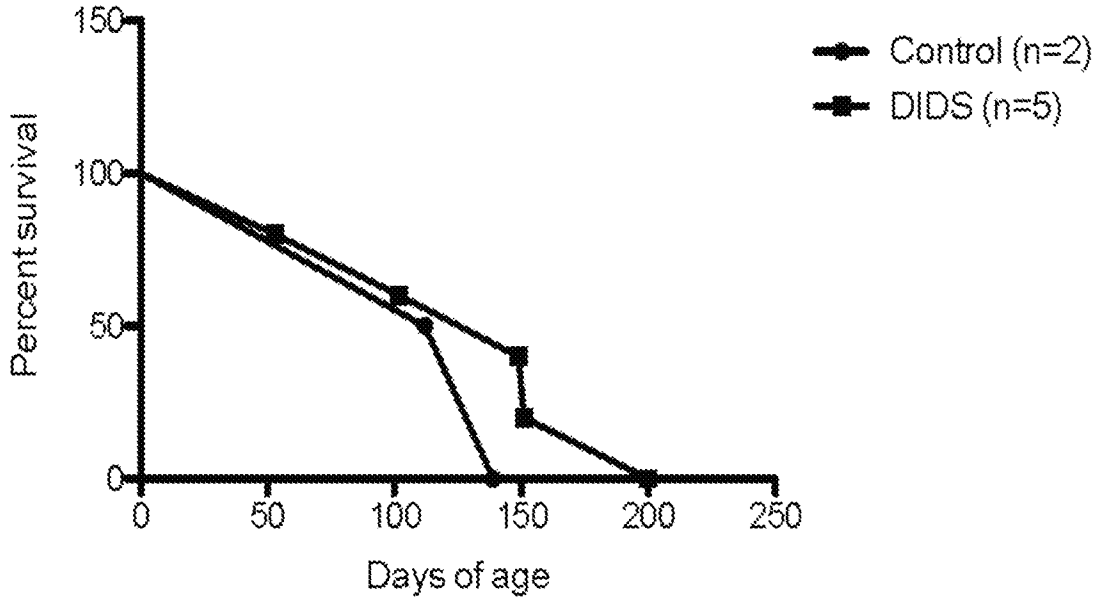


FIG. 21A

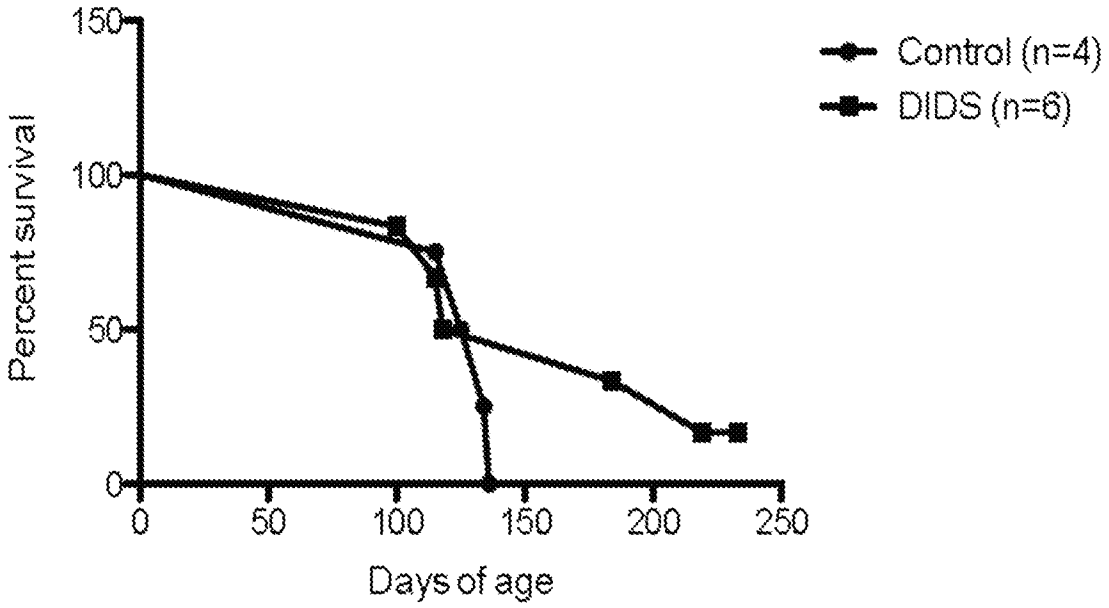


FIG. 21B

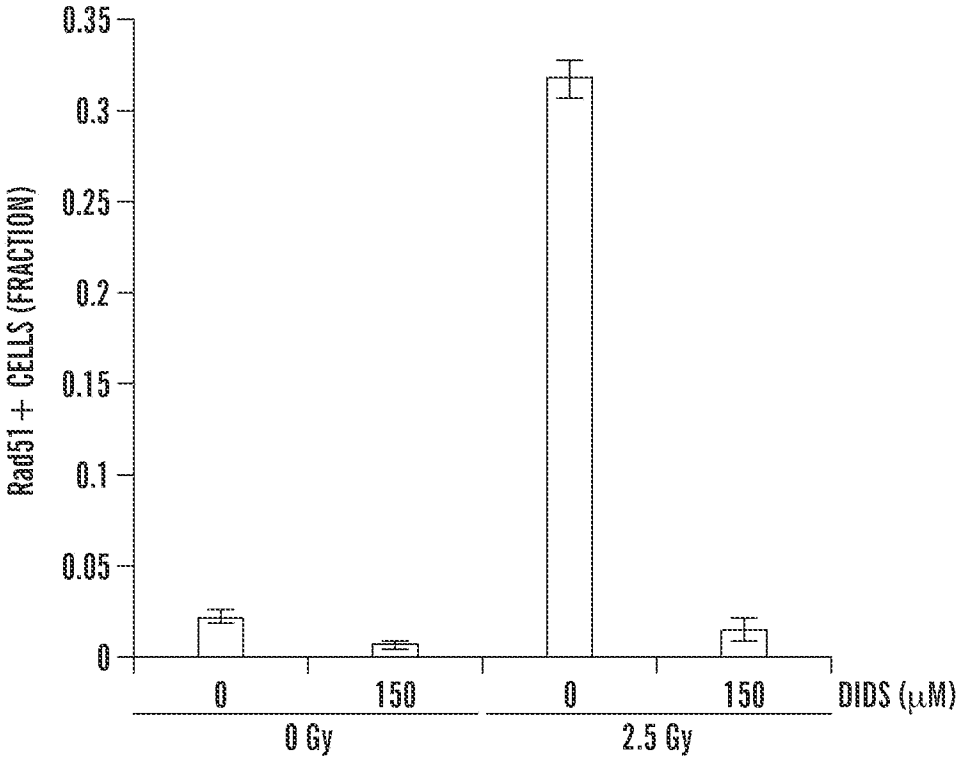

0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Rad51 + CELLS (FRACTION)
0
150
0
150
DIDS (μM)
0 Gy
2.5 Gy

FIG. 22

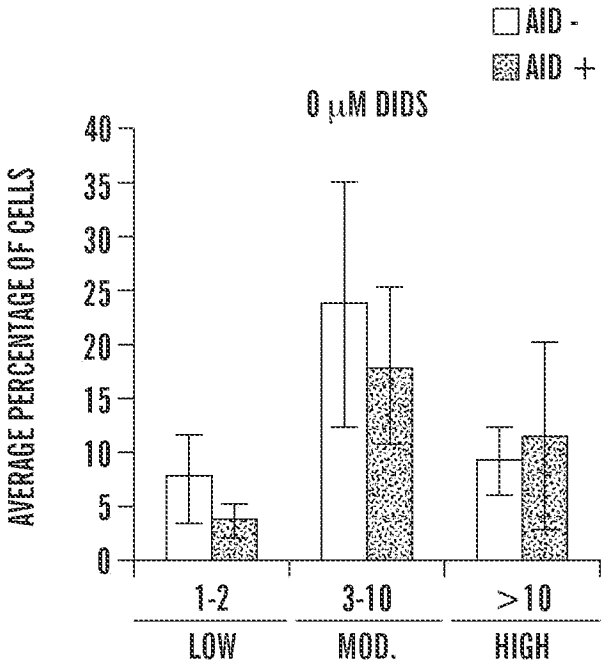


FIG. 23A

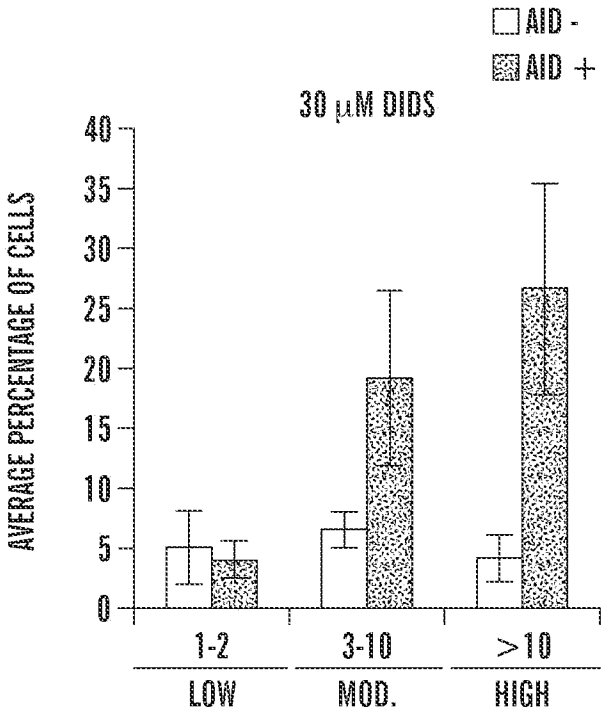


FIG. 23B

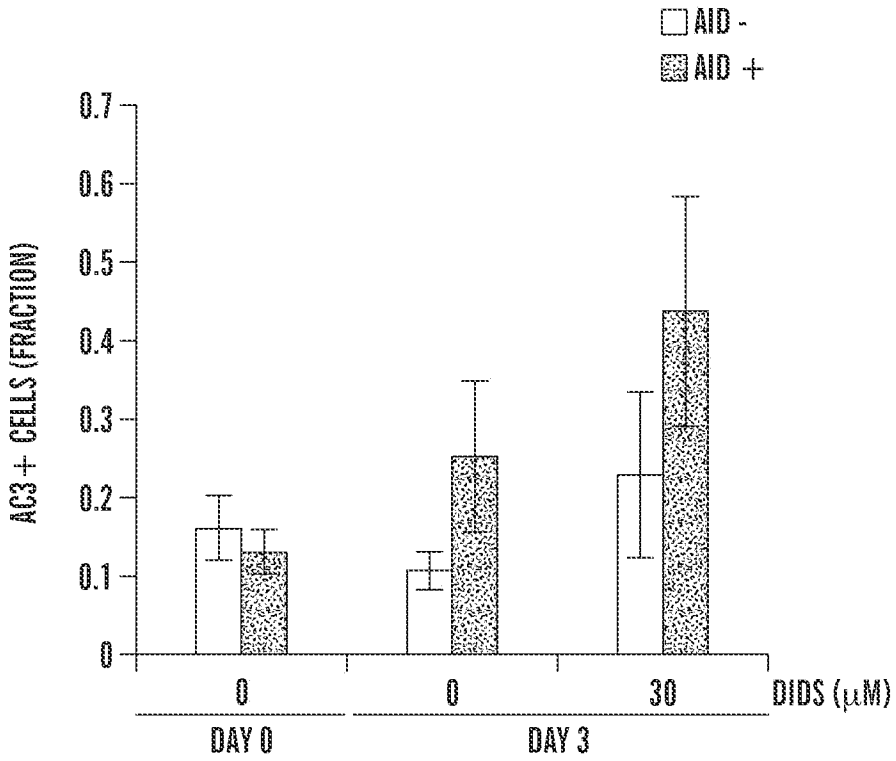

AID -
AID +
AC3 + CELLS (FRACTION)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0
30
DIDS (μM)
DAY 0
DAY 3

FIG. 24

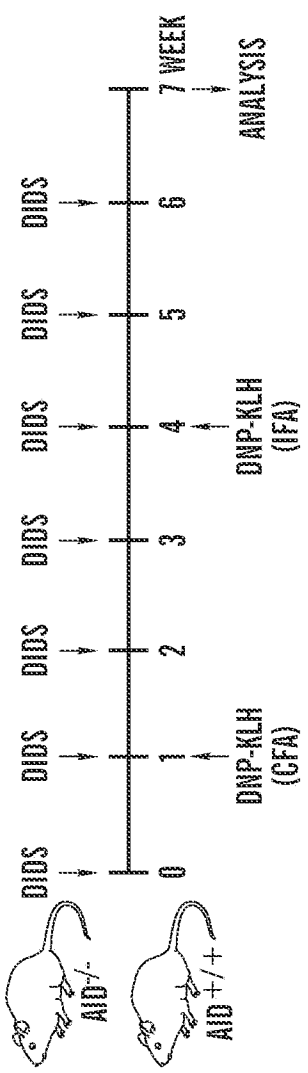


FIG. 25A

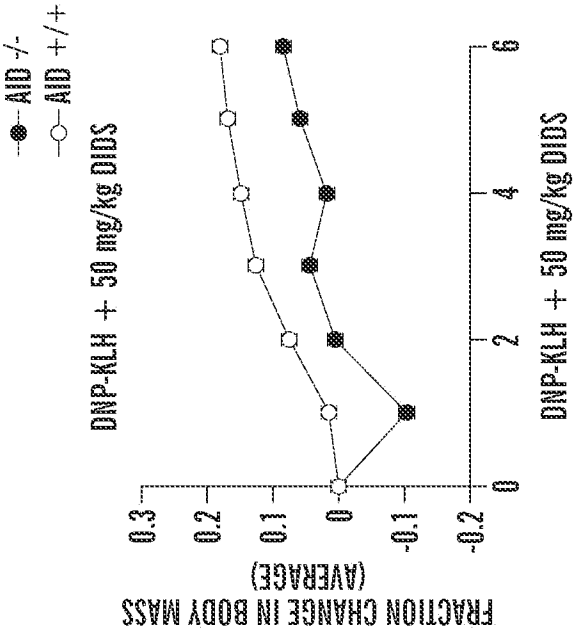


FIG. 25C

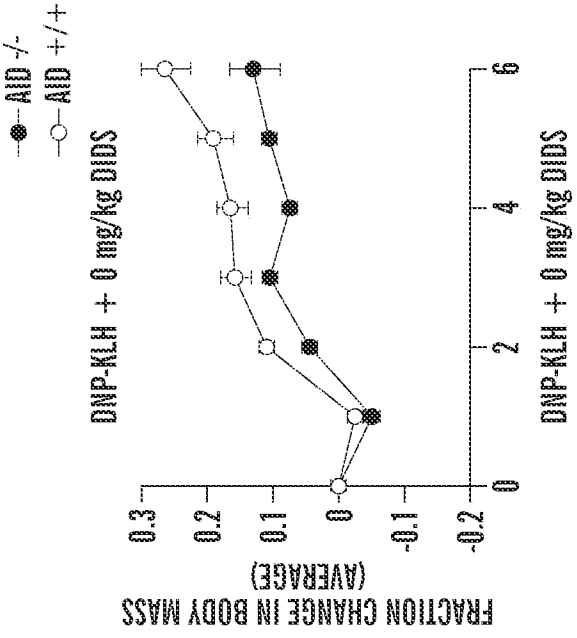


FIG. 25B

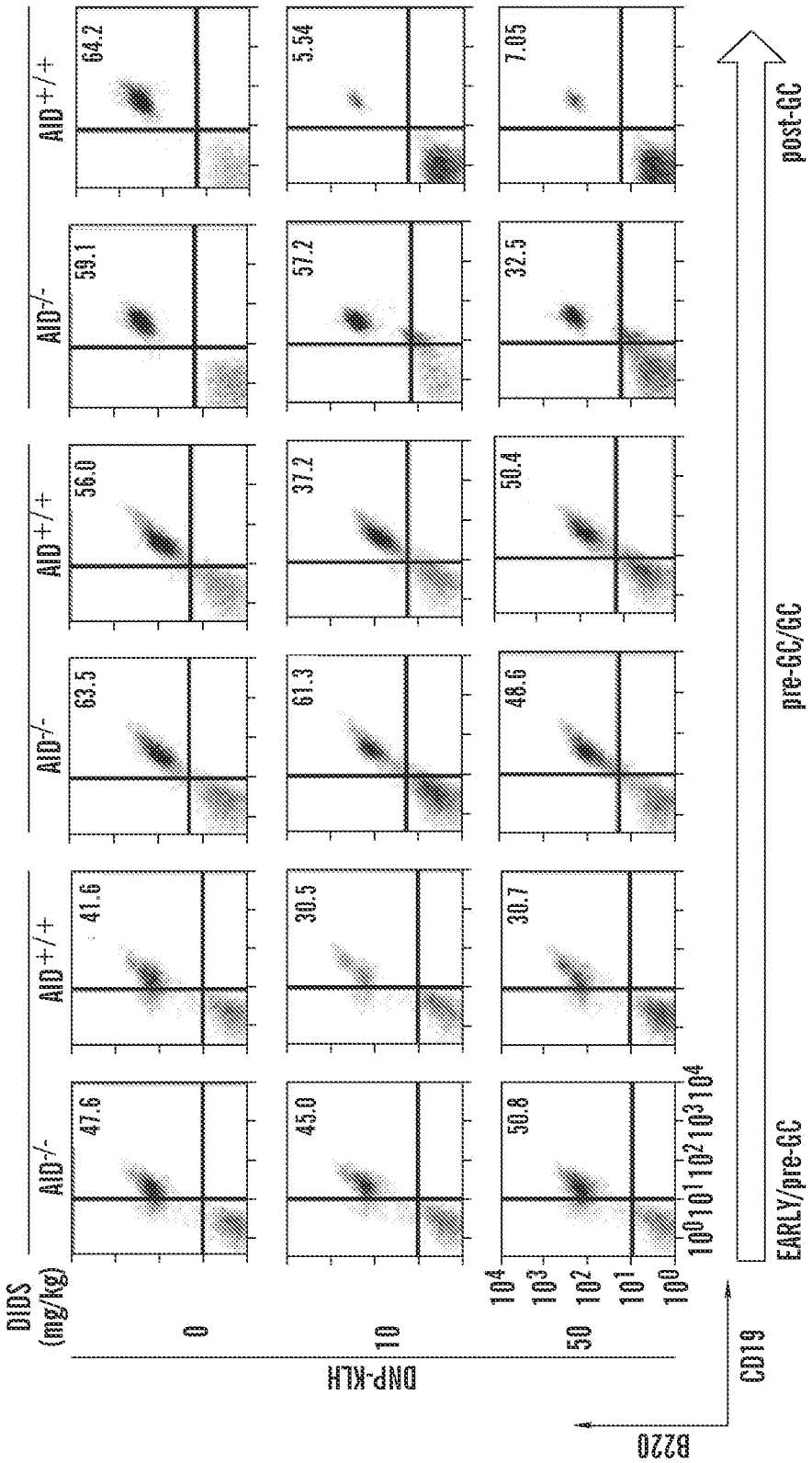

DIDS (mg/kg)
0
10
50
DNP-KLH
B220
CD19
AID-/-
AID+/+
47.6
41.6
45.0
30.5
50.8
30.7
63.5
56.0
61.3
37.2
48.6
50.4
59.1
64.2
57.2
5.54
32.5
7.05
EARLY/pre-GC
pre-GC/GC
post-GC

FIG. 26

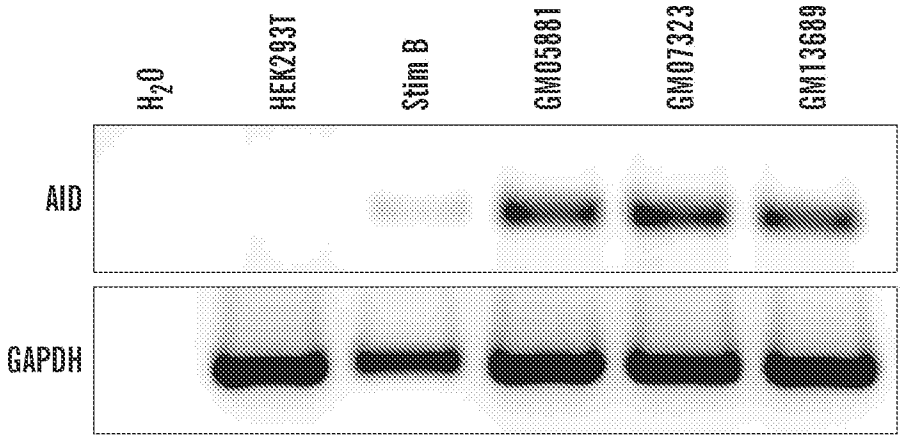


FIG. 27

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/043074

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50 A61K31/00 A61K31/255 A61K31/26 A61P35/00
A61P35/02 A61P37/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, COMPENDEX, INSPEC, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. ISHIDA ET AL: "DIDS, a chemical compound that inhibits RAD51-mediated homologous pairing and strand exchange", NUCLEIC ACIDS RESEARCH, vol. 37, no. 10, 30 March 2009 (2009-03-30), pages 3367-3376, XP055036178, ISSN: 0305-1048, DOI: 10.1093/nar/gkp200 cited in the application abstract figures 1,2 Relevant for non unity ----- -/--	1

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2012	19/11/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUNEER G HASHAM ET AL: "Widespread genomic breaks generated by activation-induced cytidine deaminase are prevented by homologous recombination", NATURE IMMUNOLOGY, vol. 11, no. 9, 25 July 2010 (2010-07-25), pages 820-826, XP055036263, ISSN: 1529-2908, DOI: 10.1038/ni.1909 abstract page 821, column 1, line 16, paragraph 1 - line 21 page 821, column 1, paragraph 2 - column 2, paragraph 1	1-22, 32-44, 73-94, 104-115
A	HAITAO LI ET AL: "2,3',4,4',5'-Pentamethoxy-trans-stilbene, a resveratrol derivative, inhibits colitis-associated colorectal carcinogenesis in mice", BRITISH JOURNAL OF PHARMACOLOGY, vol. 160, no. 6, 1 July 2010 (2010-07-01), pages 1352-1361, XP055036726, ISSN: 0007-1188, DOI: 10.1111/j.1476-5381.2010.00785.x abstract	1-27, 32-44, 73-99, 104-115
A	KIM Y H ET AL: "Piceatannol, a stilbene present in grapes, attenuates dextran sulfate sodium-induced colitis", INTERNATIONAL IMMUNOPHARMACOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 8, no. 12, 10 December 2008 (2008-12-10), pages 1695-1702, XP025473993, ISSN: 1567-5769, DOI: 10.1016/J.INTIMP.2008.08.003 [retrieved on 2008-09-04] abstract figure 1a	1-27, 32-44, 73-99, 104-115
A	BADGER A M ET AL: "Idoxifene, a novel selective estrogen receptor modulator, is effective in a rat model of adjuvant-induced arthritis", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, vol. 291, no. 3, 1 December 1999 (1999-12-01), pages 1380-1386, XP002372594, ISSN: 0022-3565 abstract figure 1	1-27, 32-44, 73-99, 104-115

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/039557 A1 (UNIV CALIFORNIA [US]; DAVID MICHAEL I [US]) 15 May 2003 (2003-05-15) claims 1-6,16-31; figures 1-9	1-27, 32-44, 73-99, 104-115
A	WO 2004/021987 A2 (MERCK & CO INC [US]; MERCK FROSST CANADA INC [CA]; MANCINI JOSEPH ANTH) 18 March 2004 (2004-03-18) claims 1,3,5	1-27, 32-44, 73-99, 104-115
A	JIN-MING HWANG ET AL: "Reduction of anion exchanger 2 expression induces apoptosis of human hepatocellular carcinoma cells", MOLECULAR AND CELLULAR BIOCHEMISTRY, KLUWER ACADEMIC PUBLISHERS, BO, vol. 327, no. 1-2, 18 February 2009 (2009-02-18), pages 135-144, XP019684248, ISSN: 1573-4919 abstract	1-27, 32-44, 73-99, 104-115
A	CHUNG-JUNG LIU ET AL: "Anion exchanger inhibitor DIDS induces human poorly-differentiated malignant hepatocellular carcinoma HA22T cell apoptosis", MOLECULAR AND CELLULAR BIOCHEMISTRY, KLUWER ACADEMIC PUBLISHERS, BO, vol. 308, no. 1-2, 16 October 2007 (2007-10-16), pages 117-125, XP019578300, ISSN: 1573-4919 abstract	1-27, 32-44, 73-99, 104-115
A	HORVAT B ET AL: "Tumour cell proliferation is abolished by inhibitors of Na<+>H<+> and HCO3<->Cl<-> exchange", EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 29, no. 1, 1 January 1993 (1993-01-01), pages 132-137, XP026201861, ISSN: 0959-8049, DOI: 10.1016/0959-8049(93)90591-3 [retrieved on 1993-01-01] abstract	1-27, 32-44, 73-99, 104-115

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MONA LEUENBERGER ET AL: "AID protein expression in chronic lymphocytic leukemia/small lymphocytic lymphoma is associated with poor prognosis and complex genetic alterations", MODERN PATHOLOGY, vol. 23, no. 2, 1 February 2010 (2010-02-01), pages 177-186, XP055036781, ISSN: 0893-3952, DOI: 10.1038/modpathol.2009.156 abstract -----	1-27, 32-44, 73-99, 104-115

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/043074

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

23-27, 95-99(completely); 1-22, 32-44, 73-94, 104-115(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 23-27, 95-99(completely); 1-22, 32-44, 73-94, 104-115(partially)

   Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of a compound of formula V to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

   ---

2. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

   Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 4-methylquinazoline-2-carboxamide to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

   ---

3. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

   Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of benz[h]isoquinolin-6-amine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

   ---

4. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

   Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 5,6-dimethyl-2-mercaptomethylbenzimidazole to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

   ---

5. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

   Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of (E)-1-(2-hydroxyphenyl)-3-(pyridine-3-yl)prop-2-en-1-one to

a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

6. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of N4-butyl-6-chloropyrimidine-2,4-diamine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

7. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 1-thermopsine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

8. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 6-amino-5-nitroso-2-phenylpyrimidin-4(1H)-one to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

9. claims: 1-22, 28, 32-44, 73-94, 100, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 4-(2-amino-4-nitrophenylamino)phenyl to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

10. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 7-azaindole-3-carboxaldehyde to a

subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

11. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-amino-4-phenylphenol to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

12. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 3-(1-methyl-3-pyrrolidinyl)indole to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

13. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 1-methyl-[1,2,4]triazolo[4,3-a]quinolone to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

14. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-amino-5-nitro-1H-benzimidazole to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

15. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-(5-nitro-2-fufurylidene)aminoethanol-N-oxide to a subject

with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

16. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of nifuratrone to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

17. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of alpha-mercapto-N,2-naphthylacetamide to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

18. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 1-thermospine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

19. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of N4-butyl-6-chloro-2,4-pyrimidinediamine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

20. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-(2-hydroxy-6-propan-2-yloxy-cyclohexyl)acetic acid to a subject with a detectable level of a DNA editing enzyme, the

compound being an inhibitor of DNA double strand break repair.

---

21. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 4-amino-2-hydroxyphenyl)arsonic acid to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

22. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of spiro[1,2-dihydroindene-3,5'-imidazolidine]-2',4'-dione to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

23. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of N~4~-(4-methoxyphenyl)-6-methylpyrimidine-2,4-diamine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

24. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-amino-9-pentyl-3H-purine-6-thione to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

25. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically

effective amount of 2-(4-methoxyphenyl)-3-(pyridin-3yl)prop-2-enenitrile to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

26. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-chloropyrimidine-4,6-dicarboxamide to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

27. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-amino-3H-phenoxazin-3-one to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

28. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-methyl-N-benzyl-7H-pyrrolo[2,3-d]pyrimidine-4-amine or 4-(benzylamino)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine to a subject with a detectable level of a DNA editing enzyme, the compounds being an inhibitor of DNA double strand break repair.

---

29. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-amino-1-naphthalenesulfonic acid to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

30. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of N-sec-butyl-3-methylbenzamide to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

31. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of benz[h]isoquinolin-6-amine to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

32. claims: 1-22, 29, 32-44, 73-94, 101, 104-115(all partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of 2-(2-methylcyclohexylidene)hydrazinecarboxamide to a subject with a detectable level of a DNA editing enzyme, the compound being an inhibitor of DNA double strand break repair.

---

33. claims: 30, 102(completely); 1-22, 32-44, 73-94, 104-115(partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of an antibody or polypeptide comprising an antigen-binding fragment of an antibody or a protein binding protein to a subject with a detectable level of a DNA editing enzyme, the antibody, polypeptide or protein being an inhibitor of DNA double strand break repair.

---

34. claims: 31, 103(completely); 1-22, 32-44, 73-94, 104-115(partially)

Method of treatment comprising a). obtaining a biological sample derived from a subject; b). measuring a level of a DNA editing enzyme and c), administering a therapeutically effective amount of an RNAi agent to a subject with a detectable level of a DNA editing enzyme, the agent being an inhibitor of DNA double strand break repair.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

35. claims: 45-48

A methof of sensitizing a cell to cell death

---

36. claims: 49-56

A method of determining if a test agent is an inhibitor of DNA double strand break repair

---

37. claims: 57, 58

Compound of Formula XXIV

---

38. claim: 59

Compound of formula VII

---

39. claim: 60

Compound of formula X

---

40. claims: 61, 62

Compound of formula XXV

---

41. claims: 63, 64

Compound of formula XXXI

---

42. claims: 65, 66

Compound of formula XXXII

---

43. claims: 67, 68

Compound of formula XXXIII

---

44. claims: 69, 70

Compound of formula XXXIV

---

45. claims: 71, 72

Compound of formula XXXV

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/043074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03039557 A1	15-05-2003	CN 1729007 A	01-02-2006
		CN 101810600 A	25-08-2010
		EP 1450819 A1	01-09-2004
		EP 2060255 A2	20-05-2009
		EP 2289499 A2	02-03-2011
		US 2004242500 A1	02-12-2004
		US 2010324149 A1	23-12-2010
		US 2012071561 A1	22-03-2012
		WO 03039557 A1	15-05-2003
WO 2004021987 A2	18-03-2004	AU 2003288901 A1	29-03-2004
		EP 1536794 A2	08-06-2005
		US 2006019932 A1	26-01-2006
		WO 2004021987 A2	18-03-2004