blocking of ligand-mediated cell signaling in cell growth differentiation, and/or proliferation pathways (*see, e.g.*, Ludwig *et al., Oncogene* (2003) 22: 9097-9106).

[0005] Apoptosis, or programmed cell death, can be triggered by several different mechanisms. For example, the activation of signaling pathways through cell membrane-bound "death receptors," e.g., members of the tumor necrosis factor receptor (TNFR) superfamily, can lead to induction of apoptosis. Likewise, dimerization or cross-linking of surface antigen, e.g., CD20, can also induce apoptosis (*see, e.g.*, Ludwig *et al., Oncogene* (2003) 22: 9097-9106).

[0006] There remains a need for enhanced therapeutic approaches targeting antigens associated with cell signaling, including, but not limited to, the induction of apoptosis, for the treatment of disease in primates, including, but not limited to, humans.

SUMMARY

[0007] Recognizing the tremendous therapeutic potential of modified antigen binding molecules (ABMs) that have altered ability to mediate cell signaling activity by a target antigen, and/or altered ability to mediate cross-linking of one or more target antigens, the present inventors developed such ABMs, as well as a method for producing such ABMs. *Inter alia*, this method involves producing recombinant, chimeric antibodies or chimeric fragments thereof. The efficacy of these modified ABMs is further enhanced by engineering the glycosylation profile of the antibody Fc region.

[0008] Accordingly, in one embodiment, the disclosure is directed to a modified antigen binding molecule comprising a heavy chain or light chain variable region comprising at least one amino acid residue substitution in at least one framework region of said heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent antigen binding molecule, wherein said substitution results in altered cell signaling activity of a target antigen when said modified antigen binding molecule is complexed with said target antigen. In a particular embodiment, the altered cell signaling activity is apoptosis. In one embodiment, the modified antigen binding molecule has an increased ability to

induce apoptosis. In another embodiment, the modified antigen binding molecule has a reduced ability to induce apoptosis.

[0009] In another embodiment, the disclosure is directed to a modified antigen binding molecule comprising a heavy chain or light chain variable region comprising at least one amino acid residue substitution in at least one framework region of said heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent antigen binding molecule, wherein said modified antigen binding molecule has altered ability to mediate cross-linking of one or more target antigens as a result of said substitution.

[0010] In one embodiment, the modified antigen binding molecule of the present disclosure comprises a substitution in FR1 of the heavy chain variable region. In another embodiment, the substitution comprises a replacement selected from the group consisting of at least 2, at least 3, or at least 4 amino acids.

[0011] In one embodiment, the substitution comprises a replacement of the entire FR1 of the heavy chain variable region. In a further embodiment, the entire FR1 is replaced by a germline VH FR1. In particular embodiments, the germline VH FR1 comprises an amino acid sequence at Kabat positions 8 to 13 selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO: 65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105.

[0012] In one embodiment, the modified ABM comprises a substitution in FR1 of the heavy chain variable region which comprises a replacement of an amino acid residue at one or more of Kabat positions 8, 9, 10, 11, 12, or 13.

[0013] In a particular embodiment, the substitution in FR1 of the heavy chain variable region comprises a replacement of the amino acid residue at Kabat position 8. In a more specific embodiment, the substitution in FR1 of the heavy chain variable region comprises a replacement of the amino acid residue at Kabat position 8 with an amino acid residue selected from the group consisting of arginine, and glycine.

[0014] In another particular embodiment, the substitution in FR1 of the heavy chain variable region comprises a replacement of the amino acid residue at Kabat

12 with an isoleucine; or a replacement of the amino acid residue at Kabat position 11 with a valine and at Kabat position 12 with a valine.

[0019] In another particular embodiment, the substitution in FR1 of the heavy chain variable region comprises a replacement of the amino acid residue at Kabat position 13. In a specific embodiment, the substitution comprises a replacement of the amino acid residue at Kabat position 13 with an amino acid residue selected from the group consisting of lysine, arginine, glutamine and glutamate.

[0020] In another embodiment of the present disclosure, the substitution in the ABM comprises replacement of at least one amino acid residue in FR4 of the heavy chain variable region. In a particular embodiment, the substitution in FR4 of the heavy chain variable region comprises a replacement of an amino acid residue at one or more of Kabat positions 110 or 112.

[0021] In a particular embodiment, the substitution comprises a replacement of the amino acid residue at Kabat position 110 with an amino acid selected from the group consisting of leucine, isoleucine, threonine or serine. In a more specific embodiment, the susbstitution comprises a replacement of the amino acid residue at Kabat position 110 with an isoleucine.

[0022] In another embodiment, the substitution comprises a replacement of the amino acid residue at Kabat position 112 with an amino acid selected from the group consisting of valine, leucine, isoleucine, or threonine. In a more specific embodiment, the susbstitution comprises a replacement of the amino acid residue at Kabat position 112 with an isoleucine.

[0023] In one embodiment, the present disclosure is further directed to a modified antigen binding molecule comprising a CH1 domain comprising at least one amino acid residue substitution as compared to the CH1 domain of a parent polypeptide, wherein the substitution results in altered cell signaling activity of a target antigen when the modified antigen binding molecule is complexed with the target antigen.

[0024] In another embodiment, the present disclosure is further directed to a modified antigen binding molecule comprising a CH1 domain comprising at least one amino acid residue substitution as compared to the CH1 domain of a parent polypeptide, wherein the antigen binding molecule has altered ability to mediate cross-linking of one or more target antigens as a result of the substitution.

[0025] In a particular embodiment, the substitution in CH1 comprises a replacement of an amino acid residue at one or more of positions 148, 149 or 150. In a more specific embodiment, the substitution comprises a replacement of the amino acid residue position 149 with a leucine. In another embodiment, the substitution comprises a replacement of the entire CH1 domain. In another embodiment, the substitution comprises a replacement of an IgG CH1 domain with an IgM CH1 domain.

[0026] In another embodiment, the disclosure is directed to a modified antigen binding molecule comprising at least one amino acid substitution, wherein said substitution comprises a replacement of an amino acid residue in the light chain in the region of the interface between the variable and constant regions, wherein the substitution results in altered cell signaling activity of a target antigen binding molecule when said modified antigen binding molecule is complexed with said target antigen.

[0027] In another embodiment, the disclosure is directed to a modified antigen binding molecule comprising at least one amino acid substitution, wherein said substitution comprises a replacement of an amino acid residue in the light chain in the region of the interface between the variable and constant regions, wherein said modified antigen binding molecule has altered ability to mediate cross-linking of one or more target antigens as a result of said substitution.

[0028] In a particular embodiment, the substitution in the light chain variable region of the ABM comprises a replacement of an amino acid at one or more of Kabat positions 10, 12, 39, 40, 41, 80, 81, 83, 84, 103, 105, 106, and 108. In a particular embodiment, the substitution in the light chain variable region of the ABM comprises a replacement of an amino acid residue at one or more of Kabat positions 40, 80, 83, 105, or 106.

[0029] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at one or more of Kabat positions 40, 80, 83, 105, or 106 with a non-polar amino acid.

[0030] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 40 with an alanine.

[0031] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 80 with a proline.

[0032] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 83 with a phenylalanine.

[0033] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 105 with an alanine.

[0034] In another particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 106 with an alanine. In a more particular embodiment, the substitution in the light chain of the ABM comprises a replacement of an amino acid residue at Kabat position 106, wherein the antigen binding molecule is reduced in its ability to induce apoptosis.

[0035] In some embodiments, the substitutions of the present disclosure comprise a combination of any of the amino acid residue replacements in the heavy and/or light chain variable and/or constant regions as described herein.

[0036] In one embodiment, the amino acid substitution(s) in the modified ABMs of the present disclosure result in altered cell signaling activity of a target antigen when the modified ABM is complexed with the target antigen.

[0037] In one embodiment of the disclosure, the altered cell signaling activity is increased agonist activity. In one embodiment, the increased agonist activity is selected from the group consisting induction of apoptosis and induction of cell differentiation.

[0038] In another embodiment of the disclosure, the altered cell signaling activity is increased antagonist activity. In one embodiment, the antagonist activity is blockade of a cell signaling pathway selected from the group consisting of cell survival, cell growth, cell proliferation, and angiogenesis.

[0039] In a further embodiment, the modified antigen binding molecule of the present disclosure binds specifically to human CD20. In one aspect, there is provided a modified anti-CD20 antibody, wherein said modified antibody induces higher levels of apoptosis when complexed with CD20 as compared to when the chimeric B-Ly1 antibody is complexed with CD20, and wherein said modified antibody comprises: a first polypeptide comprising a heavy chain variable region sequence of SEQ ID NO: 128 and a second polypeptide comprising a light chain variable region sequence of SEQ ID NO: 48; or a first polypeptide comprising a heavy chain variable region sequence of SEQ ID NO: 129 and a second polypeptide comprising a light chain variable region sequence of SEQ ID NO: 48. In another embodiment, the modified antigen binding molecule binds specifically to a member of the human TNF receptor superfamily. In a particular embodiment, the TNF receptor superfamily

is selected from the group consisting of TNFR1, CD95, TRAILR1, TRAILR2, EDAR, and p75NGFR.

[0040] In another embodiment of the disclosure, the modified antigen binding molecule binds specifically to a receptor tyrosine kinase. In a particular embodiment, the receptor tyrosine kinase is selected from the group consisting of HER1 (EGFR1), HER2/neu, HER3, HER4, IGF-1R, FGFR, PDGFR, VEGFR1, VEGFR2, and VEGFR3. In a more specific embodiment, the receptor tyrosine kinase is HER1 (EGFR1).

[0041] In another embodiment, the present disclosure is further directed to a modified ABM that can be selected from, but is not limited to, the group consisting of a whole antibody, an Fab fragment or a fusion protein thereof, an F(ab')2 fragment or a fusion protein thereof, a minibody, a diabody, a triabody, and a tetrabody. In a particular embodiment, the modified ABM is chimeric or fully human. In a more particular embodiment, the chimeric modified ABM is humanized. In another particular embodiment, the modified ABM is multispecific. In a more particular embodiment, the modified ABM is bispecific.

[0042] In another embodiment, the parent antigen binding molecule according to the present disclosure comprises a heavy chain variable region selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62.

[0043] In another embodiment, the parent antigen binding molecule according to the present disclosure comprises a light chain selected from the group consisting of SEQ ID NO: 48, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, and SEQ ID NO:134.

[0044] In a further embodiment, the present disclosure is also directed to a modified ABM further comprising a human Fc region. According to one embodiment, the Fc region of the modified ABM has been modified to have altered oligosaccharides. In a more specific embodiment, the Fc region has been modified to have a decreased proportion of fucose residues compared to a non-modified Fc region. In another specific embodiment, the Fc region has an increased proportion of bisected oligosaccharides compared to a non-modified Fc region. In another specific embodiment, the modified oligosaccharides are bisected complex. In another specific embodiment, the modified oligosaccharides have an increased proportion of bisected, nonfucosylated

oligosaccharides in the Fc region compared to a non-modified Fc region. In another specific embodiment, the Fc region has an increased proportion of GlcNAc residues to fucose residues in the modified Fc region compared to a non-modified Fc region. In another specific embodiment, the bisected, nonfucosylated oligosaccharides are hybrid. In another specific embodiment, the bisected, nonfucosylated oligosaccharides are complex.

[0045] According to another embodiment, the target antigen according to the present disclosure is a cell surface receptor selected from the group consisting of a membrane transport receptor, a G-protein-linked receptor, and an enzyme-linked receptor. In a particular embodiment, the membrane transport receptor is a channel-linked receptor. In another particular embodiment, the enzyme-linked receptor is selected from the group consisting of receptor guanylyl cyclases, receptor tyrosine kinases, tyrosine-kinase associated receptors, receptor tyrosine phosphatases, and receptor serine/threonine kinases.

[0046] In another embodiment, the disclosure is related to a pharmaceutical composition comprising the modified ABM of the disclosure. It is contemplated that the pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, an adjuvant or a combination thereof. In another aspect, there is provided a pharmaceutical composition comprising the antibody described herein and a pharmaceutically acceptable carrier

[0047] The present disclosure is also directed to a method of treating a disease treatable by altered cell signaling activity in a patient, the method comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a modified ABM according to the disclosure and a pharmaceutically acceptable carrier.

[0048] In another embodiment, the disclosure is directed to an isolated polynucleotide encoding a polypeptide comprising a heavy chain or light chain variable region, wherein the heavy chain or light chain variable region comprises at least one amino acid residue substitution in at least one framework region as compared to a parent heavy chain or light chain variable region, and wherein the substitution results in altered cell signaling activity of a target antigen when the polypeptide is complexed with the target antigen.

[0049] In a further embodiment, the disclosure is directed to an isolated polynucleotide encoding a polypeptide comprising a heavy chain or light chain variable region, wherein the heavy chain or light chain variable region comprises at least one amino acid residue substitution in at least one framework region as compared to a

parent heavy chain or light chain variable region, and wherein the polypeptide has altered ability to mediate cross-linking of one or more target antigens as a result of the substitution. In another aspect, there is provided an isolated polynucleotide comprising a sequence that encodes a light chain variable region sequence of SEQ ID NO: 48 and a sequence that encodes a heavy chain variable region sequence of SEQ ID NO: 128. In another aspect, there is provided an isolated polynucleotide comprising a sequence that encodes a light chain variable region sequence of SEQ ID NO: 48 and a sequence that encodes a heavy chain variable region sequence of SEQ ID NO: 129.

[0050] In one embodiment, a polynucleotide according to the present disclosure encodes a polypeptide, wherein the polypeptide comprises an antibody heavy chain or light chain. In another embodiment, a polynucleotide according to the present disclosure encodes a polypeptide, wherein the polypeptide comprises a fusion protein. The present disclosure is also directed to polypeptides encoded by the polynucleotides of the present disclosure

[0051] The present disclosure is also directed to a vector comprising a polynucleotide according to the disclosure, and a host cell comprising the vector. In one aspect, there is provided an expression vector comprising the polynucleotide described herein. In another aspect, there is provided a host cell comprising the expression vector described herein.

[0052] The disclosure is further directed to a polynucleotide encoding a polypeptide comprising a heavy chain or light chain variable region which comprises at least one amino acid residue substitution in at least one framework region of the heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent antigen binding molecule, wherein the polypeptide is a modified ABM according to the disclosure.

[0053] The present disclosure is also directed to a host cell engineered to express at least one nucleic acid encoding a polypeptide having β(1,4)-N-acetylglucosaminyltransferase III activity in an amount sufficient to modify the oligosaccharides in the Fc region of a polypeptide produced by the host cell, wherein the polypeptide is a modified ABM according to the disclosure. In another aspect, there is provided a host cell expressing at least one nucleic acid encoding a first polypeptide having β(1,4)-N-acetylglucosaminyltransferase III activity in an amount sufficient to glycoengineer the Fc region of a second polypeptide produced by said host cell, wherein said second polypeptide is the antibody described herein. In one embodiment, the polypeptide having β(1,4)-N-acetylglucosaminyltransferase III activity is a fusion polypeptide. In a particular embodiment, the fusion polypeptide comprises the catalytic domain of β(1,4)-N-acetylglucosaminyltransferase III. In another embodmient the fusion polypeptide further comprises the Golgi localization domain of a heterologous Golgi resident polypeptide. The Golgi localization domain can be selected from, but is not limited to, the group consisting of the localization domain of mannosidase II, the localization domain of β(1,2)-N-acetylglucosaminyltransferase I, the localization domain of β(1,2)-N-acetylglucosaminyltransferase II, the localization domain of mannosidase I, and the localization domain of α1-6 core fucosyltransferase.

[0054] In another embodiment, the modified ABM comprises a region equivalent to the Fc region of a human IgG.

[0055] In a further embodiment, the modified ABM produced by the host cell of the present disclosure exhibits increased Fc receptor binding affinity and/or increased effector function as a result of the oligosaccharide modification. According to the present disclosure, the increased effector function is selected from the group consisting of increased Fc-mediated cellular cytotoxicity, increased binding to NK cells, increased binding to macrophages, increased binding to polymorphonuclear cells, increased binding to monocytes, increased direct signaling inducing apoptosis, increased dendritic cell maturation, and increased T cell priming. In one embodiment, the Fc receptor is Fcγ activating receptor. In another embodiment, the Fc receptor is FcγRIIIA receptor. In another aspect, there is provided a method for producing in a host cell an anti-CD20 antibody having an Fc region with modified oligosaccharides and engineered to have increased effector function, said method comprising:

a. culturing a host cell engineered to express at least one nucleic acid encoding a polypeptide having β(1,4)-N-acetylglucosaminyltransferase III activity under conditions which permit the production of said antibody, and which permit the modification of the oligosaccharides present on the Fc region of said antibody; and

b. isolating said antibody; wherein said antibody is the modified antibody described herein.

[0056] The host cell of the present disclosure may be selected from the group that includes, but is not limited to, a CHO cell, an HEK293-EBNA cell, a BHK cell, a NSO cell, a SP2/0 cell, a YO myeloma cell, a P3X63 mouse myeloma cell, a PER cell, a PER.C6 cell or a hybridoma cell.

[0057] In another embodiment, the present disclosure is directed to a method for producing a modified ABM comprising a heavy chain or light chain variable region comprising at least one amino acid residue substitution in at least one framework region of the heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent ABM, wherein the substitution results in altered cell signaling activity of a target antigen when the modified ABM is complexed with the target antigen, the method comprising: (i) culturing the host cell of the present disclosure under conditions permitting the expression of the polynucleotide; and (ii) recovering the modified ABM from the culture medium.

[0058] In a further embodiment, the disclosure is directed to a method for producing a modified ABM comprising a heavy chain or light chain variable region comprising at least one amino acid residue substitution in at least one framework region of the heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent antigen binding molecule, wherein the modified antigen binding molecule has altered ability to mediate cross-linking as a result of the substitution, the method comprising: (i) culturing the host cell of the present disclosure under conditions permitting the expression of the polynucleotide; and (ii) recovering the modified ABM from the culture medium.

[0059] In a further embodiment, the disclosure is directed to a method of altering the ability of an ABM to facilitate formation of complexes comprising the target antigen of the ABM, the method comprising: replacing at least one amino acid residue in at least one heavy chain or light chain variable region framework region of a parent ABM. In one embodiment, the ABM increases induction of apoptosis in a cell expressing the target antigen. In another embodiment, the ABM increases induction of cell differentiation in a cell expressing the target antigen.

[0060] The present disclosure is also directed to a method of inducing apoptosis in a cell, the method comprising contacting the cell with a modified ABM comprising a heavy chain or light chain variable region which comprises at least one amino acid residue substitution in at least one framework region of said heavy chain or light chain variable region as compared to the heavy chain or light chain variable region of a parent ABM, wherein the modified ABM has increased ability to induce apoptosis compared to the parent polypeptide. In a particular embodiment, the cell is a tumor cell. In one embodiment, the contacting occurs in vivo.

[0061] In another embodiment, the present disclosure is also directed method of treating a disease or disorder that is treatable by altered cell signaling activity of a target antigen, the method comprising administering to a subject in need thereof a therapeutically effective amount of a modified ABM, wherein the modified ABM comprises a heavy chain or light chain variable region comprising at least one amino acid substitution in at least one framework region of the heavy chain or light chain variable region compared to the heavy chain or light chain variable region of a parent ABM, and wherein the substitution results in altered cell signaling activity of a target antigen when the modified ABM is complexed with the target antigen.

[0062] In a further embodiment, the disclosure is directed to a method of treating a disease or disorder that is treatable by altered ability to mediate cross linking of one or more target antigens, the method comprising administering to a subject in need thereof a therapeutically effective amount of a modified ABM, wherein the modified ABM comprises a heavy chain or light chain variable region comprising at least one amino acid substitution in at least one framework region of the heavy chain or light chain variable region compared to the heavy chain or light chain

variable region of a parent ABM, and wherein the modified ABM has altered ability to mediate cross-linking of one or more target antigens as a result of the substitution.

[0063] In a particular embodiment, the modified ABM administered according to the present disclosure comprises a heavy chain variable region selected from the group consisting of SEQ ID NO:4, SEQ ID NO:36, and SEQ ID NO:38.

[0064] In one embodiment, the disease or disorder to be treated with a modified ABM of the present disclosure is a cell proliferation disorder. In one embodiment, cell proliferation disorder is cancer. In another embodiment, the disease or disorder to be treated with a modified ABM of the present disclosure is a B cell disorder. In a specific embodiment, the B cell disorder is a B cell lymphoma.

[0065] The present disclosure is also directed to use of a modified ABM according to the present disclosure for the manufacture of a medicament for the treatment or prophylaxis of cancer.

[0066] In a particular embodiment, the present disclosure is also directed to use of a modified ABM according to the present disclosure for the manufacture of a medicament for the treatment or prophylaxis of cancer, wherein said cancer is selected from the group consisting of B-cell lymphoma, breast cancer, bladder cancer, head and neck cancer, skin cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, kidney cancer, and brain cancer. In another aspect, there is provided use of the antibody described herein for the manufacture of a medicament to treat a haematological malignancy, wherein said haematological malignancy is B-cell lymphoma, non-Hodgkin's lymphoma, or B-cell chronic lymphocytic leukaemia. In another aspect, there is provided use of the antibody described herein for the manufacture of a medicament to treat an autoimmune disease, wherein said autoimmune disease is rheumatoid arthritis or lupus.

[0067] In another particular embodiment, the present disclosure is also directed to use of a modified ABM according to the present disclosure for the manufacture of a medicament for the treatment or prophylaxis of cancer, wherein said antigen binding molecule is used in a therapeutically effective amount from about 1.0 mg/kg to about 15 mg/kg. In a further embodiment, the therapeutically effective amount is from about 1.5 mg/kg to about 12 mg/kg. In a further embodiment, the therapeutically effective amount is from about 1.5 mg/kg to about 4.5 mg/kg. In a further embodiment, the therapeutically effective amount is from about 4.5 mg/kg to about 12 mg/kg. In a further embodiment, the therapeutically effective amount is about 1.5 mg/kg. In a further embodiment, the therapeutically effective amount is about 4.5 mg/kg. In a further embodiment, the therapeutically effective amount is about 12 mg/kg.

[0068] The present disclosure is also directed to a method for the treatment or prophylaxis of cancer comprising administering a therapeutically effective

amount of a pharmaceutical composition of the disclosure to a patient in need thereof. In a particular embodiment, the cancer is selected from the group consisting of B-cell lymphoma, breast cancer, bladder cancer, head and neck cancer, skin cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, kidney cancer, and brain cancer.

[0069] The present disclosure is also directed to a method for the treatment or prophylaxis of a precancerous condition or lesion comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 85 or 158 to a patient in need thereof. In a particular embodiment, the precancerous condition or lesion is selected from the group consisting of oral leukoplakia, actinic keratosis (solar keratosis)**,** precancerous polyps of the colon or rectum, gastric epithelial dysplasia, adenomatous dysplasia, hereditary nonpolyposis colon cancer syndrome (HNPCC), Barrett's esophagus, bladder dysplasia, and precancerous cervical conditions**.**

[0070] The present disclosure is also directed to a modified antigen binding molecule of the present disclosure for use in the treatment or prophylaxis of cancer. In a particular embodiment, the cancer is selected from the group consisting of B-cell lymphoma, breast cancer, bladder cancer, head and neck cancer, skin cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, kidney cancer, and brain cancer. In another aspect, there is provided an antibody described herein for use as a medicament to treat B-cell lymphoma.

[0071] The present disclosure is also directed to a modified antigen binding molecule of the present disclosure for use in the treatment or prophylaxis of a precancerous condition or lesion. In a particular embodiment, the precancerous condition or lesion is selected from the group consisting of oral leukoplakia, actinic keratosis (solar keratosis)**,** precancerous polyps of the colon or rectum, gastric epithelial dysplasia, adenomatous dysplasia, hereditary nonpolyposis colon cancer syndrome (HNPCC), Barrett's esophagus, bladder dysplasia, and precancerous cervical conditions**.**

[0072] The present disclosure is also directed to a modified antigen binding molecule according to the present disclosure for use in therapy of a disorder that is related to altered cell signaling activity and/or altered cross-linking of one or more target antigens.