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(54) Title: ANTIBODY THERAPEUTICS THAT BIND JAG1

(57) Abstract: There is disclosed compositions and methods relating to or derived from anti-JAGl antibodies. More specifically, there is disclosed fully human antibodies that bind JAGl, JAGl -binding fragments and derivatives of such antibodies, and JAGl -binding polypeptides comprising such fragments. Further still, there is disclosed nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having JAGl related disorders or conditions. There is also disclosed a method for treating JAGl -expressing tumors, including hepatocellular carcinomas and squamous carcinomas, and non-oncology diseases selected from the group consisting of rheumatoid arthritis, experimental lung injury, atherosclerosis, chronic liver disease induced by hepatitis C virus, ischemic myocardial injury and heart failure.

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Antibody Therapeutics That Bind JAG1

Related Applications

This application claims priority to United States Provisional Application No. 62/129,180 filed on March 6, 2015, the entire contents of which are incorporated by reference in their entirety herein.

Technical Field

The present disclosure provides compositions and methods relating to or derived from anti-JAG1 antibodies. More specifically, the present disclosure provides fully human antibodies that bind JAG1, JAG1-antibody binding fragments and derivatives of such antibodies, and JAG1-binding polypeptides comprising such fragments. Further still, the present disclosure provides nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having JAG1 related disorders or conditions. The present disclosure further provides a method for treating Notch-signaling tumors, including breast, prostate, colorectal, lung and other solid tumors.

Background

The Notch signaling pathway is one of several critical regulators of embryonic pattern formation, post-embryonic tissue maintenance, and stem cell biology. More specifically, Notch signaling is involved in the process of lateral inhibition between adjacent cell fates and plays an important role in cell fate determination during asymmetric cell divisions. Unregulated Notch signaling is associated with numerous human cancers where it can alter the developmental fate of tumor cells to maintain them in an undifferentiated and proliferative state (Brennan and Brown, 2003, *Breast Cancer Res.* 5:69). Thus carcinogenesis can proceed by usurping homeostatic mechanisms controlling normal development and tissue repair by stem cell populations (Beachy et al., 2004, *Nature* 432:324).

The Notch receptor was first identified in *Drosophila* mutants with haploinsufficiency resulting in notches at the wing margin, whereas loss-of-function produces an embryonic lethal "neurogenic" phenotype where cells of the epidermis switch fate to neural tissue (Moohr, 1919, *Genet.* 4:252; Poulson, 1937, *PNAS* 23:133; Poulson, 1940, *J. Exp. Zool.* 83:271). The Notch receptor is a single-pass transmembrane receptor containing numerous tandem epidermal growth factor (EGF)-like repeats and three cysteine-rich Notch/LIN-12 repeats within a large extracellular domain (Wharton et al., 1985, *Cell* 43:567; Kidd et al.,

1986, *Mol. Cell. Biol.* 6:3094; reviewed in Artavanis et al., 1999, *Science* 284:770). Four mammalian Notch proteins have been identified (Notch1, Notch2, Notch3, and Notch4), and mutations in these receptors invariably result in developmental abnormalities and human pathologies including several cancers as described in detail below (Gridley, 1997, *Mol. Cell. Neurosci.* 9:103; Joutel & Tournier-Lasserve, 1998, *Semin. Cell Dev. Biol.* 9:619-25).

Notch receptors are activated by single-pass transmembrane ligands of the Delta, Serrated, Lag-2 (DSL) family. There are five known Notch ligands in mammals: Delta-like 1 (DLL1), Delta-like 3 (DLL3), Delta-like 4 (DLL4), Jagged 1 (JAG1) and Jagged 2 (JAG2) characterized by a DSL domain and tandem EGF-like repeats within the extracellular domain. The extracellular domain of the Notch receptor interacts with that of its ligands, typically on adjacent cells, resulting in two proteolytic cleavages of Notch, one extracellular cleavage mediated by an ADAM (A Disintegrin And Metallopeptidase) protease and one cleavage within the transmembrane domain mediated by gamma secretase. This latter cleavage generates the Notch intracellular domain (ICD), which then enters the nucleus where it activates the CBF1, Suppressor of Hairless [Su(H)], Lag-2 (CSL) family of transcription factors as the major downstream effectors to increase transcription of nuclear basic helix-loop-helix transcription factors of the Hairy and Enhancer of Split [E(spl)] family (Artavanis et al., 1999, *Science* 284:770; Brennan and Brown, 2003, *Breast Cancer Res.* 5:69; Iso et al., 2003, Arterioscler. *Thromb. Vasc. Biol.* 23:543). Alternative intracellular pathways involving the cytoplasmic protein Deltex identified in *Drosophila* may also exist in mammals (Martinez et al., 2002, *Curr. Opin. Genet. Dev.* 12:524-33), and this Deltex-dependent pathway may act to suppress expression of Wnt target genes (Brennan et al., 1999, *Curr. Biol.* 9:707-710; Lawrence et al., 2001, *Curr. Biol.* 11:375-85).

Mammalian Notch receptors undergo cleavage to form the mature receptor and also following ligand binding to activate downstream signaling. A furin-like protease cleaves the Notch receptors during maturation to generate juxtamembrane heterodimers that comprise a non-covalently associated extracelluar subunit and a transmembrane subunit held together in an auto-inhibitory state. Ligand binding relieves this inhibition and induces cleavage of the Notch receptor by an ADAM-type metalloprotease and a gamma-secretase, the latter of which releases the intracellular domain (ICD) into the cytoplasm, allowing it to translocate into the nucleus to activate gene transcription. Cleavage by ADAM occurs within the non-ligand binding cleavage domain within the membrane proximal negative regulatory region.

Hematopoietic stem cells (HSCs) are the best understood stem cells in the body, and Notch signaling is implicated in their normal maintenance as well as in leukemic

transformation (Kopper & Hajdu, 2004, *Pathol. Oncol. Res.* 10:69-73). HSCs are a rare population of cells that reside in a stromal niche within the adult bone marrow. These cells are characterized both by a unique gene expression profile as well as an ability to continuously give rise to more differentiated progenitor cells to reconstitute the entire hematopoietic system. Constitutive activation of Notch1 signaling in HSCs and progenitor cells establishes immortalized cell lines that generate both lymphoid and myeloid cells in vitro and in long-term reconstitution assays (Varnum-Finney et al., 2000, *Nat. Med.* 6:1278-81), and the presence of Jagged1 increases engraftment of human bone marrow cell populations enriched for HSCs (Karanu et al., 2000, *J. Exp. Med.* 192:1365-72). More recently, Notch signaling has been demonstrated in HSCs *in vivo* and shown to be involved in inhibiting HSC differentiation. Furthermore, Notch signaling appears to be required for Wnt-mediated HSC self-renewal (Duncan et al., 2005, *Nat. Immunol.* 6:314).

The Notch signaling pathway also plays a central role in the maintenance of neural stem cells and is implicated in their normal maintenance as well as in brain cancers (Kopper & Hajdu, 2004, *Pathol. Oncol. Res.* 10:69-73; Purow et al., 2005, *Cancer Res.* 65:2353-63; Hallahan et al., 2004, *Cancer Res.* 64:7794-800). Neural stem cells give rise to all neuronal and glial cells in the mammalian nervous system during development, and more recently have been identified in the adult brain (Gage, 2000, *Science* 287:1433-8). Mice deficient for Notch1; the Notch target genes Hes1, 3, and 5; and a regulator of Notch signaling presenilin1 (PS1) show decreased numbers of embryonic neural stem cells. Furthermore, adult neural stem cells are reduced in the brains of PS1 heterozygote mice (Nakamura et al., 2000, *J. Neurosci.* 20:283-93; Hitoshi et al., 2002, *Genes Dev.* 16:846-58). The reduction in neural stem cells appears to result from their premature differentiation into neurons (Hatakeyama et al., 2004, *Dev.* 131:5539-50) suggesting that Notch signaling regulates neural stem cell differentiation and self-renewal.

Aberrant Notch signaling is implicated in a number of human cancers. The Notch1 gene in humans was first identified in a subset of T-cell acute lymphoblastic leukemias as a translocated locus resulting in activation of the Notch pathway (Ellisen et al., 1991, *Cell* 66:649-61). Constitutive activation of Notch1 signaling in T-cells in mouse models similarly generates T-cell lymphomas suggesting a causative role (Robey et al., 1996, *Cell* 87:483-92; Pear et al., 1996, *J. Exp. Med.* 183:2283-91; Yan et al., 2001, *Blood* 98:3793-9; Bellavia et al., 2000, *EMBO J.* 19:3337-48). Notch1 point mutations, insertions, and deletions producing aberrant Notch1 signaling have also been found to be frequently present in both childhood

and adult T-cell acute lymphoblastic leukemia/lymphoma (Pear & Aster, 2004, *Curr. Opin. Hematol.* 11:416-33).

The frequent insertion of the mouse mammary tumor virus into both the Notch1 and Notch4 locus in mammary tumors and the resulting activated Notch protein fragments first implicated Notch signaling in breast cancer (Gallahan & Callahan, 1987, *J. Virol.* 61:66-74; Brennan & Brown, 2003, *Breast Cancer Res.* 5:69; Politi et al., 2004, *Semin. Cancer Biol.* 14:341-7). Further studies in transgenic mice have confirmed a role Notch in ductal branching during normal mammary gland development, and a constitutively active form of Notch4 in mammary epithelial cells inhibits epithelial differentiation and results in tumorigenesis (Jhappan et al., 1992, *Genes & Dev.* 6:345-5; Gallahan et al., 1996, *Cancer Res.* 56:1775-85; Smith et al., 1995, *Cell Growth Differ.* 6:563-77; Soriano et al., 2000, *Int. J. Cancer* 86:652-9; Uyttendaele et al., 1998, *Dev. Biol.* 196:204-17; Politi et al., 2004, *Semin. Cancer Biol.* 14:341-7). Evidence for a role Notch in human breast cancer is provided by data showing the expression of Notch receptors in breast carcinomas and their correlation with clinical outcome (Weijzen et al., 2002, *Nat. Med.* 8:979-86; Parr et al., 2004, *Int. J. Mol. Med.* 14:779-86). Furthermore, overexpression of the Notch pathway has been observed in cervical cancers (Zagouras et al., 1995, PNAS 92:6414-8), renal cell carcinomas (Rae et al., 2000, *Int. J. Cancer* 88:726-32), head and neck squamous cell carcinomas (Leethanakul et al., 2000, *Oncogene* 19:3220-4), endometrial cancers (Suzuki et al., 2000, *Int. J. Oncol.* 17:1131-9), and neuroblastomas (van Limpt et al., 2000, *Med. Pediatr. Oncol.* 35:554-8), suggestive of a potential role for Notch in the development of a number of neoplasms. Notch signaling may play a role in the maintenance of the undifferentiated state of Apc-mutant neoplastic cells of the colon (van Es & Clevers, 2005, *Trends in Mol. Med.* 11:496-502).

The Notch pathway is also involved in multiple aspects of vascular development including proliferation, migration, smooth muscle differentiation, angiogenesis and arterial-venous differentiation (Iso et al., 2003, *Arterioscler. Thromb. Vasc. Biol.* 23:543). Furthermore, DLL1-deficient and Notch2-hypomorphic mice embryos show hemorrhaging that likely results from poor development of vascular structures (Gale et al., 2004, *PNAS*, 101:15949-54; Krebs et al., 2000, *Genes Dev.* 14:1343-52; Xue et al., 1999, *Hum. Mel. Genet.* 8:723-30; Hrabe de Angelis et al., 1997, *Nature* 386:717-21; McCright et al., 2001, *Dev.* 128:491-502).

Accordingly, there is a need in the art for therapeutic antibodies that bind to Jagged-1 (JAG1) epitopes and could be used as therapeutic agents for treating Notch-signaling tumors, including breast, prostate, colorectal, lung and other solid tumors.

Summary of the Invention

The invention generally provides novel antibodies and antibody fragments that bind to JAG1, *e.g.,* human JAG1, including anti-JAG1 human antibodies.

In certain embodiments, the present disclosure provides a fully human antibody of an IgG class that binds to a JAG1 epitope with a binding affinity of at least 10^{-6}M, which comprises a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and combinations thereof, and comprises a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2 (called JG1A1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called JG1A10 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called JG1A12 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called JG1A3 herein), SEQ ID NO.

9/SEQ ID NO. 10 (called JG1A4 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called JG11A5 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called JG1A6 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called JG1A7 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called JG1B1 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called JG1B10 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called JG1B11 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called JG1B12 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called JG1B4 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called JG1B5 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called JG1B6 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called JG1B8 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called JG1C3 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called JG1C4 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called JG1C5 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called JG1C8 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called JG1D1 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called JG1D10 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called JG1D11 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called JG1D7 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called JG1D8 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called JG1E1 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called JG1E11 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called JG1E7 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called JG1E8 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called JG1F1 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called JG1F10 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called JG1F7 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called JG1F8 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called JG1G11 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called JG1G5 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called JG1H1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called JG1H11 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called JG1H5 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called JG1H7 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called JH1A1 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called JH1A11 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called JH1A2 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called JH1A4 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called JH1B1 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called JH1B3 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called JH1B7 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called JH1C10 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called JH1C2 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called JH1D7 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called JH1E11 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called JH1F3 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called JH1F4 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called JH1F6 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called JH1H2 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called JH1H7 herein), and combinations thereof.

In one embodiment, the present disclosure provides a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region

from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human antibody Fab fragment comprises both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ

ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, and combinations thereof.

In one embodiment, the present disclosure provides a single chain human antibody, comprising a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence comprises a sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and wherein the light chain variable domain sequence comprises a sequence that is at least 95% identical to an amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ

ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human single chain antibody comprises both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, and combinations thereof.

In one embodiment, the present disclosure provides a method for treating Notch-signaling tumors, comprising administering an anti-JAG1 polypeptide, wherein the fully

human antibody comprises a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and combinations thereof, and comprises a light chain variable domain sequence that is at least 95% identical to the amino acid consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human antibody comprises both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called JG1A1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called JG1A10 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called JG1A12 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called JG1A3 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called JG1A4 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called JG11A5 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called JG1A6 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called JG1A7 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called JG1B1 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called JG1B10 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called JG1B11 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called JG1B12

herein), SEQ ID NO. 25/SEQ ID NO. 26 (called JG1B4 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called JG1B5 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called JG1B6 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called JG1B8 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called JG1C3 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called JG1C4 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called JG1C5 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called JG1C8 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called JG1D1 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called JG1D10 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called JG1D11 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called JG1D7 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called JG1D8 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called JG1E1 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called JG1E11 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called JG1E7 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called JG1E8 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called JG1F1 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called JG1F10 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called JG1F7 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called JG1F8 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called JG1G11 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called JG1G5 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called JG1H1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called JG1H11 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called JG1H5 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called JG1H7 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called JH1A1 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called JH1A11 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called JH1A2 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called JH1A4 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called JH1B1 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called JH1B3 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called JH1B7 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called JH1C10 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called JH1C2 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called JH1D7 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called JH1E11 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called JH1F3 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called JH1F4 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called JH1F6 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called JH1H2 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called JH1H7 herein), and combinations thereof.

In one embodiment, the present disclosure provides a method for treating Notch-signaling tumors, comprising administering a Fab fully human antibody fragment comprising a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO.

27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and combinations thereof, and comprising a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human antibody Fab fragment comprises both a heavy chain variable domain region and a light chain variable domain region wherein the antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called JG1A1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called JG1A10 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called JG1A12 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called JG1A3 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called JG1A4 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called JG11A5 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called JG1A6 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called JG1A7 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called JG1B1 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called JG1B10 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called JG1B11 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called JG1B12 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called JG1B4 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called JG1B5 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called JG1B6 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called JG1B8 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called JG1C3 herein), SEQ ID NO. 35/SEQ

ID NO. 36 (called JG1C4 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called JG1C5 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called JG1C8 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called JG1D1 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called JG1D10 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called JG1D11 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called JG1D7 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called JG1D8 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called JG1E1 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called JG1E11 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called JG1E7 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called JG1E8 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called JG1F1 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called JG1F10 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called JG1F7 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called JG1F8 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called JG1G11 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called JG1G5 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called JG1H1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called JG1H11 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called JG1H5 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called JG1H7 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called JH1A1 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called JH1A11 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called JH1A2 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called JH1A4 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called JH1B1 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called JH1B3 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called JH1B7 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called JH1C10 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called JH1C2 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called JH1D7 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called JH1E11 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called JH1F3 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called JH1F4 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called JH1F6 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called JH1H2 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called JH1H7 herein), and combinations thereof.

In one embodiment, the present disclosure provides a method for treating Notch-signaling tumors, comprising administering a single chain human antibody comprising a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69,

SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, and combinations thereof, and comprising a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, and combinations thereof. In one embodiment, the fully human single chain antibody comprises both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, and combinations thereof.

In one embodiment, the invention provides an isolated anti-JAG1 fully human antibody of an IgG class, said antibody comprising a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104,

SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

In one embodiment, the fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of: SEQ ID NO. 1/SEQ ID NO. 2 (JG1A1), SEQ ID NO. 3/SEQ ID NO. 4 (JG1A10), SEQ ID NO. 5/SEQ ID NO. 6 (JG1A12), SEQ ID NO. 7/SEQ ID NO. 8 (JG1A3), SEQ ID NO. 9/SEQ ID NO. 10 (JG1A4), SEQ ID NO. 11/SEQ ID NO. 12 (JG11A5), SEQ ID NO. 13/SEQ ID NO. 14 (JG1A6), SEQ ID NO. 15/SEQ ID NO. 16 (JG1A7), SEQ ID NO. 17/SEQ ID NO. 18 (JG1B1), SEQ ID NO. 19/SEQ ID NO. 20 (JG1B10), SEQ ID NO. 21/SEQ ID NO. 22 (JG1B11), SEQ ID NO. 23/SEQ ID NO. 24 (JG1B12), SEQ ID NO. 25/SEQ ID NO. 26 (JG1B4), SEQ ID NO. 27/SEQ ID NO. 28 (JG1B5), SEQ ID NO. 29/SEQ ID NO. 30 (JG1B6), SEQ ID NO. 31/SEQ ID NO. 32 (JG1B8), SEQ ID NO. 33/SEQ ID NO. 34 (JG1C3), SEQ ID NO. 35/SEQ ID NO. 36 (JG1C4), SEQ ID NO. 37/SEQ ID NO. 38 (JG1C5), SEQ ID NO. 39/SEQ ID NO. 40 (JG1C8), SEQ ID NO. 41/SEQ ID NO. 42 (JG1D1), SEQ ID NO. 43/SEQ ID NO. 44 (JG1D10), SEQ ID NO. 45/SEQ ID NO. 46 (JG1D11), SEQ ID NO. 47/SEQ ID NO. 48 (JG1D7), SEQ ID NO. 49/SEQ ID NO. 50 (JG1D8), SEQ ID NO. 51/SEQ ID NO. 52 (JG1E1), SEQ ID NO. 53/SEQ ID NO. 54 (JG1E11), SEQ ID NO. 55/SEQ ID NO. 56 (JG1E7), SEQ ID NO. 57/SEQ ID NO. 58 (JG1E8), SEQ ID NO. 59/SEQ ID NO. 60 (JG1F1), SEQ ID NO. 61/SEQ ID NO. 62 (JG1F10), SEQ ID NO. 63/SEQ ID NO. 64 (JG1F7), SEQ ID NO. 65/SEQ ID NO. 66 (JG1F8), SEQ ID NO. 67/SEQ ID NO. 68 (JG1G11), SEQ ID NO. 69/SEQ ID NO. 70 (JG1G5), SEQ ID NO. 71/SEQ ID NO. 72 (JG1H1), SEQ ID NO. 73/SEQ ID NO. 74 (JG1H11), SEQ ID NO. 75/SEQ ID NO. 76 (JG1H5), SEQ ID NO. 77/SEQ ID NO. 78 (JG1H7), SEQ ID NO. 79/SEQ ID NO. 80 (JH1A1), SEQ ID NO. 81/SEQ ID NO. 82 (JH1A11), SEQ ID NO. 83/SEQ ID NO. 84 (JH1A2), SEQ ID NO. 85/SEQ ID NO. 86 (JH1A4), SEQ ID NO. 87/SEQ ID NO. 88 (JH1B1 n), SEQ ID NO. 89/SEQ ID NO. 90 (JH1B3), SEQ ID NO. 91/SEQ ID NO. 92 (JH1B7), SEQ ID NO. 93/SEQ ID NO. 94 (JH1C10), SEQ ID NO. 95/SEQ ID NO. 96 (JH1C2), SEQ ID NO. 97/SEQ ID NO. 98 (JH1D7), SEQ ID NO. 99/SEQ ID NO. 100 (JH1E11), SEQ ID NO. 101/SEQ ID NO. 102 (JH1F3), SEQ ID NO. 103/SEQ ID NO. 104 (JH1F4), SEQ ID NO. 105/SEQ ID NO. 106 (JH1F6), SEQ ID NO. 107/SEQ ID NO. 108 (JH1H2), SEQ ID NO. 109/SEQ ID NO. 110 (JH1H7), SEQ ID NO. 111/SEQ ID NO.112

(G1H73-2), SEQ ID NO. 111/SEQ ID NO.113 (JG1H7-2B2S), SEQ ID NO.111/SEQ ID NO.114 (JG1H7-2AS), SEQ ID NO. 111/SEQ ID NO.115 (JG1H73-2A7S), SEQ ID NO. 111/SEQ ID NO.116 (JG1H7-2A10S), SEQ ID NO.111/SEQ ID NO.117 (JG1H7-2A2S), SEQ ID NO. 111/SEQ ID NO.118 (JG1H73-2A9S), SEQ ID NO. 111/SEQ ID NO.119 (JG1H7-2A1S), SEQ ID NO.111/SEQ ID NO.120 (JG1H7-E11S), SEQ ID NO. 111/SEQ ID NO.121 (JG1H73-C11S), SEQ ID NO. 111/SEQ ID NO.122 (JG1H7-D10S), SEQ ID NO.111/SEQ ID NO.123 (JG1H7-2B7S), SEQ ID NO.124/SEQ ID NO.112 (JG1H7-1A8S), SEQ ID NO. 125/SEQ ID NO.112 (JG1H73-1A6S), SEQ ID NO. 126/SEQ ID NO.112 (JG1H7-1A2S), SEQ ID NO.127/SEQ ID NO.112 (JG1H7-1B1S), SEQ ID NO. 128/SEQ ID NO.112 (JG1H73-1A8S), SEQ ID NO. 129/SEQ ID NO.112 (JG1H7-5B5S), SEQ ID NO.130/SEQ ID NO.112 (JG1H7-3E5S), SEQ ID NO.127/SEQ ID NO.131 (JG1H7-G6C), SEQ ID NO. 132/SEQ ID NO.133 (JG1H73-A6C), SEQ ID NO. 132/SEQ ID NO.123 (JG1H7-E11C), SEQ ID NO.142/SEQ ID NO.123 (JG1H7-C6C), SEQ ID NO. 127/SEQ ID NO.123 (JG1H73-C9C), SEQ ID NO. 132/SEQ ID NO.134 (JG1H7-F4C), SEQ ID NO. 135/SEQ ID NO.133 (JG1H7-F2C), SEQ ID NO.132/SEQ ID NO.136 (JG1H7-F1C), SEQ ID NO.132/SEQ ID NO.137 (JG1H7-D4C), SEQ ID NO. 132/SEQ ID NO.138 (JG1H73-D5C), SEQ ID NO. 139/SEQ ID NO.123 (JG1H7-A5C), SEQ ID NO.139/SEQ ID NO.140 (JG1H7-B2C), and SEQ ID NO. 127/SEQ ID NO.141 (JG1H73-B6C).

In one embodiment, the invention features an anti-JAG1 fully human antibody Fab fragment, comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and comprising a light chain

variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141. In one embodiment, the fully human antibody Fab fragment comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ

ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112 , SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115 , SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112 , SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134 , SEQ ID NO. 135/SEQ ID NO.133, SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, and SEQ ID NO. 127/SEQ ID NO.141.

In one embodiment, the invention provides an anti-JAG1 single chain human antibody, comprising a heavy chain variable domain and a light chain variable domain which are connected by a peptide linker, wherein the heavy chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142;

and the light chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

In one embodiment, the single chain fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO.

84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112 , SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115 , SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112 , SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134 , SEQ ID NO. 135/SEQ ID NO.133, SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, and SEQ ID NO. 127/SEQ ID NO.141.

In one embodiment, the invention provides an isolated anti-JAG1 antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain comprising complementarity determining regions (CDRs) as set forth in a heavy chain variable domain amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135,

SEQ ID NO. 139 and SEQ ID NO. 142; and comprising a light chain variable domain comprising CDRs as set forth in a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

In one embodiment, an anti-JAG1 antibody or an anti-JAG1 antibody fragment described herein may be used in a method for treating a Notch-signaling tumor in a subject in need thereof, said method comprising administering an effective amount of an anti-JAG1 antibody, or anti-JAG1 antibody fragment, to the subject in need thereof. In one embodiment, the tumor is selected from the group consisting of breast tumor, prostate, colorectal, lung, head and neck squamous cell carcinoma, T-cell acute lymphoblastic leukemia and melanoma and other solid tumors.

In one embodiment, the invention provides a method of treating cancer in a human subject in need thereof, comprising administering an effective amount of an anti-JAG1 antibody, or antigen-binding fragment thereof, disclosed herein to the subject, such that cancer is treated. In one embodiment, the cancer is associated with Notch-signaling. In one embodiment, the cancer is selected from the group consisting of breast, prostate, colorectal, lung, head and neck squamous cell carcinoma, T-cell acute lymphoblastic leukemia, melanoma, and a solid tumor.

In one embodiment, the method of the invention is for treating Notch-signaling tumors wherein the disease is selected from the group consisting of breast, prostate, colorectal, lung and other solid tumors.

In certain embodiments, the anti-JAG1 antibody, or antigen-binding fragment thereof, of the invention has a binding affinity (K_D) of at least 1 x 10^{-6} M. In other embodiments, the antibody, or antigen-binding fragment thereof, of the invention has a K_D of at least 1 x 10^{-7} M. In other embodiments, the antibody, or antigen-binding fragment thereof, of the invention has a K_D of at least 1 x 10^{-8} M.

In certain embodiments, the antibody is an IgG1 isotype. In other embodiments, the antibody is an IgG4 isotype.

In certain embodiments, the antibody, or antigen-binding fragment, described herein is recombinant. In certain embodiments, the antibody, or antigen-binding fragment, described herein, is a human antibody, or antigen binding fragment of an antibody.

In certain embodiments, the invention provides a pharmaceutical composition comprising an effective amount of an anti-JAG1 antibody, or antibody fragment disclosed herein, and a pharmaceutically acceptable carrier.

Description of the Drawings

Figure 1A is a graph that shows the cytotoxic potential of anti-JAG-1 antibodies complexed with Protein G –DM1 molecules (PG-DM1) on JAG-1- overexpressing cancer cells. Corresponding naked antibodies were used as controls.

Figure 1B illustrates the non-specific cell killing effect observed on normal human fibroblasts (HFF cells) with anti-JAG-1 antibodies complexed with Protein G –DM1 molecules. Corresponding naked antibodies were used as controls.

Figure 2 is a graph that shows the results of a binding ELISA of two antibodies, JG1H7 and JG1B10, to human JAG-1.

Figure 3 is a graph that shows the results of a binding ELISA of JG1H7 and variants (F2C, D4C, D5C, B6C, C6C, C9C) to human JAG-1.

Figure 4 is a graph that shows the results of a binding ELISA of two antibodies, JG1H7 and B10, to human JAG-2. In Figure 4, the designation of antibody "B10" refers to "JG1B10." The terms are used interchangeably. The designation of antibody "H7" refers to "JG1H7." The terms are used interchangeably.

Figure 5 is a graph that shows the results of a binding ELISA of JG1H7 and variants to human JAG-2.

Figure 6 is a graph that shows the results of a binding ELISA of JG1H7 and variants to murine JAG-2.

Figure 7A is a graph that shows the results of a binding ELISA of antibody JG1H7 to human JAG-1, human DLL1 and human DLL2.

Figure 7B is a graph that shows the results of a binding ELISA of antibody JG1B10 to human JAG-1, human DLL1 and human DLL2. In Figure 7B, B10JAG1 refers to the antibody "JG1B10."

Detailed Description

Definitions

The terms "peptide," "polypeptide" and "protein" each refers to a molecule comprising two or more amino acid residues joined to each other by peptide bonds. These terms encompass, *e.g.*, native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

A "variant" of a polypeptide (for example, a variant of an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Disclosed variants include, for example, fusion proteins.

A "derivative" of a polypeptide is a polypeptide (*e.g.*, an antibody) that has been chemically modified, *e.g.*, via conjugation to another chemical moiety (such as, for example, polyethylene glycol or albumin, *e.g.*, human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a confirmation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (*e.g.*, an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129; Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics

("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

An antigen binding protein can have, for example, the structure of an immunoglobulin. An "immunoglobulin" is a tetrameric molecule composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa or lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Preferably, the anti-JAG1 antibodies disclosed herein are characterized by their variable domain region sequences in the heavy V_H and light V_L amino acid sequences. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

The variable regions of immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. Other numbering systems for the amino acids in immunoglobulin chains include IMGT.RTM. (international ImMunoGeneTics information system; Lefranc et al, Dev. Comp. Immunol. 29:185-203; 2005) and AHo (Honegger and Pluckthun, J. Mol. Biol. 309(3):657-670; 2001).

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. In one embodiment, an antibody is an IgG and comprises four polypeptide chains including two identical heavy chains each comprising a heavy chain variable domain and heavy chain constant regions C_{H1}, C_{H2} and C_{H3}, and two identical light chains each comprising a light chain variable domain and a light chain constant region (C_L). In certain

embodiments, the antibody is an IgG4. The heavy and light chain variable domain sequences may be selected from those described herein in SEQ ID Nos: 1 to 142.

Antigen binding portions of an antibody may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, inter alia, Fab, Fab', F(ab')2, Fv, domain antibodies (dAbs), and complementarity determining region (CDR) fragments, chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (*e.g.*, a synthetic sequence of amino acid residues) to form a continuous protein chain. The linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., 1988, *Science* 242:423-26 and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83).

In certain embodiments, antibodies can be obtained from sources such as serum or plasma that contain immunoglobulins having varied antigenic specificity. If such antibodies are subjected to affinity purification, they can be enriched for a particular antigenic specificity. Such enriched preparations of antibodies usually are made of less than about 10% antibody having specific binding activity for the particular antigen. Subjecting these preparations to several rounds of affinity purification can increase the proportion of antibody having specific binding activity for the antigen. Antibodies prepared in this manner are often referred to as "monospecific."

The term “monospecific”, as used herein, refers to an antibody that displays an affinity for one particular epitope. Monospecific antibody preparations can be made up of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 99.9% antibody having specific binding activity for the particular antigen.

An "antibody fragment" or “antigen binding fragment of an antibody” comprises a portion of an intact antibody, and preferably comprises the antibody antigen binding or variable domains. Examples of an antibody fragment include a Fab, a Fab', a F(ab')2, an Fv fragment, and a linear antibody.

A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_{H1} domains; a $F(ab')_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_{H1} domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an antigen-binding fragment of a V_H or V_L domain (U.S. Patents 6,846,634;

6,696,245, US App. Pub.20/0202512; 2004/0202995; 2004/0038291; 2004/0009507;20 03/0039958, and Ward et al., *Nature* 341:544-546, 1989).

Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises VH and VL domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, Proc. Natl. Acad. Sci. USA 90:6444-48, and Poljak et al., 1994, Structure 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

An antigen binding protein, such as an antibody, may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

The term "human antibody" includes antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains of the antibody are derived from human immunoglobulin sequences (referred to as “a fully human antibody”). These antibodies may be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes. In a preferred embodiment, a fully human antibody is made using recombinant methods such that the glycosylation pattern of the antibody is different than an antibody having the same sequence if it were to exist in nature.

A “humanized antibody” has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another

embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Patents 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of the CDRs are derived from a human anti-JAG1 antibody. In another embodiment, all of the CDRs are derived from a human anti-JAG1 antibody. In another embodiment, the CDRs from more than one human anti-JAG1 antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-PAR-2 antibody, a CDR2 and a CDR3 from the light chain of a second human anti-JAG1 antibody, and the CDRs from the heavy chain from a third anti-JAG1 antibody. Other combinations are possible.

Further, the framework regions may be derived from one of the same anti-JAG1 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to, or derived from an antibody (-ies) from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*i.e.*, the ability to specifically bind JAG1).

A "CDR grafted antibody" is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

An antigen binding protein "specifically binds" to an antigen (*e.g.*, human JAG1) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

An "antigen binding domain," "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

The term "Fc polypeptide" includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

An "epitope" is the portion of a molecule that is bound by an antigen binding protein (*e.g.*, by an antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*, in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

The “percent identity” or "percent homology" of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, Calif.)) using its default parameters.

The terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably throughout and include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs (*e.g.*, peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof.

Two single-stranded polynucleotides are "the complement" of each other if their sequences can be aligned in an anti-parallel orientation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5' or the 3' end of either sequence. A polynucleotide is "complementary" to another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a

polynucleotide can be complementary to another polynucleotide without being its complement.

A "vector" is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

A nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (*e.g.*, the level, timing, or location of expression) of the nucleotide sequence. A "regulatory sequence" is a nucleic acid that affects the expression (*e.g.*, the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (*e.g.*, polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: *Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

A "host cell" is a cell that can be used to express a nucleic acid, *e.g.*, a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman et al., 1981, *Cell* 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen et al., 1998, *Cytotechnology* 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:4216-20), HeLa

cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan et al., 1991, *EMBO J.* 10:2821), human embryonic kidney cells such as 293,293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. In one embodiment, a host cell is a mammalian host cell, but is not a human host cell. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, *e.g.,* mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term “recombinant antibody” refers to an antibody that is expressed from a cell or cell line transfected with an expression vector (or possibly more than one expression vector) comprising the coding sequence of the antibody, or a portion thereof (*e.g.,* a DNA sequence encoding a heavy chain or a light chain). In one embodiment, said coding sequence is not naturally associated with the cell. In one embodiment, a recombinant antibody has a glycosylation pattern that is different than the glycosylation pattern of an antibody having the same sequence if it were to exist in nature. In one embodiment, a recombinant antibody is expressed in a mammalian host cell which is not a human host cell. Notably, individual mammalian host cells have unique glycosylation patterns.

The term “effective amount” as used herein, refers to that amount of an antibody, or an antigen binding portion thereof that binds JAG1, which is sufficient to effect treatment of a disease associated with JAG1 signaling, as described herein, when administered to a subject. Therapeutically effective amounts of antibodies provided herein, when used alone or in combination, will vary depending upon the relative activity of the antibodies and combinations (*e.g.*, in inhibiting cell growth) and depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease

condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "isolated" refers to a protein (*e.g.*, an antibody) that is substantially free of other cellular material. In one embodiment, an isolated antibody is substantially free of other proteins from the same species. In one embodiment, an isolated antibody is expressed by a cell from a different species and is substantially free of other proteins from the different species. A protein may be rendered substantially free of naturally associated components (or components associated with the cellular expression system used to produce the antibody) by isolation, using protein purification techniques well known in the art. In one embodiment, the antibodies, or antigen binding fragments, of the invention are isolated.

A "neutralizing antibody" or an "inhibitory antibody" is an antibody that inhibits the proteolytic activation of JAG1 when an excess of the anti-JAG1 antibody reduces the amount of activation by at least about 20% using an assay such as those described herein in the Examples. In various embodiments, the antigen binding protein reduces the amount of amount of proteolytic activation of JAG1 by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.

JAG-1 Antigen Binding Proteins

The present invention pertains to JAG1 binding proteins, particularly anti-JAG1 antibodies, or antigen-binding portions thereof, that bind JAG1, and uses thereof. Various aspects of the invention relate to antibodies and antibody fragments, pharmaceutical compositions, nucleic acids, recombinant expression vectors, and host cells for making such antibodies and fragments. Methods of using the antibodies of the invention to detect human JAG1, to inhibit JAG1 activity, either *in vitro* or *in vivo*, and to prevent or treat disorders such as cancer are also encompassed by the invention. Methods of using the antibodies of the invention to detect human JAG2, to inhibit JAG2 activity, either *in vitro* or *in vivo*, and to prevent or treat disorders such as cancer are also encompassed by the invention.

As described in Table 5 below, included in the invention are novel antibody heavy and light chain variable regions that are specific to JAG1. In one embodiment, the invention provides an anti-JAG1 antibody, or an antigen-binding fragment thereof, that comprises a heavy chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31,

SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142. In one embodiment, the invention provides an anti-JAG1 antibody, or an antigen-binding fragment thereof, that comprises a light chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141. In one embodiment, the invention provides an anti-JAG1 antibody, or an antigen-binding fragment thereof, that comprises a light chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO.

52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141; and a heavy chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142.

Complementarity determining regions (CDRs) are known as hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework (FR). Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat et al. supra; Lefranc et al., supra and/or Honegger and Pluckthun, supra. Also familiar to those in the art is the numbering system described in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). In this regard Kabat et al. defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this

system of "Kabat numbering" to any variable domain amino acid sequence, without reliance on any experimental data beyond the sequence itself.

In certain embodiments, the present invention provides an anti-JAG1 antibody comprising the CDRs of a heavy and a light chain variable domain as described in Table 5 (SEQ ID Nos: 1 to 142). For example, the invention provides an anti-JAG1 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region having CDRs described in an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142. In one embodiment, the invention provides an anti-JAG1 antibody, or antigen-binding fragment thereof, comprising a light chain variable region having CDRs described in an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120,

SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141. In one embodiment, the invention provides an anti-JAG1 antibody, or antigen-binding fragment thereof, comprising a light chain variable region having CDRs described in an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141; and a heavy chain variable region having CDRs described in an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142.

It should be noted that throughout, antibodies (and corresponding sequences) are referred to interchangeably with or without a "JG1" preceding the name. For example, the antibody name "JG1H7" is also referred to herein as "H7".

One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein.

An antigen binding protein may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

In one embodiment, the present disclosure provides a fully human antibody of an IgG class that binds to a JAG1 epitope with a binding affinity of 10^{-6}M or less, that has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139, SEQ ID NO. 142, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78,

SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 141, and combinations thereof.

In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called JG1A1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called JG1A10 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called JG1A12 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called JG1A3 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called JG1A4 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called JG11A5 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called JG1A6 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called JG1A7 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called JG1B1 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called JG1B10 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called JG1B11 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called JG1B12 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called JG1B4 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called JG1B5 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called JG1B6 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called JG1B8 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called JG1C3 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called JG1C4 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called JG1C5 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called JG1C8 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called JG1D1 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called JG1D10 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called JG1D11 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called JG1D7 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called JG1D8 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called JG1E1 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called JG1E11 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called JG1E7 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called JG1E8 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called JG1F1 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called JG1F10 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called JG1F7 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called JG1F8 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called JG1G11 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called JG1G5 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called JG1H1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called JG1H11 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called JG1H5 herein), SEQ ID NO.

77/SEQ ID NO. 78 (called JG1H7 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called JH1A1 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called JH1A11 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called JH1A2 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called JH1A4 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called JH1B1 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called JH1B3 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called JH1B7 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called JH1C10 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called JH1C2 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called JH1D7 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called JH1E11 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called JH1F3 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called JH1F4 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called JH1F6 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called JH1H2 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called JH1H7 herein), SEQ ID NO. 111/SEQ ID NO.112 (called JG1H73-2 herein), SEQ ID NO. 111/SEQ ID NO.113 (called JG1H7-2B2S herein), SEQ ID NO.111/SEQ ID NO.114 (called JG1H7-2AS herein), SEQ ID NO. 111/SEQ ID NO.115 (called JG1H73-2A7S herein), SEQ ID NO. 111/SEQ ID NO.116 (called JG1H7-2A10S herein), SEQ ID NO.111/SEQ ID NO.117 (called JG1H7-2A2S herein), SEQ ID NO. 111/SEQ ID NO.118 (called JG1H73-2A9S herein), SEQ ID NO. 111/SEQ ID NO.119 (called JG1H7-2A1S herein), SEQ ID NO.111/SEQ ID NO.120 (called JG1H7-E11S herein), SEQ ID NO. 111/SEQ ID NO.121 (called JG1H73-C11S herein), SEQ ID NO. 111/SEQ ID NO.122 (called JG1H7-D10S herein), SEQ ID NO.111/SEQ ID NO.123 (called JG1H7-2B7S herein), SEQ ID NO.124/SEQ ID NO.112 (called JG1H7-1A8S herein), SEQ ID NO. 125/SEQ ID NO.112 (called JG1H73-1A6S herein), SEQ ID NO. 126/SEQ ID NO.112 (called JG1H7-1A2S herein), SEQ ID NO.127/SEQ ID NO.112 (called JG1H7-1B1S herein), SEQ ID NO. 128/SEQ ID NO.112 (called JG1H73-5A8S herein), SEQ ID NO. 129/SEQ ID NO.112 (called JG1H7-5B5S herein), SEQ ID NO.130/SEQ ID NO.112 (called JG1H7-3E5S herein), SEQ ID NO.127/SEQ ID NO.131 (called JG1H7-G6C herein), SEQ ID NO. 132/SEQ ID NO.133 (called JG1H73-A6C herein), SEQ ID NO. 132/SEQ ID NO.123 (called JG1H7-E11C herein), SEQ ID NO.142/SEQ ID NO.123 (called JG1H7-C6C herein), SEQ ID NO. 127/SEQ ID NO.123 (called JG1H73-C9C herein), SEQ ID NO. 132/SEQ ID NO.134 (called JG1H7-F4C herein), SEQ ID NO. 135/SEQ ID NO.133 (called JG1H7-F2C herein), SEQ ID NO.132/SEQ ID NO.136 (called JG1H7-F1C herein), SEQ ID NO.132/SEQ ID NO.137 (called JG1H7-D4C herein), SEQ ID NO. 132/SEQ ID NO.138 (called JG1H73-D5C herein), SEQ ID NO. 139/SEQ ID NO.123 (called JG1H7-A5C herein), SEQ ID NO.139/SEQ ID NO.140 (called JG1H7-B2C herein), SEQ ID NO. 127/SEQ ID NO.141 (called JG1H73-B6C herein), and combinations thereof.

In one embodiment, the invention provides an anti-JAG1 antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising a CDR3 domain as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142, and comprising a variable domain comprising an amino acid sequence that has at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142. In one embodiment, the invention provides an anti-JAG1 antibody, or an antigen-binding fragment thereof, comprising a light chain comprising a CDR3 domain as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO.

24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and having a light chain variable domain comprising an amino acid sequence that has at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141. Thus, in certain embodiments, the CDR3 domain is held constant, while variability may be introduced into the remaining CDRs and/or framework regions of the heavy and/or light chains, while the antibody, or antigen binding fragment thereof, retains the ability to bind to JAG1 and retains the functional characteristics, *e.g.,* binding affinity, of the parent.

In one embodiment, the substitutions made within a heavy or light chain that is at least 95% identical (or at least 96% identical, or at least 97% identical, or at least 98% identical, or at least 99% identical) are conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having the antigen binding regions of any of the antibodies described in Table 5. The antibodies of the invention, including those described in Table 5, bind to human JAG1.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 77, and a light chain variable domain sequence as set forth in SEQ ID NO: 78. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 77, and a light chain variable domain comprising the CDRs of SEQ ID NO: 78. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 77, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99%

identical to the sequence set forth in SEQ ID NO: 78. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7.3-2 In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2B2S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 113. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:113. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 113. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A3S. In one

embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 114. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:114. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 114. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A7S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 115. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:115. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 115. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A10S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 116. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:116. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 116. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A2S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 117. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:117. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 117. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A9S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 118. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:118. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97%

identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 118. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2A1S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 119. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:119. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 119. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-E11S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 120. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:120. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at

least 99% identical to the sequence set forth in SEQ ID NO: 120. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-C11S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 121. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:121. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 121. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-D10S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 122. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:122. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 122. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-2B7S. In one

embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 111, and a light chain variable domain sequence as set forth in SEQ ID NO: 123. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 111, and a light chain variable domain comprising the CDRs of SEQ ID NO:123. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 111, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 123. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-1A8S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 124, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 124, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 124, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-1A6S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 125, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 125, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 125, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-1A2S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 126, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 126, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 126, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-1B1S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 127, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In on7 embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 127, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97%

identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 127, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-5A8S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 128, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 128, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 128, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-5B5S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 129, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 129, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 129, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at

least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-3E5S. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 130, and a light chain variable domain sequence as set forth in SEQ ID NO: 112. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 130, and a light chain variable domain comprising the CDRs of SEQ ID NO:112. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 130, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 112. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-G6C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 127, and a light chain variable domain sequence as set forth in SEQ ID NO: 131. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 127, and a light chain variable domain comprising the CDRs of SEQ ID NO:131. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 127, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 131. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-A6C. In one

embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 133. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:133. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 133. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-E11C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 123. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:123. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 123. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-C6C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 142, and a light chain variable domain sequence as set forth in SEQ ID NO: 123. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 142, and a light chain variable domain comprising the CDRs of SEQ ID NO:123. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 142, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 123. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-C9C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 127, and a light chain variable domain sequence as set forth in SEQ ID NO: 123. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 127, and a light chain variable domain comprising the CDRs of SEQ ID NO:123. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 127, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 123. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-F4C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 134. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:134. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97%

identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 134. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-F2C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 135, and a light chain variable domain sequence as set forth in SEQ ID NO: 133. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 135, and a light chain variable domain comprising the CDRs of SEQ ID NO:133. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 135, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 133. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-F1C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 136. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:136. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at

least 99% identical to the sequence set forth in SEQ ID NO: 136. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-D4C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 137. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:137. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 137. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-D5C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 132, and a light chain variable domain sequence as set forth in SEQ ID NO: 138. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 132, and a light chain variable domain comprising the CDRs of SEQ ID NO:138. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 132, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 138. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-A5C. In one

embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 139, and a light chain variable domain sequence as set forth in SEQ ID NO: 123. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 139, and a light chain variable domain comprising the CDRs of SEQ ID NO:123. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 139, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 123. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-B2C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 139, and a light chain variable domain sequence as set forth in SEQ ID NO: 140. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 139, and a light chain variable domain comprising the CDRs of SEQ ID NO:140. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 139, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 140. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody JG1H7-B6C. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 127, and a light chain variable domain sequence as set forth in SEQ ID NO: 141. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 127, and a light chain variable domain comprising the CDRs of SEQ ID NO:141. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 127, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 141. The antibody may further be an IgG1 or an IgG4 isotype.

As described in Table 5, a number of heavy chain variable domains have amino acid sequences that are at least 95% identical to SEQ ID NO:111, including SEQ ID NO: 135 (as described for antibody JG1H7-F2C), SEQ ID NO: 142 (as described for antibody JG1H7-C6C), SEQ ID NO: 132 (as described for antibodies JG1H7-A6C, JG1H7-E11C, JG1H7-F1C, JG1H7-D4C and JG1H7-D5C), SEQ ID NO: 130 (as described for antibody JG1H7-3E5S), SEQ ID NO: 129 (as described for antibody JG1H7-5B5S), SEQ ID NO: 128 (as described for antibody JG1H7-5A8S), SEQ ID NO: 127 (as described for antibodies JG1H7-1B1S, JG1H7-G6C, JG1H7-C9C and JG1H7-B6C), SEQ ID NO: 132 (as described for antibody JG1H7-F4C), SEQ ID NO: 126 (as described for antibody JG1H7-1A2S), SEQ ID NO: 125 (as described for antibody JG1H7-1A6S), SEQ ID NO: 124 (as described for antibody JG1H7-1A8S) and SEQ ID NO: 139 (as described for antibodies JG1H7-A5C and JG1H7-B2C).

As also described in Table 5, a number of light chain variable domains have amino acid sequences that are at least 95% identical to SEQ ID NO:112, including SEQ ID NO: 140 (as described for antibody JG1H7-B2C), SEQ ID NO: 138 (as described for antibody JG1H7-D5C), SEQ ID NO: 137 (as described for antibody JG1H7-D4C), SEQ ID NO: 136 (as described for antibody JG1H7-F1C), SEQ ID NO: 134 (as described for antibody JG1H7-F4C), SEQ ID NO: 133 (as described for antibodies JG1H7-A6C and JG1H7-F2C), SEQ ID NO: 131 (as described for antibody JG1H7-G6C), SEQ ID NO: 123 (as described for antibodies JG1H7-2B7S, JG1H7-E11C, JG1H7-C6C, JG1H7-A5C and JG1H7-C9C), SEQ ID NO: 122 (as described for antibody JG1H7-D10S), SEQ ID NO: 121 (as described for antibody JG1H7-C11S), SEQ ID NO: 120 (as described for antibody JG1H7-E11S) , SEQ ID NO: 119 (as described for antibody JG1H7-2A1S), SEQ ID NO: 118 (as described for antibody JG1H7-2A9S), SEQ ID NO: 117 (as described for antibody JG1H7-2A2S) , SEQ ID NO: 116 (as described for antibody JG1H7-2A10S), SEQ ID NO: 115 (as described for

antibody JG1H7-2A7S), SEQ ID NO: 114 (as described for antibody JG1H7-2A3S) , SEQ ID NO: 141(as described for antibody JG1H7-B6C), and SEQ ID NO: 113 (as described for antibody JG1H7-2B2S).

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and F(ab')2 fragments.

In certain embodiments, the present disclosure provides a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142 and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO.

84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112, SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115, SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID

NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112, SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112 , SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134, SEQ ID NO. 135/SEQ ID NO.133 , SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, SEQ ID NO. 127/SEQ ID NO.141, and combinations thereof.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, *Prot. Eng.* 10:423; Kortt et al., 2001, *Biomol. Eng.* 18:95-108). By combining different V_L and V_H-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent 4,946,778; Bird, 1988, *Science* 242:423; Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879; Ward et al., 1989, *Nature* 334:544, de Graaf et al., 2002, *Methods Mol. Biol.* 178:379-87.

In one embodiment, the present disclosure provides a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67,

SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and combinations thereof. In one embodiment, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ

ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112, SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115, SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112, SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112 , SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134, SEQ ID NO. 135/SEQ ID NO.133 , SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, SEQ ID NO. 127/SEQ ID NO.141, and combinations thereof.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, *i.e.*, subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired isotype

(Lantto et al., 2002, *Methods Mol. Biol.* 178:303-16). Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation (CPSCP->CPPCP) (SEQ ID NOS 143 and 144, respectively) in the hinge region (Bloom et al., 1997, *Protein Science* 6:407) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies. Thus, in one embodiment, the antibody of the invention is a human IgG1 antibody. Thus, in one embodiment, the antibody of the invention is a human IgG4 antibody.

The present disclosure provides a number of antibodies structurally characterized by the amino acid sequences of their variable domain regions. However, the amino acid sequences can undergo some changes while retaining their high degree of binding to their specific targets. More specifically, many amino acids in the variable domain region can be changed with conservative substitutions and it is predictable that the binding characteristics of the resulting antibody will not differ from the binding characteristics of the wild type antibody sequence. There are many amino acids in an antibody variable domain that do not directly interact with the antigen or impact antigen binding and are not critical for determining antibody structure. For example, a predicted nonessential amino acid residue in any of the disclosed antibodies is preferably replaced with another amino acid residue from the same class. Methods of identifying amino acid conservative substitutions which do not eliminate antigen binding are well- known in the art (see, e.g., Brummell et al., *Biochem.* 32: 1180-1187 (1993); Kobayashi et al. *Protein Eng.* 12(10):879-884 (1999); and Burks et al. *Proc. Natl. Acad. Sci. USA* 94:412-417 (1997)). Near et al. *Mol. Immunol.* 30:369-377, 1993 explains how to impact or not impact binding through site-directed mutagenesis. Near et al. only mutated residues that they thought had a high probability of changing antigen binding. Most had a modest or negative effect on binding affinity (Near et al. Table 3) and binding to different forms of digoxin (Near et al. Table 2).

Thus, the invention also includes, in certain embodiments, variable sequences having at least 95% identity to those sequences disclosed herein.

In certain embodiments, an antibody, or antigen-binding fragment thereof, provided herein has a dissociation constant (K_D) of 1×10^{-6} M or less; 5×10^{-7} M or less' 1×10^{-7} M or less; 5×10^{-8} M or less; 1×10^{-8} M or less; 5×10^{-9} M or less; or 1×10^{-9} M or less. In one embodiment, the antibody, or antigen-binding fragment thereof, of the invention as a K_D from 1×10^{-7} M to 1×10^{-10} M. In one embodiment, the antibody, or antigen-binding fragment thereof, of the invention as a K_D from 1×10^{-8} M to 1×10^{-10} M.

Those of ordinary skill in the art will appreciate standard methods known for determining the K_D of an antibody, or fragment thereof. For example, in one embodiment, K_D is measured by a radiolabeled antigen binding assay (RIA). In one embodiment, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen *et al.*, J. Mol. Biol. 293:865-881(1999)).

According to another embodiment, K_D is measured using a BIACORE surface plasmon resonance assay. The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

In particular embodiments, antigen binding proteins of the present invention have a binding affinity (K_a) for JAG1 of at least 10^6 M^{-1}. In other embodiments, the antigen binding proteins exhibit a K_a of at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 10^9 M^{-1}, or at least 10^{10} M^{-1}. In another embodiment, the antigen binding protein exhibits a K_a substantially the same as that of an antibody described herein in the Examples.

In another embodiment, the present disclosure provides an antigen binding protein that has a low dissociation rate from JAG1. In one embodiment, the antigen binding protein has a K_{off} of 1 X 10^{-4} to $^{-1}$ sec^{-1} or lower. In another embodiment, the K_{off} is 5 X 10^{-5} to $^{-1}$ sec^{-1} or lower. In another embodiment, the K_{off} is substantially the same as an antibody described herein. In another embodiment, the antigen binding protein binds to JAG1 with substantially the same K_{off} as an antibody described herein.

In another aspect, the present disclosure provides an antigen binding protein that inhibits an activity of JAG1. In one embodiment, the antigen binding protein has an IC_{50} of 1000 nM or lower. In another embodiment, the IC_{50} is 100 nM or lower; in another embodiment, the IC_{50} is 10 nM or lower. In another embodiment, the IC_{50} is substantially the same as that of an antibody described herein in the Examples. In another embodiment, the antigen binding protein inhibits an activity of JAG1 with substantially the same IC_{50} as an antibody described herein.

In another aspect, the present disclosure provides an antigen binding protein that binds to human JAG1 expressed on the surface of a cell and, when so bound, inhibits JAG1 signaling activity in the cell without causing a significant reduction in the amount of JAG1 on

the surface of the cell. Any method for determining or estimating the amount of JAG1 on the surface and/or in the interior of the cell can be used. In other embodiments, binding of the antigen binding protein to the JAG1-expressing cell causes less than about 75%, 50%, 40%, 30%, 20%, 15%, 10%, 5%, 1%, or 0.1% of the cell-surface JAG1 to be internalized.

In another aspect, the present disclosure provides an antigen binding protein having a half-life of at least one day *in vitro* or *in vivo* (*e.g.*, when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO2000/09560, incorporated by reference herein.

The present disclosure further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, *e.g.*, antigen binding protein that bind to two different epitopes of JAG1, or to an epitope of JAG1 and an epitope of another molecule, via two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise a JAG1 binding site from one of the herein-described antibodies and a second JAG1 binding region from another of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another JAG1 antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art. Such methods include the use of hybrid-hybridomas as described by Milstein et al., 1983, *Nature* 305:537, and chemical coupling of antibody fragments (Brennan et al., 1985, *Science* 229:81; Glennie et al., 1987, *J. Immunol.* 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties (*i.e.*, from the *Fos* and *Jun* proteins, which preferentially form heterodimers; Kostelny et al., 1992, *J. Immunol.* 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in U.S. Patents 5,959,083; and 5,807,706.

In another aspect, the antigen binding protein comprises a derivative of an antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (*e.g.*, a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (*e.g.*, gold) bead), or a molecule that binds to another molecule (*e.g.*, biotin or streptavidin), a therapeutic or diagnostic moiety (*e.g.*, a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (*e.g.*, administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antibody include albumin (*e.g.*, human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyurrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

An alternative approach to antibody-targeted therapy is to utilize anti-JAG1 antibodies of the invention for delivery of cytotoxic drugs specifically to JAG1 antigen-expressing cancer cells. In one embodiment, an anti-JAG1 antibody, or fragment, of the invention is conjugated to a cytotoxic agent via a linker, to form an anti-JAG1 Antibody Drug Conjugate (ADC). Various cytotoxic drugs are known in the art which can be conjugated with any of the antibodies disclosed herein to form an ADC, including the cytotoxic drug maytansinoid. Maytansinoids, derivatives of the anti-mitotic drug maytansine, bind to microtubules in a manner similar to vinca alkaloid drugs (Issell B F *et al* (1978) Cancer Treat. Rev. 5:199-207; Cabanillas F *et al.* (1979) Cancer Treat Rep, 63:507-9. Antibody-drug conjugates (ADCs) composed of the maytansinoid DM1 linked to an anti-JAG1 antibody, as described in Example 2 below, show potent anti-tumor activity in JAG1-overexpressing tumor cell lines. Thus, in one embodiment, an anti-JAG1 antibody, or fragment thereof, of the invention is conjugated to an anti-mitotic tubulin inhibitor, *e.g.,* maytansinoid *N*(2′)-deacetyl-*N*(2′)-(3-mercapto-1-oxopropyl)-maytansine (also referred to as "DM1").

Oligomers that contain one or more antigen binding proteins may be employed as JAG1 antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen

binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, *e.g.*, variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have JAG1 binding activity.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, *FEBS Letters* 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, *Semin. Immunol.* 6:267-78. In one approach, recombinant fusion proteins comprising an anti-JAG1 antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti- JAG1 antibody fragments or derivatives that form are recovered from the culture supernatant.

Antigen binding proteins directed against JAG1 can be used, for example, in assays to detect the presence of JAG1 polypeptides, either *in vitro* or *in vivo*. The antigen binding proteins also may be employed in purifying JAG1 proteins by immunoaffinity chromatography. Blocking antigen binding proteins can be used in the methods disclosed herein. Such antigen binding proteins that function as JAG1 antagonists may be employed in treating any JAG1-induced condition, including but not limited to various cancers.

Antigen binding proteins may be employed in an *in vitro* procedure, or administered *in vivo* to inhibit JAG1-induced biological activity. Disorders that would benefit (directly or indirectly) from activation of JAG1, examples of which are provided herein, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising *in vivo* administration of a JAG1 blocking antigen binding protein to a mammal in need thereof in an amount effective for reducing a JAG1-induced biological activity.

In certain embodiments of the invention, antigen binding proteins include fully human monoclonal antibodies that inhibit a biological activity of JAG1.

Antigen binding proteins, including antibodies and antibody fragments described herein, may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (*e.g.*, an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.), Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1988).

Any expression system known in the art can be used to make the recombinant polypeptides, including antibodies and antibody fragments described herein, of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired polypeptide. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *bacilli.* Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, *Cell* 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) as described by McMahan et al., 1991, *EMBO J.* 10: 2821. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., 1985).

The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, *e.g.*, over a matrix having all or a portion (*e.g.*, the extracellular domain) of JAG1 bound thereto.

Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian anti-JAG1 antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (*e.g.*, an anti- JAG1 antibody), and manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (*e.g.*, by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

Polypeptides of the present disclosure can be produced using any standard methods known in the art. In one example, the polypeptides are produced by recombinant DNA methods by inserting a nucleic acid sequence (a cDNA) encoding the polypeptide into a recombinant expression vector and expressing the DNA sequence under conditions promoting expression.

Nucleic acids encoding any of the various polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for *E. coli* and other bacteria, as well as mammalian cells, plant cells, yeast cells and insect cells.

General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., *Current Protocols in Molecular Biology* (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

The recombinant DNA can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and

expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, N.Y., 1985).

The expression construct is introduced into the host cell using a method appropriate to the host cell. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent). Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells.

Suitable bacteria include gram negative or gram positive organisms, for example, *E. coli* or *Bacillus spp*. Yeast, preferably from the *Saccharomyces* species, such as *S. cerevisiae*, may also be used for production of polypeptides. Various mammalian or insect cell culture systems can also be employed to express recombinant proteins. *Baculovirus* systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, (*Bio/Technology*, 6:47, 1988). Examples of suitable mammalian host cell lines include endothelial cells, COS-7 monkey kidney cells, CV-1, L cells, C127, 3T3, Chinese hamster ovary (CHO), human embryonic kidney cells, HeLa, 293, 293T, and BHK cell lines. Purified polypeptides are prepared by culturing suitable host/vector systems to express the recombinant proteins. For many applications, the small size of many of the polypeptides disclosed herein would make expression in *E. coli* as the preferred method for expression. The protein is then purified from culture media or cell extracts.

Proteins can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial cell-free translation system.

JAG1-binding polypeptides can also be produced by chemical synthesis (such as by the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984, The Pierce Chemical Co., Rockford, Ill.). Modifications to the protein can also be produced by chemical synthesis.

The polypeptides of the present disclosure can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (*e.g.*, with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity

chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification, polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

The purified polypeptide is preferably at least 85% pure, more preferably at least 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently pure for use as a pharmaceutical product.

In certain embodiments, the present disclosure provides monoclonal antibodies that bind to JAG1. Monoclonal antibodies may be produced using any technique known in the art, *e.g.*, by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 48210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques known in the art.

Post-Translational Modifications of Polypeptides

In certain embodiments, the binding polypeptides of the invention may further comprise post-translational modifications. Exemplary post-translational protein modifications include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while also reducing the possible immunogeneticity of the protein. See Raju et al. *Biochemistry*. 2001 31; 40(30):8868-76.

In one embodiment, modified forms of the subject soluble polypeptides comprise linking the subject soluble polypeptides to nonproteinaceous polymers. In one embodiment, the polymer is polyethylene glycol ("PEG"), polypropylene glycol, or polyoxyalkylenes, in the manner as set forth in U.S. Patents 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

PEG is a water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). The term "PEG" is used broadly to encompass any polyethylene glycol molecule, without regard to size or to modification at an end of the PEG, and can be represented by the formula: $X--O(CH_2CH_2O)_n-CH_2CH_2OH$ (1), where n is 20 to 2300 and X is H or a terminal modification, *e.g.*, a C_{1-4} alkyl. In one embodiment, the PEG of the invention terminates on one end with hydroxy or methoxy, *i.e.*, X is H or CH_3 ("methoxy PEG"). A PEG can contain further chemical groups which are necessary for binding reactions; which results from the chemical synthesis of the molecule; or which is a spacer for optimal distance of parts of the molecule. In addition, such a PEG can consist of one or more PEG side-chains which are linked together. PEGs with more than one PEG chain are called multiarmed or branched PEGs. Branched PEGs can be prepared, for example, by the addition of polyethylene oxide to various polyols, including glycerol, pentaerythriol, and sorbitol. For example, a four-armed branched PEG can be prepared from pentaerythriol and ethylene oxide. Branched PEG are described in, for example, EP-A 0 473 084 and U.S. Patent. 5,932,462. One form of PEGs includes two PEG side-chains (PEG2) linked via the primary amino groups of a lysine (Monfardini et al., *Bioconjugate Chem.* 6 (1995) 62-69).

The serum clearance rate of PEG-modified polypeptide may be decreased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or even 90%, relative to the clearance rate of the unmodified binding polypeptide. The PEG-modified polypeptide may have a half-life ($t_{1/2}$) which is enhanced relative to the half-life of the unmodified protein. The half-life of PEG-binding polypeptide may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% or 500%, or even by 1000% relative to the half-life of the unmodified binding polypeptide. In some embodiments, the protein half-life is determined *in vitro*, such as in a buffered saline solution or in serum. In other embodiments, the protein half-life is an *in vivo* half life, such as the half-life of the protein in the serum or other bodily fluid of an animal.

Therapeutic Methods, Formulations and Modes of Administration

The present disclosure features methods for treating Notch-signaling tumors, including breast, prostate, colorectal, lung and other solid tumors, comprising administering anti-JAG1 antibodies or antigen binding fragments of the present invention. As used herein, a "Notch-signaling tumor" or a "tumor associated with Notch signaling" refers to a tumor or malignant growth in which Notch signaling is detrimental. In one example, Notch signaling is associated with tumor growth. In other examples, Notch signaling is involved in tumor progression or metastasis. Exemplary tumors that may be treated by targeting the Notch pathway using the anti-JAG1 antibodies and antigen binding fragments of the invention, include, but are not limited to, head and neck squamous cell carcinoma (Zeng et al. 2005, Cancer Cell 8:13–23), T-cell acute lymphoblastic leukemia (Roy et al. Curr Opin Genet Dev 17: 52–59, 2007), breast cancer (Reedijk et al., Cancer Res 65: 8530–8537, 2005; Dickson et al., Mod Pathol 20: 685–693, 2007), melanoma (Pinnix and Herlyn, Pigment Cell Res 20: 458–465, 2007), lung adenocarcinoma (Chen et al., Cancer Res 67: 7954–7959, 2007), prostate (Leong et al., Differentiation Volume 76, Issue 6, July 2008, Pages 699–716) and colorectal (Guilmeau S. Adv Exp Med Biol. 2012;727:272-88).

Any of the antibodies or antigen binding fragments disclosed herein may be used in such therapeutic methods.

The present disclosure further provides a method for treating Notch-signaling tumors, comprising administering an anti-JAG1 polypeptide selected from the group consisting of a fully human antibody of an IgG class that binds to a JAG1 epitope with a binding affinity of at least 10^{-6}M, a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connecting the heavy chain and light chain variable domain regions, including the heavy and light chain variable regions (and CDRs within said sequences) described in SEQ ID Nos. 1-142 (Table 5).

For example, in one embodiment, the methods disclosed herein include the use of a fully human antibody comprising a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33,

SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and combinations thereof.

In one embodiment, the methods described herein include the use of a fully human Fab antibody fragment has a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23,

SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142 and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and combinations thereof.

In one embodiment, the methods described herein include the use of a single chain human antibody comprising a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23,

SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142, and combinations thereof, and comprising a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141, and combinations thereof.

In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO.

21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112, SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115, SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112, SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112 , SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134, SEQ ID NO. 135/SEQ ID NO.133 , SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, SEQ ID NO. 127/SEQ ID NO.141 , and combinations thereof. In one embodiment, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID

NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112, SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115, SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112, SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112 , SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134, SEQ ID NO. 135/SEQ ID NO.133 , SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, SEQ ID NO. 127/SEQ ID NO.141

, and combinations thereof.

In one embodiment, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain

fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112, SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115, SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112, SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112 , SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134, SEQ ID NO. 135/SEQ ID NO.133 , SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, SEQ ID NO. 127/SEQ ID NO.141

and combinations thereof.

In one embodiment, the anti-JAG1 antibodies and antibody fragments of the invention are used to treat Notch-signaling tumors. As discussed above, any tumor or malignant growth with detrimental Notch signaling pathway activity can be treated by the anti-JAG1 antibodies and antibody fragments of the invention. For example, in one embodiment, the tumor is selected from the group consisting of breast, prostate, colorectal, lung and other solid tumors.

In one embodiment, the anti-JAG1 antibodies and antibody fragments of the invention can be administered alone or in combination with one or more additional therapies such as chemotherapy radiotherapy, immunotherapy, surgical intervention, or any combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above.

In certain embodiments of such methods, one or more anti-JAG1 antibodies and antibody fragments of the invention can be administered, together (simultaneously) or at different times (sequentially). In addition, anti-JAG1 antibodies and antibody fragments of the invention can be administered with another type of compounds for treating cancer or for inhibiting angiogenesis.

In certain embodiments, the anti-JAG1 antibodies and antibody fragments of the invention can be used alone.

In certain embodiments, the anti-JAG1 antibodies and antibody fragments of the invention can be labeled or unlabeled for diagnostic purposes. Typically, diagnostic assays entail detecting the formation of a complex resulting from the binding of a binding polypeptide to JAG1. The anti-JAG1 antibodies and antibody fragments of the invention can be directly labeled, similar to antibodies. A variety of labels can be employed, including, but not limited to, radionuclides, fluorescers, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors and ligands (*e.g.*, biotin, haptens). Numerous appropriate immunoassays are known to the skilled artisan (see, for example, U.S. Patents. 3,817,827; 3,850,752; 3,901,654; and 4,098,876). When unlabeled, the binding polypeptides can be used in assays, such as agglutination assays. Unlabeled binding polypeptides can also be used in combination with another (one or more) suitable reagent which can be used to detect the binding polypeptide, such as a labeled antibody reactive with the binding polypeptide or other suitable reagent (*e.g.*, labeled protein A).

Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated but can be readily determined by the

skilled artisan. In general, regulatory agencies require that a protein reagent to be used as a therapeutic is formulated so as to have acceptably low levels of pyrogens. Accordingly, therapeutic formulations will generally be distinguished from other formulations in that they are substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (*e.g.*, FDA).

Therapeutic compositions of the present disclosure may be administered with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be parenteral (*e.g.*, intravenous, subcutaneous), oral, or topical, as non-limiting examples. In addition, any gene therapy technique, using nucleic acids encoding the polypeptides of the invention, may be employed, such as naked DNA delivery, recombinant genes and vectors, cell-based delivery, including *ex vivo* manipulation of patients' cells, and the like.

A therapeutically effective dose refers to a dose that produces the therapeutic effects for which it is administered. The exact dose will depend on the disorder to be treated, and may be ascertained by one skilled in the art using known techniques. In general, the polypeptide is administered at about 0.01 μg/kg to about 50 mg/kg per day, preferably 0.01 mg/kg to about 30 mg/kg per day, most preferably 0.1 mg/kg to about 20 mg/kg per day. The polypeptide may be given daily (*e.g.*, once, twice, three times, or four times daily) or preferably less frequently (*e.g.*, weekly, every two weeks, every three weeks, monthly, or quarterly). In addition, as is known in the art, adjustments for age as well as the body weight, general health, sex, diet, time of administration, drug interaction, and the severity of the disease may be necessary.

Example 1

A screen was performed to identify human anti-human JAG1 antibodies. The heavy and light chain variable sequences from the antibodies identified in the screen are provided below in Table 5.

This example provides an analysis of the cross-reactivity of JAG1 binders to recombinant mouse JAG1. A 96-well plate was coated with 25 μl recombinant mouse JAG1/Fc (2 μg/μL in PBS) at 4 °C overnight. Washed 3 times with PBS-Tween (PBST). Added 5 μl scFv phage soup that diluted in 20 μl Casein in each well and incubated 30 min with shaking. The plate was washed 3 times with PBST, then horseradish peroxidase (HRP)-conjugated M13 (1:2000 in casein) was added, then 3,3',5,5'-Tetramethylbenzidine (TMB)

was added as substrate and developed 30 min. 2M H_2SO_4 was used to stop the reaction and the OD was read at 450nm. The results showed that more than 80% of the JAG1 binding antibodies can also bind to murine antigen.

The binding affinity of antibody JG1H7 for human JAG1 was tested using a BiaCore assay. Specifically, anti-human Fc antibody (GE, BR-1008-39) was immobilized on a CM5 sensor chip to approximately 700 RU using standard NHS/EDC coupling methodology. Antibodies (about 10 μg/ml) were captured for 60 s at a flow rate 10 μl/min. Recombinant human JAG1/His was serially diluted in running buffer (HBS-EP). All measurements were conducted with a flow rate of 30 μL/min. Surfaces were regenerated with 3M $MgCl_2$ for 60 s. A 1:1 (Langmuir) binding model was used to fit the data. The results are shown in Table 1, where the K_D of antibody JG1H7 was determined to be 2.08 x 10^{-7} M for human JAG1.

Table 1

name	ka (1/Ms)	kd (1/s)	Rmax (RU)	KA (1/M)	KD (M)	Chi2
JG1H7	1.97E5	0.0411	85.1	4.8E6	2.08E-7	0.147

Example 2

This example illustrates *in vitro* data showing the assessment of anti-JAG-1 antibodies in a cytotoxicity assay using secondary antibody-drug conjugate technique ("Secondary Antibody-Drug Conjugates As Tools for ADC Discovery". Helen Mao, Poster, IBC 24th Annual, 2013). This example demonstrates the potential of anti-JAG-1 to be used as antibody drug conjugates.

JAG-1 expressing cells (Calu-6; lung cancer cells) were harvested with enzyme-free Cell Dissociation Buffer (GIBCO), seeded into white 96-Well Clear Bottom plates (1,000 cells/well in 90 μl) and allowed to adhere overnight at 37 °C. Anti-human JAG1 antibodies JG1B10, JG1H7, JG1C8 and JG1H11were pre-complexed with Protein G-DM1 (DM1; maytansinoid *N*(2')-deacetyl-*N*(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1)) (Concortis Biosystems) in cell culture media, at a 1:4 molar ratio. The same anti-human JAG1 antibodies JG1B10, JG1H7, JG1C8 and JG1H11 were also used as naked antibodies (not complexed) as controls. After 10 min at room temperature, serial dilutions of the antibody-ProteinG-DM1 complex (as well as the un-complexed antibody controls) were prepared in cell culture media, incubated 10 more minutes at room temperature, and added to cells (10 μl/well) in triplicate. After 6 days incubation at 37 °C, cells proliferation was analyzed as follows: 100 μl of Cell Titer Glo buffer (Promega) was added to each well. Plates were

incubated with shaking at room temperature for 20 min. Luminescence signal was then measured on a Flexstation 3 plate reader (Molecular Device). Data were reported as relative Luminescent Units. Dose-response curves were generated in GraphPad prism, and IC_{50} values were calculated using non-linear regression fit (Log (inhibitor) vs. response - Variable slope equation).

The same method was also used with normal human fibroblasts (HFF) to assess the non-specificity of cell killing of anti- JAG-1 antibodies/Protein G-DM1 complexes.

The results are shown in Figures 1A (Calu-6 cancer cells) and 1B (HFF cells), and Table 2. Figure 1A shows that that anti- JAG-1 antibodies, especially antibodies JG1B10 and JG1H7, can induce cell killing when complexed with a cytotoxin such as DM-1, with IC_{50} values of 1.35 and 3.89 nM respectively (Table 2). These data illustrate the potential of JAG-1 antibodies as antibody-drug conjugates. In Figure 1B, data shows that very little non-specific cell killing was observed on normal HFF cells which do not overexpress JAG1, suggesting a good selectivity index for future JAG1 ADC.

Table 2

	Protein G-DM1+			
	JG1-B10	JG1-H7	JG1-C8	JG1-H11
IC50 (nM)	1.35	3.89	87.26	26.51

Example 3

An ELISA assay was carried out to determine antibody binding to human JAG1. A 96-well ELISA plate was coated overnight with goat anti-human lambda. The next morning the plate was blocked with casein solution for 1 hour, followed by addition of the JG1H7 and JG1B10 IgG antibodies at 0.3 µg/ml. After 1 hour, the plate was washed and serially diluted biotinylated human Jagged 1 (JAG1) was added. As a control, biotinylated JAG1 was added to wells that contained a control IgG. After an hour the plate was washed, labeled neutravidin was added and incubated for 30 minutes. The plate was washed, developed and the absorbance in each well measured by a spectrophotometer. As shown in Figure 2, both JG1B10 (i) and JG1H7 (ii) show specific binding to human JAG1. The control antibody used was an IgG1 that does not bind to JAG-1 or JAG-2.

A similar protocol was used to measure binding of selected JG1H7 variants JG1H7-F2C (i), JG1H7-B6C (ii), JG1H7-C9C(iii), JG1H7-D5C (iv), JG1H7-C6C(v) and JG1H7(vi).

These results are shown in Figure 3. As shown in Figure 3, all of the tested variants bound more JAG1 than the control antibody. The control antibody used was an IgG1 that does not bind to JAG1 or JAG2. In the results shown in Figure 3, JG1H7-C4C almost perfectly overlays with JGH7-C9C, which is why it the line is not visible in the graph.

An ELISA assay was also carried out to determine the ability of the identified antibodies to bind to human JAG2. A 96-well ELISA plate was coated with human JAG2-Fc overnight. The next morning the plate was blocked with casein solution for 1 hour, followed by addition of serially diluted JG1H7 and JG1B10 IgG antibodies. As a control, antibodies were added to wells that were not coated with JAG2-Fc. After incubating for an hour, the plate was washed and labeled goat anti-human F_D antibody was added for 30 minutes. The plate was washed, developed with substrate and the absorbance in each well measured on a spectrophotometer. As shown in Figure 4, both JG1B10 (i) and JG1H7 (ii) show specific binding to JAG2.

A similar protocol was used in an ELISA to show binding of JG1H7 variants with JAG-2. These results are shown in Figure 5. The control antibody used was an IgG1 that does not bind to JAG1 or JAG2. Similar to the results shown in Figure 3, all of the tested variants showed specific binding to JAG2.

An ELISA assay was also carried out to determine the ability of the identified antibodies to bind to murine JAG2. A high-binding 96-well plate was coated overnight with 1 μg/ml recombinant mouse Jagged-2 Fc Chimera protein (R&D Systems) in PBS. The plate was then blocked with a 1:1 mixture of casein:Super Block for several hours at room temperature. Each IgG was diluted to 10 μg/ml in the blocking solution, serially diluted 3-fold and added to the 96-well plate after washing. After 2h incubation and washing, anti-human F_D-HRP was added and incubated 1 hour. After washing, the plate was developed with TMB and stopped with 2M H_2SO_4 and the absorbance measured at 450 nm. As shown in Figure 6, JG1H7 and the tested variants showed specific binding to murine JAG-2. The control antibody used was an IgG1 that does not bind to JAG1 or JAG2.

Finally, an ELISA assay was carried out to determine antibody cross-reactivity to delta-like 1 (DLL1) and delta-like 2 (DLL2). One ELISA plate was coated with anti-human lambda and another ELISA plate was coated with anti-human kappa overnight at 4°C. The next morning each plate was blocked with a 1:1 mixture of casein:Super Block for 2 hours at room temperature. The B10 IgG was diluted to 0.3 μg/ml in block and added to the anti-human lambda coated wells, while the JG1H7 IgG was diluted to 0.3 μg/ml in block and

added to the anti-human kappa coated wells and incubated at room temperature for 3 hours. As a control, other wells were treated with only block. After washing, serially-diluted biotinylated antigen (JAG1, DLL1, DLL2) was added to a column with captured antibody and a control column with no antibody, and incubated 1 hour at room temperature. After washing, neutravidin-AP was added, incubated for 20 min at room temperature, the plate washed and developed with 1-step PNPP, and the plate analyzed in a plate reader. As shown in Figures 7A (JG1H7) and 7B (B10), while each antibody specifically bound to human JAG-1, little binding was observed to human DLL1 or human DLL2 under these conditions. The control antibody used was an IgG1 that does not bind to JAG1 or JAG2.

Example 4

This example describes a cellular binding assay to determine the EC_{50} for certain anti-JAG1 antibodies binding to K562 cells (ATCC CCL-243), where the concentration at which 50% binding saturation (EC_{50}) is reached. In this example, K562 cells were resuspended in FACS Buffer (2% Fetal Bovine Serum in PBS) at 1 x 10^6 cells/ml. 50 µl (0.5 x 10^5 cells) were aliquoted into the wells of a 96-well plate. Plated cells were spun down and the supernatant discarded. Cells were resuspended in serially diluted concentrations of each JAG1 IgG in 30 µl FACS Buffer done in triplicate. The antibodies and cells were incubated for 1 hr at 4 °C and then washed 2x with FACS Buffer. Cells were resuspended in 50 µl goat anti-human IgG (γ-chain specific)-PE-conjugated secondary antibody (Southern Biotech # 2040-09) diluted 1:750 in FACS Buffer. Cells were further incubated in the dark for 30 min at 4 °C and then washed 1x with FACS Buffer. The cells were resuspended in a final volume of 30 µl FACS Buffer and analyzed using an Intellicyt Flow Cytometer. Median fluorescence in the FL-2H channel was determined using FlowJo software and EC_{50} value was determined by a variable slope non-linear regression using ForeCyte software. Table 3, below, shows the EC_{50} of anti-JAG1 antibodies to human JAG1.

Table 3

Name	EC50 (nM), K562 cells
JG1A7	<1
JG1H7	16
JG1C8	16
JG1H11	27
JG1B10	32
JH-F4	97

Example 5

Having identified anti-JAG1 antibody JG1H7 as a therapeutic antibody given its high affinity for human JAG1 and neutralization characteristics, variants of the JG1H7 antibody were made.

Briefly, JG1H7 was used as the parent antibody for further mutation in an effort to frther improve affinity characteristics. Briefly, single amino acids within the CDRs (defined by Chothia or Kabat numbering) of JG1H7 were mutated such that each position within each CDR was mutated to all possible 20 amino acids. These variant antibodies were then screened for affinity changes relative to the parent antibody and antibodies that showed improvement in binding by ELISA were sequenced. Mutations that improved binding were included in a combinatorial library, which was then expressed and screened for further improved affinity antibodies. The light and heavy chain variable domain amino acid sequences of JG1H7 variants are described below in Table 4.

The amino acid sequences of the improved JG1H7 clones are shown below in Table 4.

Table 4

Clone	Heavy Chain variable domain	Light Chain variable domain
JG1H7 3-2 (germline changed variant)	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-2B2S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCPASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 113
JG1H7-2A3S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASHS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 114
JG1H7-2A7S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASPS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 115
JG1H7-2A10S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN	DIQMTQSPSSLSASVGDRVTITCRASQS TSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF

	SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 116
JG1H7-2A2S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS SSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 117
JG1H7-2A9S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS FSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO:118
JG1H7-2A1S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS PSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 119
JG1H7-E11S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISASLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 120
JG1H7-C11S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTTLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 121
JG1H7-D10S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSQNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 122
JG1H7-2B7S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSSSE Q ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-1A8S	EVQLVESGGGLIQPGGSLRLSCAAS GFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 124	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-1A6S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFSMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF

	SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 125	ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-1A2S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFGMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 126	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-1B1S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-5A8S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR ALGYYYAMDVWGQGTTVTVSS SEQ ID NO: 128	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-5B5S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 129	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-3E5S	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYALDVWGQGTTVTVSS SEQ ID NO: 130	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-G6C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQS ISTTQNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 131
JG1H7-A6C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASPS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 133
JG1H7-E11C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-C6C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF

	SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYALDVWGQGTTVTVSS SEQ ID NO: 142	ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-C9C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-F4C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASPS ISASLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 134
JG1H7-F2C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR ALGYYYALDVWGQGTTVTVSS SEQ ID NO: 135	DIQMTQSPSSLSASVGDRVTITCRASPS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 133
JG1H7-F1C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQS ISASLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 136
JG1H7-D4C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQS TSASLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 137
JG1H7-D5C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFYMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQS PSTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 138
JG1H7-A5C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 139	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-B2C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR SLGYYYALDVWGQGTTVTVSS SEQ ID NO: 139	DIQMTQSPSSLSASVGDRVTITCRASQS PSASLNWYQQKPGKAPKLLIYLASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 140
JG1H7-B6C	EVQLVESGGGLIQPGGSLRLSCAAS AFTVSNFAMTWVRQAPGKGLEWV	DIQMTQSPSSLSASVGDRVTITCRASQS SSTSLNWYQQKPGKAPKLLIYLASSLQ

	SVIDSGGNTYYADSVRGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCAR DLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	SGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 141

Table 5. Anti-JAG1 Heavy and Light Variable Domain Amino Acid Sequences

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1A1	EVQLVESGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARGTGGDGFDYWGQGTLV TVSS SEQ ID NO. 1	DVVMTQSPSSLSASVGDRVTITCRASQ GISSWLAWYQQKPGKAPKLLIYDASSL QSGVPSRFSGSGSGTDFTLSISSLQPEDF ATYYCQQANSLPLTFGGGTKVEIK SEQ ID NO. 2
JG1A10	EVQLVQSGAEVKKPGASVRVSCK ASGYNFRNFDINWVRQAPGQGLE WMGWMNPSSGLTGFAPKFQGRVT LTRDTSIRTAYMEVSSLRSEDTAV YYCVRQRSGLDSWGQGTLVTVSS SEQ ID NO. 3	QSVLTQPPSVSAAPGQKVTISCSGSSSNI GKYFVSWYQQFPGTAPKLLIYDNDQRP SGIPDRFSASKSGTSARLDITGLQTGDE ADYYCGTWDSSLSAGVFGGGTKLTVL SEQ ID NO. 4
JG1A12	EVQLVQSGAEVKKPGASVRVSCK ASGYTFTNYYIHWVRQAPGQGLE WMGIIIPSGGSTNYPPKFQGRVTLT RDTSTSTVYMELSSLRSEDTAVYY CVREYQGGHFDYWGQGTLVTVSS SEQ ID NO. 5	SYELMQPHSVSESPGKTVTISCTGSSGSI ASNYVQWYQQRPGSAPTTVIYEDNQR PSGVPDRFSGSIDSSSNSASLTISGLKTE DEADYYCQSYDSSIVVFGGGTKLTVL SEQ ID NO. 6
JG1A3	EVQLVESGGGLVKPGGSLRLSCAA SGFTFNDYYMSWIRQAPGKGLEW VSYISRSGSTMYYADSVKGRFTISR DNAKNSLYLQMNSLRDEDTAVYY CATSVGHLEQWGQGTLVTVSS SEQ ID NO. 7	DIQLTQSPSSLSASVGDRVTITCRATQGI GNYLAWYQQKPGKVPNLLIYAATTLQ SGVPSRFSGSGSGTDFTLTISSLQPEDV ASYYCQKYNSAPLTFGGGTKVEIK SEQ ID NO. 8
JG1A4	QVQLVESGGVVVQPGGSLRLSCA ASGFTFDDYTMHWVRQAPGKGLE WVSLISWDGGSTYYADSVKGRFTI SRDNSKNSLHLQMNSLRTEDTALY YCAKDIDEYSSSTGPDYWGQGTLV TVSS SEQ ID NO. 9	QAVLTQPASVSESPGQSITISCTGSSSDI GGYNYVSWYQQHPGKAPKLIIYEVTK RPSGVPDRFSGSKSGNTASLTVSGLQA EDEADYYCSSYVGSNDVYVFGTGTKL TVL SEQ ID NO. 10
JG1A5	QVQLVQSGAEVQKPGASVKVSCK VSGYTLSELSIHWVRQAPGKGLEW MGGFDPEDGKIVYAQKFQDRVSM TQDTSTDTAYLQLSSLTSGDTALY YCATLAQWGDWFDRWGQGTLVT VSS SEQ ID NO. 11	QAGLTQPPSASGTPGQRVTISCSGSSSNI GSNTVNWYQRLPGTAPKLVVYSNNQR PSGVPDRFSGSKSGTSASLVISGLQSED EADYYCAAWDYDEEGLLFGGGTQLTV L SEQ ID NO. 12

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1A6	QVQLVQSGAEVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTTVTVSS SEQ ID NO. 13	QSVLTQPPSVSVAPGKTARITCGGNNIG SKSVHWYQQKPGQAPVLVIYYDSDRP SGIPERFSGSNSGNTATLTISRVEAGDE ADYYCQVWDSSSDHVVFGGGTKLTVL SEQ ID NO. 14
JG1A7	QVQLVESGGGLVKPGGSLRLSCAA SGFTFSDYYMSWIRQAPGKGLEW VSYISSSGSTIYYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYC ARVNSGYDAVDYWGQGTLVTVSS SEQ ID NO. 15	QSALTQPPSVSGAPGQTVTISCTGSRSN IGTYDVHWYQQFAGSAPKLLIYHNND RSSGVPDRFSGSKSGTSASLAITGLQAE DEAVYFCQSHDNVLGGVFGGGTKLTV L SEQ ID NO. 16
JG1B1	EVQLVQSGAEVKKPGSSVKVSCK ASGDTFSSYGISWVRQAPGQGLEW VGRINSLLDRPDYAQNFQDRVTIT ADKSTSTAYMELNTLGPEDTAMY YCATEHYYESSEDPFFDFWGQGTL VTVSS SEQ ID NO. 17	QSVVTQPPSVSGAPGQRITISCTGSSSNI GAGYDVQWYLQFPGTAPKLLIHGSSN RPSGVPARFQGSKSGTSASLVITGLQAE DEADFYCQSFDSSLNGYVFGGGTKLTV L SEQ ID NO. 18
JG1B10	EVQLVESGGGLVQPGGSLRLSCAA SGSTFSSYGMHWVRQAPGKGLEW VAVIWYDGSNKYYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVY YCARGYNHDYWGQGTLVTVSS SEQ ID NO. 19	LPVLTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYDVS NRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCSSYTSSSTYVFGIGTKLTVL SEQ ID NO. 20
JG1B11	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARDPYSSSWYGAEYFQHWG QGTLVTVSS SEQ ID NO. 21	QAGLTQPHSVSESPGKTVTISCTRSSGSI ASNYVQWYQQRPGSAPTTVIYEDNQR PSGVPDRFSGSIDSSSNSASLTISGLKTE DEADYYCQSYDSSNHLVVFGGGTKLT VL SEQ ID NO. 22

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1B2	EVQLLESGGGVVQPGRPLRLSCAG SGFAFSGFAMHWVRQAPGKGLEW LAVISYDGRNNNYADSVKGRFTIS RDNSKNTLFLDMDSLRPDDTALY YCARDRSSGWYGLSDYWGQGTL VTVSS SEQ ID NO. 23	QPVLTQPPSASGSPGQSVTISCTGTSSD VGGYNYVSWYQQHPGKAPKLMIYDV SNRPSGVSNRFSGSKSGNTASLTISGLQ AEDEADYYCSSYTSSSTYVFGTGTKLT VL SEQ ID NO. 24
JG1B4	QVQLVQSGSELKKPGASVRVSCK ASGYTFTNYYIHWVRQAPGQGLE WMGIIIPSGGSTNYPPKFQGRVTLT RDTSTSTVYMELSSLRSEDTAVYY CVREYQGGHFDYWGQGTLVTVSS SEQ ID NO. 25	QLVLTQSHSVSESPGKTVTISCTGSSGSI ASNYVQWYQQRPGSAPTTVIYEDDLRP SGVPDRFSGSIDSSSNSASLTISGLKTED EADYYCQSYDRYNVVFGGGTKLTVL SEQ ID NO. 26
JG1B5	QVQLVQSGAEVKKPGASVKVSCK ASGNTFTSYYIHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTTVTVSS SEQ ID NO. 27	SYVLTQPPSVSVAPGKTARITCGGNNIG SKSVHWYQQKPGQAPVLVIYYDSDRP SGIPERFSGSNSGNTATLTISRVEAGDE ADYYCQVWDSSSDHVVFGGGTKLTVL SEQ ID NO. 28
JG1B6	EVQLVESGGGVVQPGRSLRLSCAA SGFPFSSYAMHWVRQAPGKGLEW VAVISYDGSNKYYADSVKGRFTIS RDNSKNTLYLQMNSLRPEDTAVY YCARDLPACSGGSCYATWGGFDY WGQGTLVTVSS SEQ ID NO. 29	SSELTQDPAVSVALGQTLTITCQGDSLR SYYASWYQQKPGQAPLLVFYGYNSRP SEIPDRFSGSFTGDTASLTITGAQAEDE ADYYCSSMSGDLVVXGGGTKVTVL SEQ ID NO. 30
JG1B8	QMQLVQSGAEVKKPGSSVKVSCK ASGATFSSYAMSWVRQAPGQGLE WMGAVIPIFGTTNYAPKFEGRVTIT ADESTSTVYMELSSLTSEDTAVYY CARQIGEVVGGIMEDYWGQGTLV TVSS SEQ ID NO. 31	DIVMTQSPSSLSASVGDRVTITCRASQG ITNSLAWYQQKPGKVPKLLIYAASTLQ SGVPSRFSGSGSGTDFTLTISSLQPEDV ASYYCQKYDSAPLTFGGGTKVEIK SEQ ID NO. 32

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1C3	QMQLVQSGAEVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTTVTVSS SEQ ID NO. 33	SYELMQPPSVSVAPGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVIYYDSDR PSGIPERFSGSNSGNTATLTISRVEAGDE ADYYCQVWDSSSDHVVFGGGTKLTVL SEQ ID NO. 34
JG1C4	QMQLVQSGADVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTMVTVSS SEQ ID NO. 35	SYELMQPPSVSVASGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVVYDDSD RPSGIPERFSGSNSGNTATLTISRVEAG DEADYYCQVWDSSSDHVVFGGGTKLT VL SEQ ID NO. 36
JG1C5	EVQLLESGGGLIQPGGSLRLSCAAS GFTVSSNYMTWVRQAPGKGLEW VSVIYSGGNTFYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYC AREMSGPYFDYWGQGTLVTVSS SEQ ID NO. 37	QAVVTQPPSASGTPGQRVTISCSGSSSN IGSNPVSWYQQLPGTAPKLLIYSNNQR PSGVPDRFSGSKSGTSASLAISGLQSED EADYYCAAWDDSLNGDVIFGGGTKLT VL SEQ ID NO. 38
JG1C8	EVQLVQSGAEVKKPGSSVKVSCK ASGGTFSSYAISWVRQAPGQGLEW MGWISAYNGNTNYAQKLQGRVT MTTDTSTSTAYMELRSLRSDDTAV YYCARSRYDFWSGYYSGMDVWG QGTTVTVSS SEQ ID NO. 39	NFMLTQPRSVSGSPGQSVTISCTGTSSD VGGYHYVSWYQQHPGKAPKLIIYDVS RRPSGVPDRFSGSKSGNTASLTVSGLQ AEDEADYYCSSYGGSNNFVFGTGTKLT VL SEQ ID NO. 40
JG1D1	QVQLVESGGGVVQPGRPLRLSCA GSGFAFSGFAMHWVRQAPGKGLE WLAVISYDGRNNNYADSVKGRFTI SRDNSKNTLFLDMDSLRPDDTALY YCARDRSSGWYGLSDYWGQGTL VTVSS SEQ ID NO. 41	QAGLTQPASVSGSPGQSITISCTGTSSD VGRYDYVSWYQQHPGKAPKLMIYDVT KRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCISYTTSSTYVFGTGTKVTV L SEQ ID NO. 42

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1D10	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYNIHWVRQAPGQRFE WMGWISTDNGYTEYSQKFQDRVT ITRDTSASTAYMELSSLRSEDTADY YCLSGYYFDYWGQGTLVTVSS SEQ ID NO. 43	EIVMTQSPATLSVSPGERATLSCRASQS VRSNLAWYQQKPGQAPRLLIYGASTR ATGIPDRFSGSGSGTEFTLTISSLQSEDF AVYSCQQYENWPTFGQGTKVEIK SEQ ID NO. 44
JG1D11	EVQLVESGAEVKKPGASVKVSCK ASGYTFTNYYMHWVRQAPGQGLE WMGIINPSSGSTTYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDRAVY YCARGQGSSGWYTFDYWGQGTL VTVSS SEQ ID NO. 45	AIQLTQSPSSLSASVGDRVTISCQASQDI SNFLNWYQQKPGKAPKLLIYAASKLQS GVPSRFSGSGSGTDFSLTINSLQPEDFA TYYCQQTNSFPLTFGQGTKVEIK SEQ ID NO. 46
JG1D7	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARDVGGEGVVDYWGQGTLVT VSS SEQ ID NO. 47	SYELMQPPSVSVAPGQTARITCGGKNI GRKSVHWYQQKPGQAPVLVVYDDRD RPSGIPERFSGSNSGNTATLTISRVEAG DEADYYCQVWDSSTDHVVFGGGTKVT VL SEQ ID NO. 48
JG1D8	QVQLVQSGAEVKKPGATVKISCK VSGYTFTDYYMHWVRQAPGQGLE WVGIINPNGDKAQYTQKLKGRVT MTRDTSTNTVYMELSSLTSEDTAV YYCTTDHNWRFDSWGQGTLVTVS S SEQ ID NO. 49	DIQMTQSPSSLSASVGDRVTITCQASQD ISNYLNWYQQKPGKAPKLLIYDASNLE TGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYTTFGQGTRLEIK SEQ ID NO. 50
JG1E1	EVQLVQSGAEVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTMVTVSS SEQ ID NO. 51	SYELMQPPSVSVAPGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVVYDDSD RPSRIPERFSGSNSGNTATLTISRVEAGD EADYYCQVWDSSSDHVVFGGGTKLTV L SEQ ID NO. 52
JG1E11	QVQLVESGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARTNSDYYDSSGYTNAFDI WGQGTMVTVSS SEQ ID NO. 53	DIVMTQSPSSLSASVGDRVTITCRASQS ISRSLNWYQKKPGKAPNLLIYGASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYTMPISFGPGTKVDIK SEQ ID NO. 54

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1E7	QVQLVQSGAEVKKPGSSVKVSCK ASGGTFSSYAISWVRQAPGQGLEW MGGIIPIFGTANYAQKFQGRVTITA DESTSTAYMELSSLRSEDTAVYYC AGYSGSYFGKFDYWGQGTLVTVS S SEQ ID NO. 55	QAGLTQPPSVSGAPGQRVSISCTGSDSN IGAPYDVHWYQQLPGTAPRLLIYANTK RPSGVPDRFSGWKSGTSASLAISGLQSE DEAAYYCAAWDDRLNAYIFGSGTKLT VL SEQ ID NO. 56
JG1E8	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARGGDSSGDYYYGMDVWGQG TTVTVSS SEQ ID NO. 57	QPVLTQPPSASGTPGQRVTISCSGSSSNI GTNYVNWYQQFPGTAPKQLIYSNNHR PSGVPDRFSGSKSGTSASLAISGLRSED EADYYCAAWDDSLSGWVFGVGTKLT VL SEQ ID NO. 58
JG1F1	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARGYYDSSGYGVGFDYWGQG TLVTVSS SEQ ID NO. 59	QTVVTQPPSVSAAPGQKVTISCSGSSSN IGNNYVSWYQQLPGTAPKLLIYDNNKR PSGIPDRFSGSKSGTSATLGITGLQTGD EADYYCGTWDNSLSAGVFGGGTKLTV L SEQ ID NO. 60
JG1F10	EVQLVQSGVEVKKPGATVKISCKV SGYTFTDYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARDRVDSSAWSPGADYWGQG TLVTVSS SEQ ID NO. 61	QSVLTQPPSVSGAPGQRVTISCTGSSSNI GAGYDVHWYQQLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQTG DEADYYCGSWDASLSAAVFGGGTKLT VL SEQ ID NO. 62
JG1F7	EVQLVQSGGEVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTTVTVSS SEQ ID NO. 63	SYELMQPPSVSVAPGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVIYYDSDR PSGIPERFSGSNSGNTATLTISRVEAGDE ADYYCQVWDSSSDHVVFGGGTQLTVL SEQ ID NO. 64

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1F8	QITLKESGGGVVQPGRSLRLSCAA SGFTFSTYGMHWVRQAPGKGLEW VAVILNDGSQSHYADSLKGRFTISR DNSRNTLYLQMDSLRVEDTAMYY CARDDDRAANAFDVWGQGTMVT VSS SEQ ID NO. 65	QSVLTQPPSVSAAPGQKVTISCSGSSSNI GNNYVSWYQQLPGTAPKLLIYDNNKR PSGIPDRFSGSKSGTSATLGITGLQTGD EADYYCGTWDSSLSAWVFGGGTKLTV L SEQ ID NO. 66
JG1G11	EVQLVQSGGEVKKPGASVKVSCK ASGNTFTSYYMHWVRQAPGQGLE WMGIISPSGDSTSYAQKFQGRVTM TKDTSTSTVSMELSSLRSEDTAVY YCARDQEGLRGSGYYGMDVWGQ GTTVTVSS SEQ ID NO. 67	SYELMQPPSVSVAPGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVIYYDSDR PSGIPERFSGSNSGNTATLTISRVEAGDE ADYYCQVWDSSSDHVVFGGGTQLTVL SEQ ID NO. 68
JG1G5	EVQLVESGAEVKKPGASVKVSCK ASGYTFTNYYLHWVRQAPGQGLE WVGLLNPSGGSTNYAQKFQGRVT MTTDTSTSTAYMELRSLRSDDTAV YYCARSPDDYYYGSGNYDYWGQ GTLVTVSS SEQ ID NO. 69	QPVLTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQYPGKAPKLLIYDVNK RPSGVSIRFSASKSGNAASLTLSGLQAE DEADYYCSSYSSRRGVVFGGGTKLTVL SEQ ID NO. 70
JG1H1	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARDRYSSSAAGYGMDVWGQG TTVTVSS SEQ ID NO. 71	QPVLTQPASVSGSPGQSITISCTGINSNV DGSDAVSWYQQHPGKAPKLIAFDVTQ RPSGVPDRFSASKSGKTASLTISGLQPE DEADYYCSSYTTSSTFVFGTGTKVTVL SEQ ID NO. 72
JG1H11	EVQLVESGGGVVQPGRSLRLSCAA SGFTFSSYGMHWVRQAPGKGLEW VAVISYDGSNKYYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVY YCAKDDWNYALDYWGQGTLVTV SS SEQ ID NO. 73	QPVLTQPASVSGSPGQSITISCTGTRSD VGGYSYVSWYQQHPGKAPKLIYDVTK RPSGVSNRFSGSKSGNTASLTISGLQAE DEADYYCSSYTSSSTYVFGTGTKVTVL SEQ ID NO. 74

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H5	QVQLVESGGGLVQPGGSLRLSCAA SGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYY CAKEDLAMRRGYSYGYPGYWGQ GTLVTVSS SEQ ID NO. 75	QSVLTQPPSASGSPGQSLAISCTGTSSD VGGYNYVSWYQHHPGKAPKLIIYDVN KRPSGVPDRFSGSKSGNTASLTISGLQA EDEADYFCSSYAVNNNSPYFFGTGTKV TVL SEQ ID NO. 76
JG1H7	QVQLVQSGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SS SEQ ID NO. 77	DIVMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO. 78
JH1A1	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARDLAYSSGWLDYWGQGT LVTVSS SEQ ID NO. 79	QAGLTQPASVSGSPGQSITMSCIVSNIDI GGFHYVSWYQHRPGEAPKLLIYDVDK RPPGVSNRFSASKSGHTASLTISGLHPE DDAEYYCSSFTSRSVLFGGGTKVTVL SEQ ID NO. 80
JH1A11	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTNYDISWVRQAPGQGLE WMGWISTYNGDTIYAQKLQDRVT MTTDTSTSTAYMEVRSLRSDDTAV YYCARGNDLDYWGQGTLVTVSS SEQ ID NO. 81	QSVLTQPASVSGSPGQSITISCTETSSDV GTYNYVSWYQQHPGKAPQLIIFDVSNR PSGVSTRFSGSKSGNTASLTISGLQTED EADYYCSSYIATYTPLYVFGTGTKLTV L SEQ ID NO. 82
JH1A2	EVQLVESGAEVKKPGASVKVSCK ASGYTFTNYYMHWVRQAPGQGLE WMGIINPSDGNTSYAQKFQGRVT MTKDTSTSTVYMELSSLRSDDTAV YYCARESSSWETYFDYWGQGTLV TVSS SEQ ID NO. 83	SYELMQPPSVSVAPGKTAKITCGGDNI GIKSVHWYQQKPGQAPILVIHHDRGRP SGIPERLSGSNSGNTATLTISRVEAGDE ADYYCQVWDGTSDHVVFGGGTKLTV L SEQ ID NO. 84

	Heavy chain variable domain sequence	Light chain variable domain sequence
JH1A4	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYYMHWVRQAPGQGLE WMGWINPNSGGTNYAQKFQGRV TITADESTSTAYMELSSLRSEDTAV YYCAREGPEYCSGGSCYSADAFDI WGQGTMVTVSS SEQ ID NO. 85	SSELTQDPAVSVALGQTVRITCQGDSL RSYYASWYQQKPGQAPVLVIYGKNNR PSGIPDRFSGSSSGNTASLTITGAQAEDE ADYYCNSRDSSGNHPLVFGTGTKLTVL SEQ ID NO. 86
JH1B1	EVQLVQSGAEVRKPGASVKVSCK PSGYIFSSRYMHWVRQAPGQGLE WMGIVNPSGGSTKYAQKFQGRIT MTRDTSTRTFYMELNSLRSEDTAV YYCARHTGNHGGWYMDGFDMW GQGTMVTVSS SEQ ID NO. 87	QAGLTQPPSVSGAPGQRVTISCSGSTSN IGSNIVNWYQQLPGTAPKLLIFNNHHRP SGVPDRFSGSKSGTSASLAISGLQSEDE ADYYCAAWDDSQNAYVFGTGTKVTV L SEQ ID NO. 88
JH1B3	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYYMHWVRQAPGQGLE WMGWINPNSGGTNYAQKFQGRV TMTRDTSISTAYMELSRLRSDDTA VYYCAREEEGGRLGFDYWGQGTL VTVSS SEQ ID NO. 89	NFMLTQPPSVSAAPGQRVTISCSGRSTN IGKNDVSWYQQFPGAAPKLLIYDNNKR PSGIPDRFSGSKSGTSATLGITGLQTGD EADYYCGTWDNGLGVVLFGGGTKLTV L SEQ ID NO. 90
JH1B7	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARDLAYSSGWLDYWGQGT LVTVSS SEQ ID NO. 91	QPVLTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPDKAPKLIIYDVSK RPSGVSTRFSGSKSAYTASLTISGLRAE DEADYYCSSFTNDSPVVFGGGTQLTVL SEQ ID NO. 92
JH1C10	EVQLVESGAEVKKPGASVKVSCK ASGYTFTGYYIHWVRQAPGQGLE WMGVINPSGGSTTYAEKFQGRITM TRDTSTKMLFMELSSLRSDDTAVY YCARSPGAALFDYWGQGTLVTVS S SEQ ID NO. 93	QSVVTQPPSVSAAPGQKVTISCSGSSSN IGNNYVSWYQQVPGTAPKLLIYDNNER PSGIPDRFSGSKSGTSATLGITGLQTGD EADYYCGTWDSSLSAGVFGGGTKLTV L SEQ ID NO. 94

	Heavy chain variable domain sequence	Light chain variable domain sequence
JH1C2	QVQLVESGGGLVKPGGSLRLSCAA SGFTFIDYSMHWVRQAPGKGLEW VSSISSSSSYIYYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYC ARDGLYDSSVRDAFDIWGQGTMV TVSS SEQ ID NO. 95	QSVLTQPRSVSGSPGQSVTISCTGTSSD VGGYNYVSWYQQHPGKAPKLMIYDV SKRPSGVPDRFSGSKSGNTASLTVSGL QAEDEADYYCSSYAGSNNLVFGGGTK VTVL SEQ ID NO. 96
JH1D7	EVQLVESGAEVKKPGASVKVSCK ASGYTFTNYYMHWVRQAPGQGLE WMGIINPSDGNTSYAQKFQGRVT MTKDTSTSTVYMELSSLRSDDTAV YYCARESSSWETYFDYWGQGTLV TVSS SEQ ID NO. 97	SYELMQPPSVSVAPGKTARITCGGNNI GSKSVHWYQQKPGQAPVLVVYDDSD RPSGIPERFSGSNSGNTATLTISRVEAG DEADYYCQVWDSSSDHVVFGGGTKLT VL SEQ ID NO. 98
JH1E11	QVQLVQSGGGLVQSGGSLRLSCA ASGFSFRSHWMHWVRQAPGKGLE WVASISPDGTDKYYVESLQGRFTIS RDNAKNSLYLQMNSLRAEDTAVY YCARDQVEQRGVYDMDVWGQGT TVTVSS SEQ ID NO. 99	VIWMTQSPSSLSASVGDRVTITCQATQ DINNNLNWYQHRPGEAPTLLIYGASTL QSGVPSRFSGSGFGTDFTLTISSLQPED VATYYCQKYDDDPLTFGGGTKVEIK SEQ ID NO. 100
JH1F3	QVQLVQSGAEVKKPGASVKVSCQ ASGYTFTSYDIHWVRQVPGQRLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVY YCARDGYSYGPSDYWGQGTLVTV SS SEQ ID NO. 101	DVVMTQSPSTLSASVGDRVTITCRASQ RISSWLAWYQQKPGKAPKSLIYAASSL QSGVPSKFSGGGSGTDFTLTISSLQPED FATYYCQQYIYYPPTFGQGTRLEIK SEQ ID NO. 102
JH1F4	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYAMHWVRHAPGQRLE WMGWINAGNGNTKYSQKFQGRV TITRDTSASTAYMELSSLRSEDTAV YYCARDLDYYYGMDVWGQGTTV TVSS SEQ ID NO. 103	QPVLTQPPSASGTPGQRVTISCSGSSSNI GSNIVNWYQQLPGTAPKLLIYSNNRRP SGVPDRFSGSKSGSSASLAISGLQSEDE ADYYCAAWDATLGGLYVFGTGTKVT VL SEQ ID NO. 104

	Heavy chain variable domain sequence	Light chain variable domain sequence
JH1F6	EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSDGNTSYAQKFQGRVT MTKDTSTSTVYMELSSLRSEDTAV YYCARESSSWETYFDYWGQGTLV TVSS SEQ ID NO. 105	QPVLTQPPSVSVAPGKTARITCGGNNIG SKSVHWYQQKPGQAPVLVIYYDTDRP SGIPERFSGSNSGNTATLTISRVEAGDE ADFYCQVWDSSSDHVVFGGGTKLTVL SEQ ID NO. 106
JH1H2	EVQLVESGGGLVKPGGSLRLSCAA SGFTFSDYYMSWIRQAPGKGLEW VSYISSSSSYTNYADSVKGRFTISR DNAKNSLYLQMNSLRAEDTAVYY CAKHSSSWYGDLDYWGQGTLVT VSS SEQ ID NO. 107	QSALTQPPSVSAAPGQKVTISCSGSSSNI ANNYVSWYQQLPGTAPKLLIYDNNKR PSGIPDRFSGSKSGTSATLGITGLQTGD EADYYCGTWDGSLSAGVFGGGTKLTV L SEQ ID NO. 108
JH1H7	QMQLVQSGAEVKKPGSSVKVSCK ASGATFSSYAMSWVRQAPGQGLE WMGAVIPIFGTTNYAPKFEGRVTIT ADESTSTVYMELSSLTSEDTAVYY CARQIGEVVGGIMEDYWGQGTLV TVSS SEQ ID NO. 109	DIVMTQSPSSLSPSIGDRVTITCRASQGI SSALAWYQQKPGKAPKLLIYHASTLQS GVPSRFSGSGSGTDFTLTISSLQPEDVA TYYCQKYNSAPLTFGGGTKVEIK SEQ ID NO. 110
JG1H7 3-2	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SS SEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-2B2S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SS SEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCPASQSI STSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 113

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-2A3S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASHS ISTSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 114
JG1H7-2A7S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASPSI STSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 115
JG1H7-2A10S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS TSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 116
JG1H7-2A2S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS SSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 117

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-2A9S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS FSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO:118
JG1H7-2A1S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS PSTSLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 119
JG1H7-E11S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISASLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 120
JG1H7-C11S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTTLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 121

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-D10S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSQNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 122
JG1H7-2B7S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SSSEQ ID NO: 111	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYLASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-1A8S	EVQLVESGGGLIQPGGSLRLSCAA SGFTVSNFYMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SS SEQ ID NO: 124	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-1A6S	EVQLVESGGGLIQPGGSLRLSCAA SAFTVSNFSMTWVRQAPGKGLEW VSVIDSGGNTYYADSVRGRFTISR DNSKNTLFLQMNSLRAEDTAVYY CARDLGYYYAMDVWGQGTTVTV SS SEQ ID NO: 125	DIQMTQSPSSLSASVGDRVTITCRASQS ISTSLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-1A2S	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFGMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 126	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-1B1S	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-5A8S	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARALGYYYAMDVWGQGTTVTVSS SEQ ID NO: 128	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-5B5S	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 129	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-3E5S	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYALDVWGQGTTVTVSS SEQ ID NO: 130	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 112
JG1H7-G6C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQSISTTQNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 131
JG1H7-A6C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASPSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 133
JG1H7-E11C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-C6C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYALDVWGQGTTVTVSS SEQ ID NO: 142	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-C9C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123
JG1H7-F4C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASPSISASLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 134
JG1H7-F2C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARALGYYYALDVWGQGTTVTVSS SEQ ID NO: 135	DIQMTQSPSSLSASVGDRVTITCRASPSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 133

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-F1C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQSISASLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 136
JG1H7-D4C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQSTSASLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 137
JG1H7-D5C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFYMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 132	DIQMTQSPSSLSASVGDRVTITCRASQSPSTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 138
JG1H7-A5C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 139	DIQMTQSPSSLSASVGDRVTITCRASQSISTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 123

	Heavy chain variable domain sequence	Light chain variable domain sequence
JG1H7-B2C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARSLGYYYALDVWGQGTTVTVSS SEQ ID NO: 139	DIQMTQSPSSLSASVGDRVTITCRASQSPSASLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 140
JG1H7-B6C	EVQLVESGGGLIQPGGSLRLSCAASAFTVSNFAMTWVRQAPGKGLEWVSVIDSGGNTYYADSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDLGYYYAMDVWGQGTTVTVSS SEQ ID NO: 127	DIQMTQSPSSLSASVGDRVTITCRASQSSSTSLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTKLEIK SEQ ID NO: 141

Incorporation by Reference

The contents of all references, patents, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

We claim:

1. An isolated anti-JAG1 fully human antibody of an IgG class that binds to a JAG1 epitope, said antibody comprising:

a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and

a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

2. The fully human antibody of claim 1, wherein the antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of: SEQ ID NO. 1/SEQ ID NO. 2 (JG1A1), SEQ ID NO. 3/SEQ ID NO. 4 (JG1A10), SEQ ID NO. 5/SEQ ID NO. 6 (JG1A12), SEQ ID NO. 7/SEQ ID NO. 8 (JG1A3), SEQ ID NO. 9/SEQ ID NO. 10 (JG1A4), SEQ ID NO. 11/SEQ ID NO. 12 (JG11A5), SEQ ID NO. 13/SEQ ID NO. 14 (JG1A6), SEQ ID NO. 15/SEQ ID NO. 16 (JG1A7), SEQ ID NO. 17/SEQ ID NO. 18 (JG1B1), SEQ ID NO. 19/SEQ ID NO. 20 (JG1B10), SEQ ID NO. 21/SEQ ID NO. 22 (JG1B11), SEQ ID NO. 23/SEQ ID NO. 24 (JG1B12), SEQ ID NO. 25/SEQ ID NO. 26 (JG1B4), SEQ ID NO. 27/SEQ ID NO. 28 (JG1B5), SEQ ID NO. 29/SEQ ID NO. 30 (JG1B6), SEQ ID NO. 31/SEQ ID NO. 32 (JG1B8), SEQ ID NO. 33/SEQ ID NO. 34 (JG1C3), SEQ ID NO. 35/SEQ ID NO. 36 (JG1C4), SEQ ID NO. 37/SEQ ID NO. 38 (JG1C5), SEQ ID NO. 39/SEQ ID NO. 40 (JG1C8), SEQ ID NO. 41/SEQ ID NO. 42 (JG1D1), SEQ ID NO. 43/SEQ ID NO. 44 (JG1D10), SEQ ID NO. 45/SEQ ID NO. 46 (JG1D11), SEQ ID NO. 47/SEQ ID NO. 48 (JG1D7), SEQ ID NO. 49/SEQ ID NO. 50 (JG1D8), SEQ ID NO. 51/SEQ ID NO. 52 (JG1E1), SEQ ID NO. 53/SEQ ID NO. 54 (JG1E11), SEQ ID NO. 55/SEQ ID NO. 56 (JG1E7), SEQ ID NO. 57/SEQ ID NO. 58 (JG1E8), SEQ ID NO. 59/SEQ ID NO. 60 (JG1F1), SEQ ID NO. 61/SEQ ID NO. 62 (JG1F10), SEQ ID NO. 63/SEQ ID NO. 64 (JG1F7), SEQ ID NO. 65/SEQ ID NO. 66 (JG1F8), SEQ ID NO. 67/SEQ ID NO. 68 (JG1G11), SEQ ID NO. 69/SEQ ID NO. 70 (JG1G5), SEQ ID NO. 71/SEQ ID NO. 72 (JG1H1), SEQ ID NO. 73/SEQ ID NO. 74 (JG1H11), SEQ ID NO. 75/SEQ ID NO. 76 (JG1H5), SEQ ID NO. 77/SEQ ID NO. 78 (JG1H7), SEQ ID NO. 79/SEQ ID NO. 80 (JH1A1), SEQ ID NO. 81/SEQ ID NO. 82 (JH1A11), SEQ ID NO. 83/SEQ ID NO. 84 (JH1A2), SEQ ID NO. 85/SEQ ID NO. 86 (JH1A4), SEQ ID NO. 87/SEQ ID NO. 88 (JH1B1 n), SEQ ID NO. 89/SEQ ID NO. 90 (JH1B3), SEQ ID NO. 91/SEQ ID NO. 92 (JH1B7), SEQ ID NO. 93/SEQ ID NO. 94 (JH1C10), SEQ ID NO. 95/SEQ ID NO. 96 (JH1C2), SEQ ID NO. 97/SEQ ID NO. 98 (JH1D7), SEQ ID NO. 99/SEQ ID NO. 100 (JH1E11), SEQ ID NO. 101/SEQ ID NO. 102 (JH1F3), SEQ ID NO. 103/SEQ ID NO. 104 (JH1F4), SEQ ID NO. 105/SEQ ID NO. 106 (JH1F6), SEQ ID NO. 107/SEQ ID NO. 108 (JH1H2), SEQ ID NO. 109/SEQ ID NO. 110 (JH1H7), SEQ ID NO. 111/SEQ ID NO.112 (G1H73-2), SEQ ID NO. 111/SEQ ID NO.113 (JG1H7-2B2S), SEQ ID NO.111/SEQ ID NO.114 (JG1H7-2AS), SEQ ID NO. 111/SEQ ID NO.115 (JG1H73-2A7S), SEQ ID NO. 111/SEQ ID NO.116 (JG1H7-2A10S), SEQ ID NO.111/SEQ ID NO.117 (JG1H7-2A2S), SEQ ID NO. 111/SEQ ID NO.118 (JG1H73-2A9S), SEQ ID NO. 111/SEQ ID NO.119 (JG1H7-2A1S), SEQ ID NO.111/SEQ ID NO.120 (JG1H7-E11S), SEQ ID NO. 111/SEQ ID

NO.121 (JG1H73-C11S), SEQ ID NO. 111/SEQ ID NO.122 (JG1H7-D10S), SEQ ID NO.111/SEQ ID NO.123 (JG1H7-2B7S), SEQ ID NO.124/SEQ ID NO.112 (JG1H7-1A8S), SEQ ID NO. 125/SEQ ID NO.112 (JG1H73-1A6S), SEQ ID NO. 126/SEQ ID NO.112 (JG1H7-1A2S), SEQ ID NO.127/SEQ ID NO.112 (JG1H7-1B1S), SEQ ID NO. 128/SEQ ID NO.112 (JG1H73-1A8S), SEQ ID NO. 129/SEQ ID NO.112 (JG1H7-5B5S), SEQ ID NO.130/SEQ ID NO.112 (JG1H7-3E5S), SEQ ID NO.127/SEQ ID NO.131 (JG1H7-G6C), SEQ ID NO. 132/SEQ ID NO.133 (JG1H73-A6C), SEQ ID NO. 132/SEQ ID NO.123 (JG1H7-E11C), SEQ ID NO.142/SEQ ID NO.123 (JG1H7-C6C), SEQ ID NO. 127/SEQ ID NO.123 (JG1H73-C9C), SEQ ID NO. 132/SEQ ID NO.134 (JG1H7-F4C), SEQ ID NO. 135/SEQ ID NO.133 (JG1H7-F2C), SEQ ID NO.132/SEQ ID NO.136 (JG1H7-F1C), SEQ ID NO.132/SEQ ID NO.137 (JG1H7-D4C), SEQ ID NO. 132/SEQ ID NO.138 (JG1H73-D5C), SEQ ID NO. 139/SEQ ID NO.123 (JG1H7-A5C), SEQ ID NO.139/SEQ ID NO.140 (JG1H7-B2C), and SEQ ID NO. 127/SEQ ID NO.141 (JG1H73-B6C).

3. The fully human antibody of claim 1 or 2, wherein the antibody has a K_D of at least 1 x 10^{-6} M.

4. An anti-JAG1 fully human antibody Fab fragment, comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and

comprising a light chain variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12,

SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

5. The fully human antibody Fab fragment of claim 4, wherein the antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ

ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO.112 , SEQ ID NO. 111/SEQ ID NO.113, SEQ ID NO.111/SEQ ID NO.114, SEQ ID NO. 111/SEQ ID NO.115 , SEQ ID NO. 111/SEQ ID NO.116, SEQ ID NO.111/SEQ ID NO.117, SEQ ID NO. 111/SEQ ID NO.118, SEQ ID NO. 111/SEQ ID NO.119, SEQ ID NO.111/SEQ ID NO.120, SEQ ID NO. 111/SEQ ID NO.121, SEQ ID NO. 111/SEQ ID NO.122, SEQ ID NO.111/SEQ ID NO.123, SEQ ID NO.124/SEQ ID NO.112 , SEQ ID NO. 125/SEQ ID NO.112, SEQ ID NO. 126/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.112, SEQ ID NO. 128/SEQ ID NO.112, SEQ ID NO. 129/SEQ ID NO.112, SEQ ID NO.130/SEQ ID NO.112, SEQ ID NO.127/SEQ ID NO.131, SEQ ID NO. 132/SEQ ID NO.133, SEQ ID NO. 132/SEQ ID NO.123, SEQ ID NO.142/SEQ ID NO.123, SEQ ID NO. 127/SEQ ID NO.123, SEQ ID NO. 132/SEQ ID NO.134 , SEQ ID NO. 135/SEQ ID NO.133, SEQ ID NO.132/SEQ ID NO.136, SEQ ID NO.132/SEQ ID NO.137, SEQ ID NO. 132/SEQ ID NO.138, SEQ ID NO. 139/SEQ ID NO.123, SEQ ID NO.139/SEQ ID NO.140, and SEQ ID NO. 127/SEQ ID NO.141.

6. The fully human antibody Fab fragment of claim 4 or 5, wherein the antibody has a K_D of at least 1 x 10^{-6} M.

7. An anti-JAG1 single chain human antibody, comprising a heavy chain variable domain and a light chain variable domain which are connected by a peptide linker, wherein the heavy chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and

the light chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

8. The fully human single chain antibody of claim 7, wherein the single chain fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, 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/SEQ ID NO. 62, 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. 80, SEQ ID NO. 81/SEQ

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9. The fully human single chain antibody of claim 7 or 8, wherein the antibody has a K_D of at least 1 x 10^{-6} M.

10. A method for treating a Notch-signaling tumor in a subject in need thereof, said method comprising administering an effective amount of an anti-JAG1 antibody or antibody fragment of any one of claims 1-9, to the subject in need thereof.

11. The method of claim 10, wherein the tumor is selected from the group consisting of breast tumor, prostate, colorectal, lung, head and neck squamous cell carcinoma, T-cell acute lymphoblastic leukemia and melanoma and other solid tumors.

12. An isolated anti-JAG1 antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain comprising complementarity determining regions (CDRs) as set forth in a heavy chain variable domain amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ

ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 127, SEQ ID NO. 128, SEQ ID NO. 129, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 135, SEQ ID NO. 139 and SEQ ID NO. 142; and

comprising a light chain variable domain comprising CDRs as set forth in a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 113, SEQ ID NO. 114, SEQ ID NO. 115, SEQ ID NO. 116, SEQ ID NO. 117, SEQ ID NO. 118, SEQ ID NO. 119, SEQ ID NO. 120, SEQ ID NO. 121, SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 137, SEQ ID NO. 138, SEQ ID NO. 140 and SEQ ID NO. 141.

13. A method of treating cancer in a human subject in need thereof, comprising administering an effective amount of the anti-JAG1 antibody, or antigen-binding fragment thereof, of claim 12 to the subject, such that cancer is treated.

14. The method of claim 13, wherein the cancer is associated with Notch-signaling.

15. The method of claim 13 or 14, wherein the cancer is selected from the group consisting of breast, prostate, colorectal, lung , head and neck squamous cell carcinoma, T-cell acute lymphoblastic leukemia, melanoma, and a solid tumor.

16. A pharmaceutical composition comprising the anti-JAG1 antibody, or antibody fragment of any one of claims 1 to 9 or 12, and a pharmaceutically acceptable carrier.

FIG. 1A

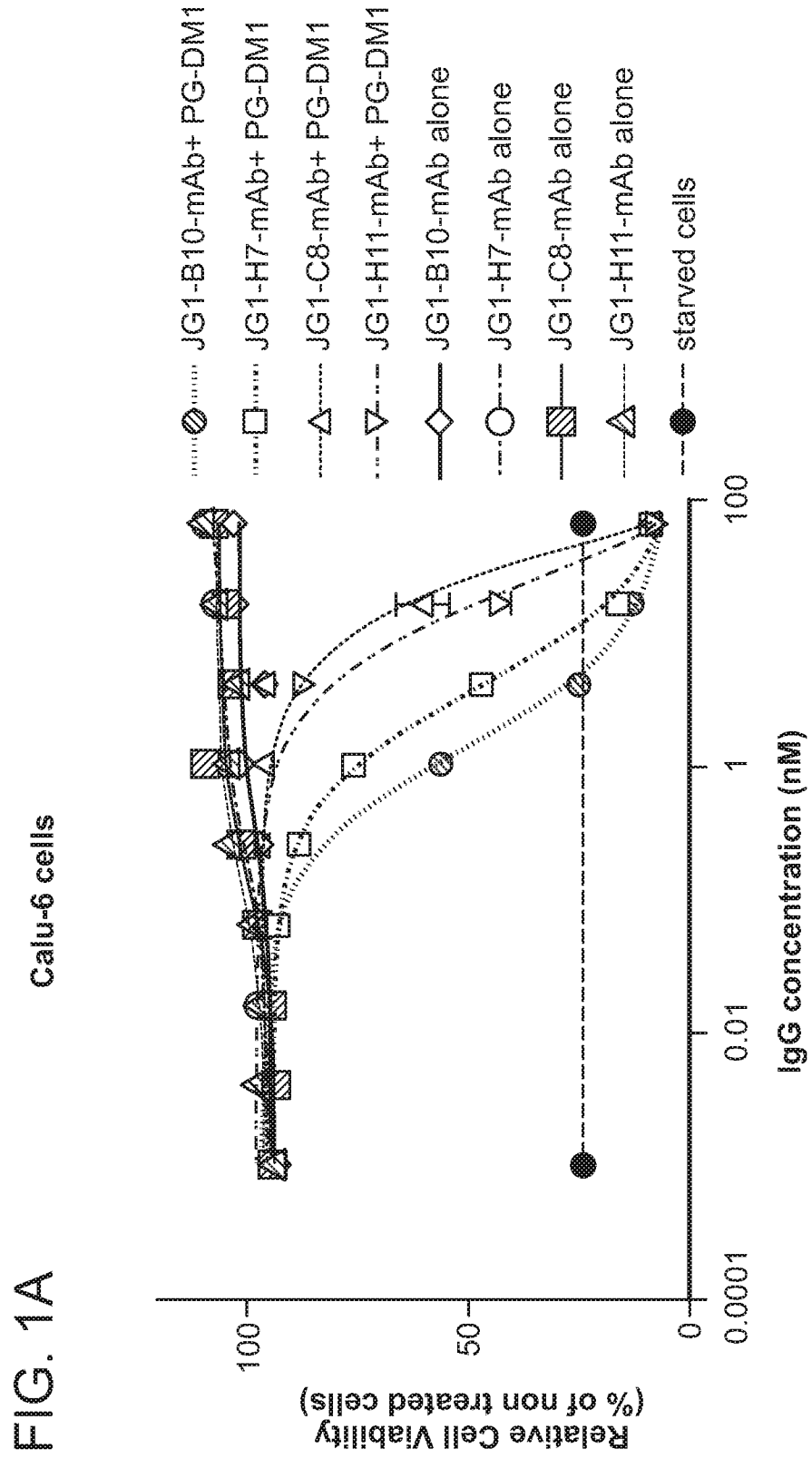

Calu-6 cells
JG1-B10-mAb+ PG-DM1
JG1-H7-mAb+ PG-DM1
JG1-C8-mAb+ PG-DM1
JG1-H11-mAb+ PG-DM1
JG1-B10-mAb alone
JG1-H7-mAb alone
JG1-C8-mAb alone
JG1-H11-mAb alone
starved cells
Relative Cell Viability
(% of non treated cells)
100
50
0
0.0001
0.01
1
100
IgG concentration (nM)

FIG. 1B

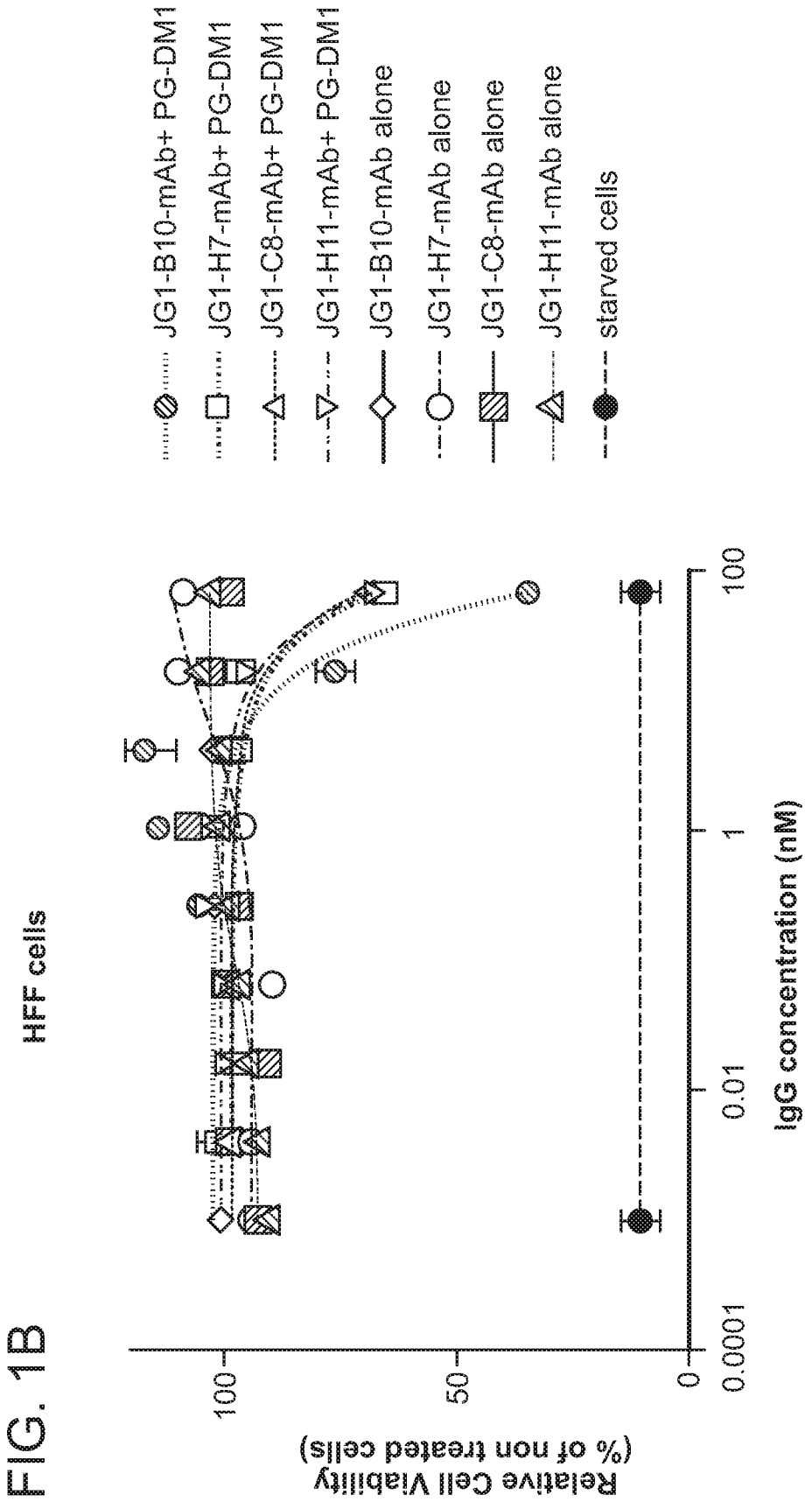

HFF cells
JG1-B10-mAb+ PG-DM1
JG1-H7-mAb+ PG-DM1
JG1-C8-mAb+ PG-DM1
JG1-H11-mAb+ PG-DM1
JG1-B10-mAb alone
JG1-H7-mAb alone
JG1-C8-mAb alone
JG1-H11-mAb alone
starved cells
Relative Cell Viability
(% of non treated cells)
100
50
0
0.0001
0.01
1
100
IgG concentration (nM)

FIG. 2

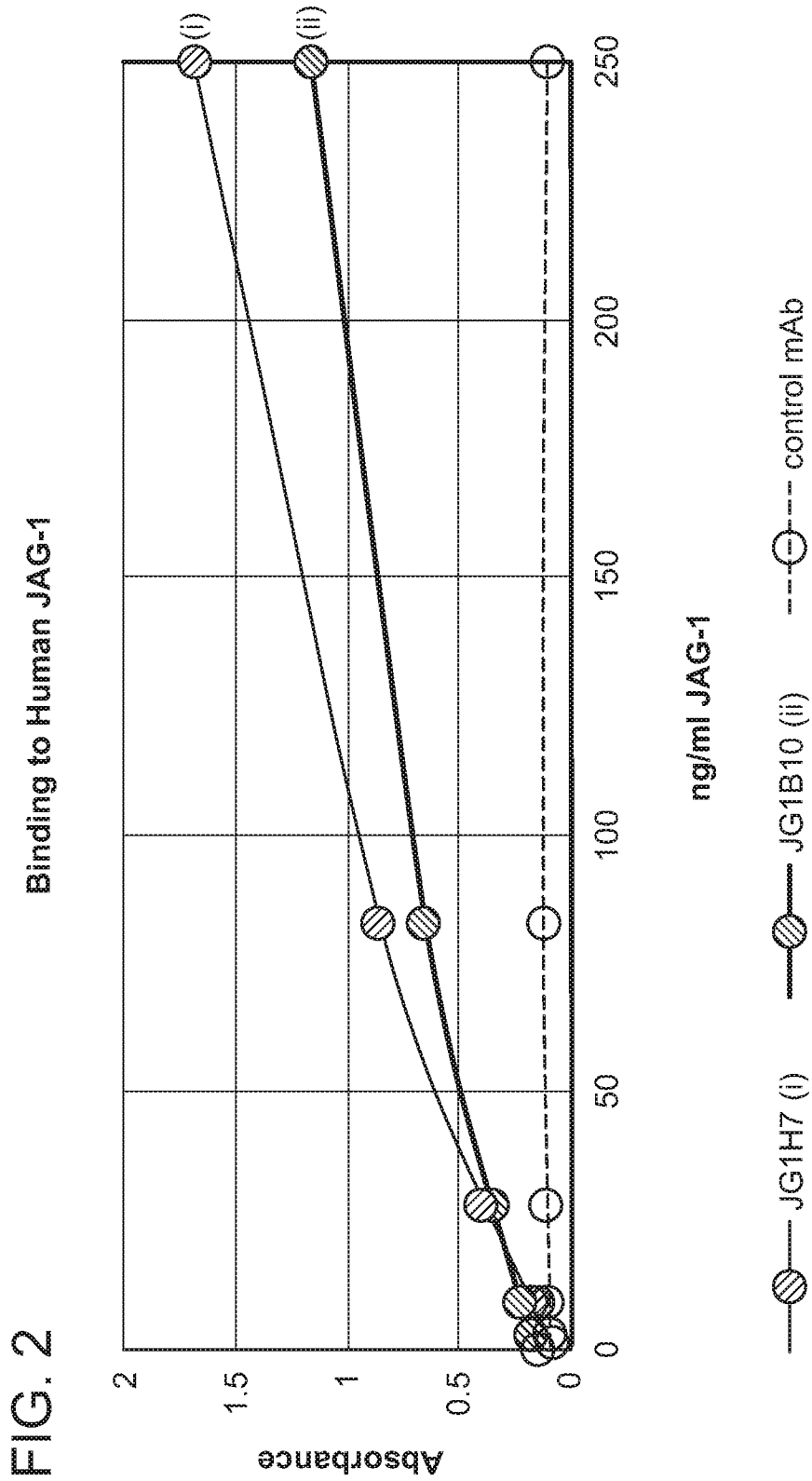

Binding to Human JAG-1
Absorbance
2
1.5
1
0.5
0
0
50
100
150
200
250
ng/ml JAG-1
(i)
(ii)
JG1H7 (i)
JG1B10 (ii)
control mAb

FIG. 3

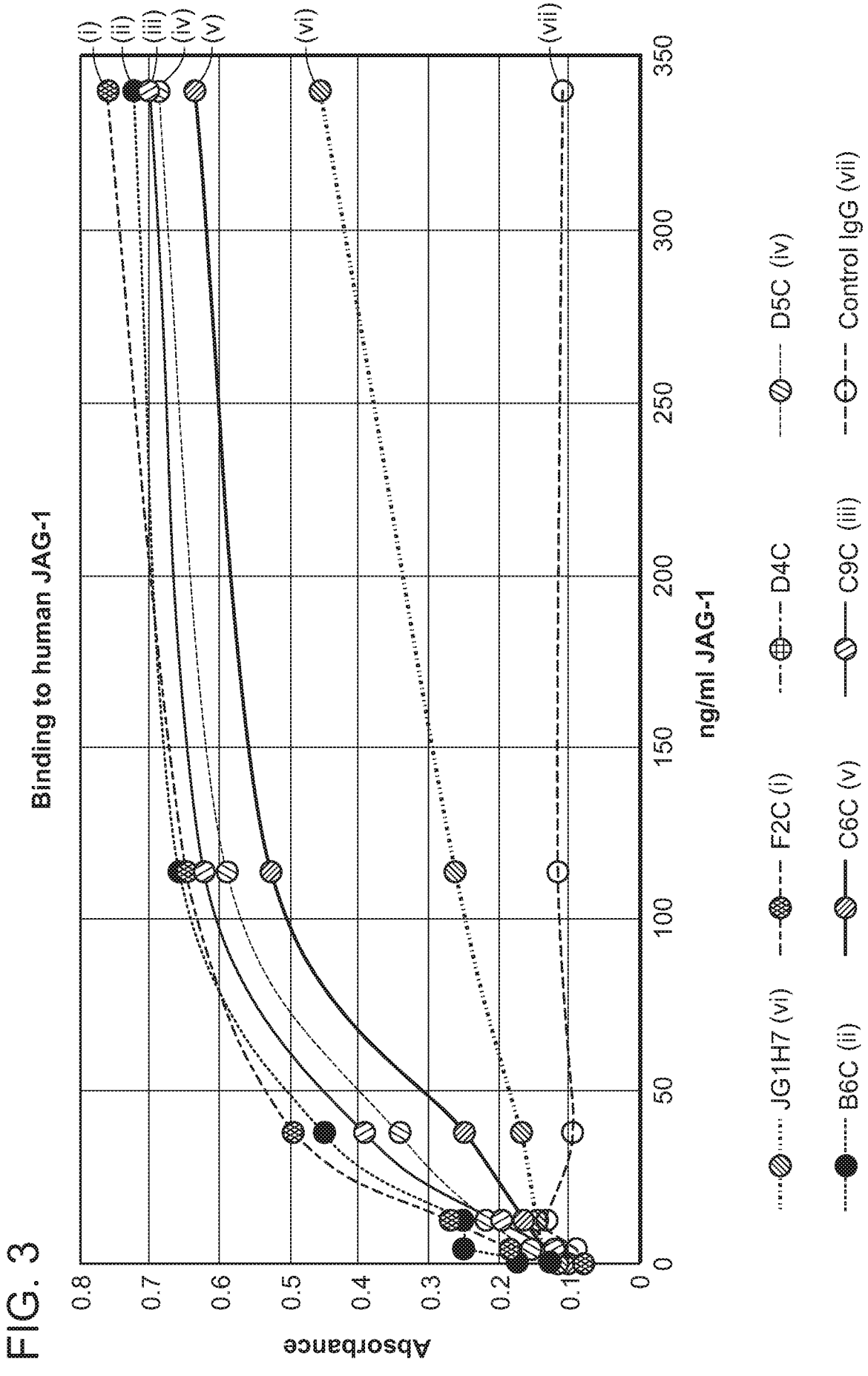

Binding to human JAG-1
Absorbance
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
250
300
350
ng/ml JAG-1
(i)
(ii)
(iii)
(iv)
(v)
(vi)
(vii)
JG1H7 (vi)
F2C (i)
D4C
D5C (iv)
Control IgG (vii)
B6C (ii)
C6C (v)
C9C (iii)

FIG. 4

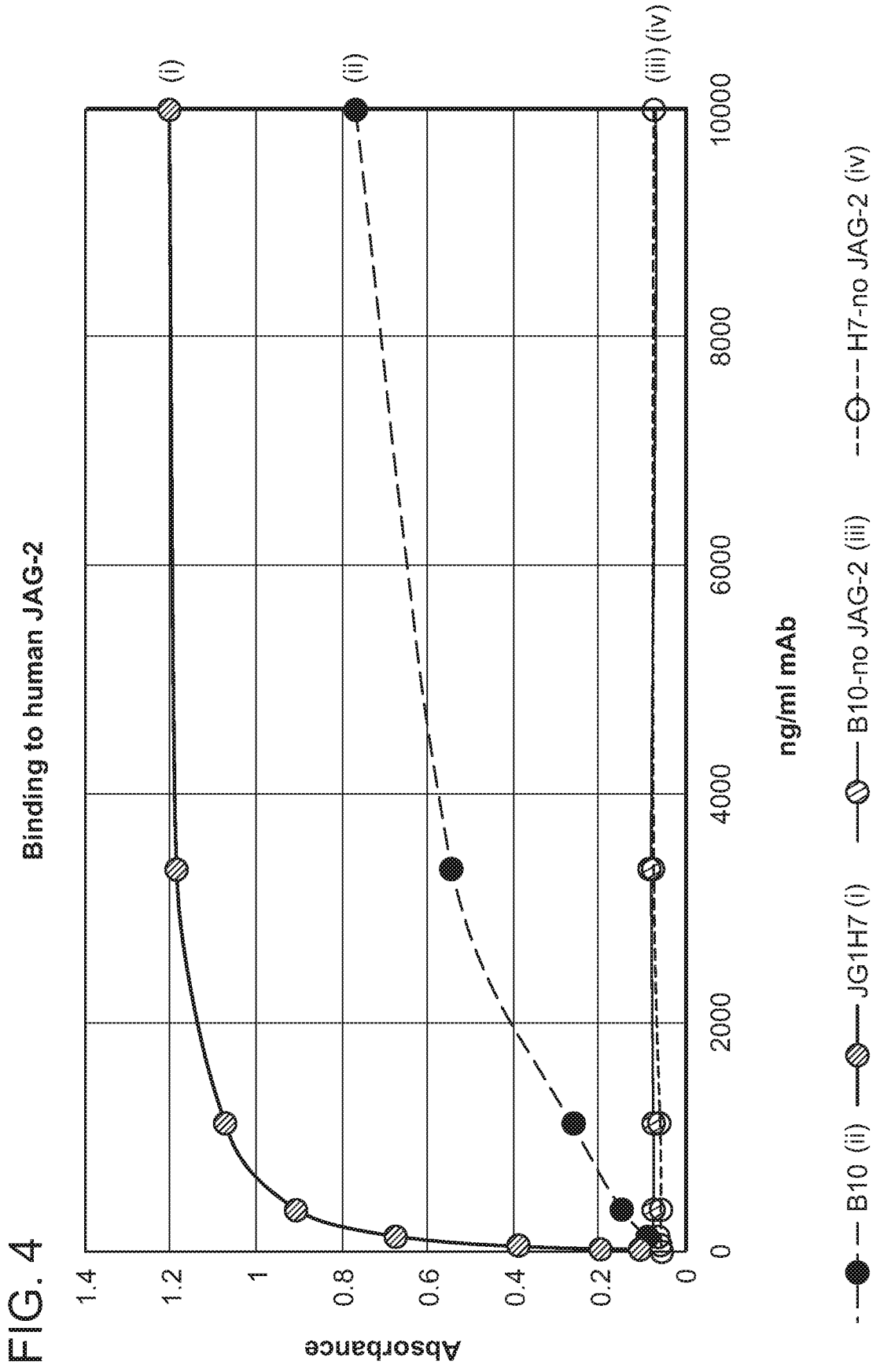

Binding to human JAG-2
Absorbance
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
2000
4000
6000
8000
10000
ng/ml mAb
(i)
(ii)
(iii) (iv)
B10 (ii)
JG1H7 (i)
B10-no JAG-2 (iii)
H7-no JAG-2 (iv)

FIG. 5

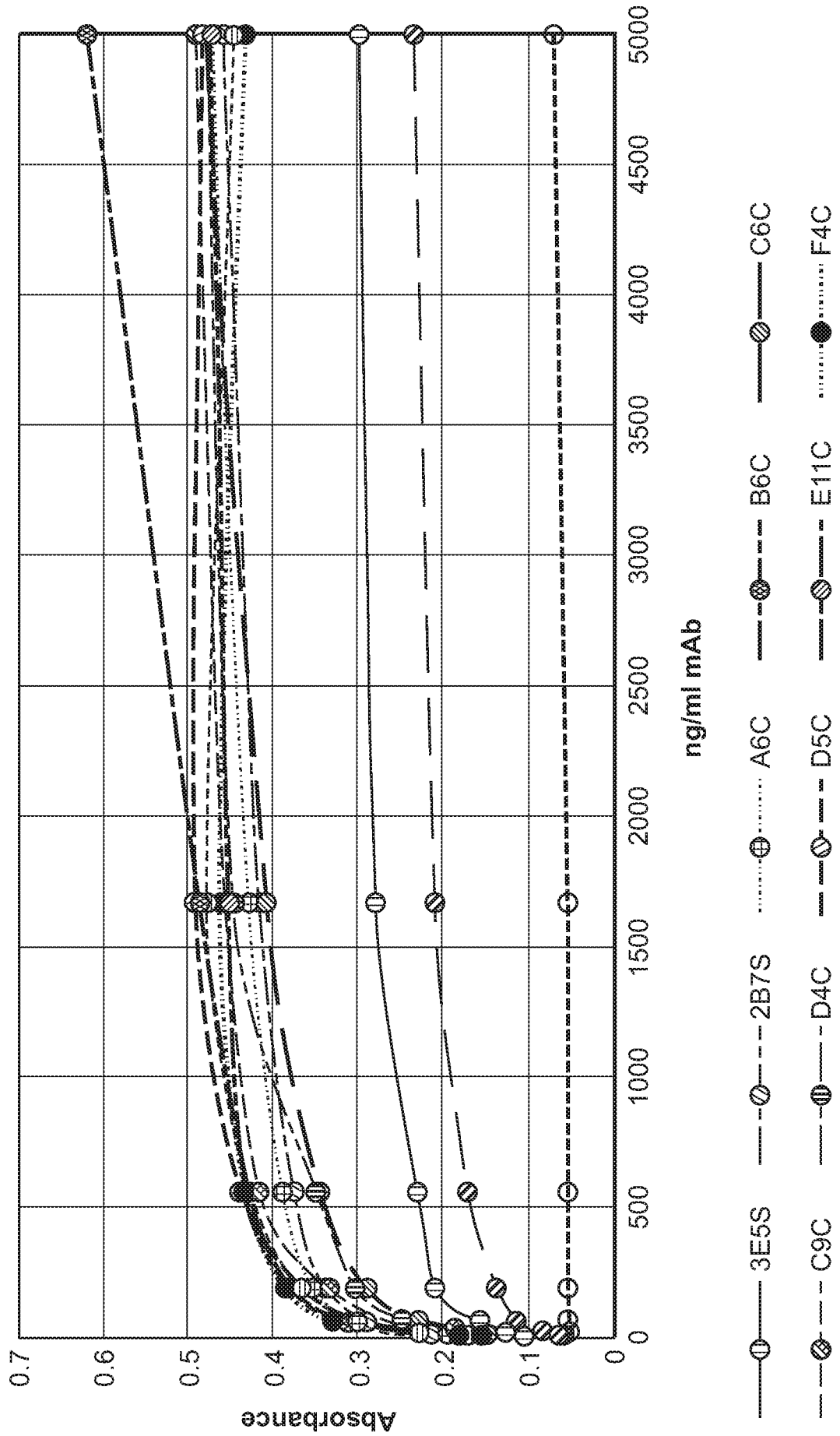

Binding to Human JAG-2
Absorbance
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
ng/ml mAb
3E5S
2B7S
A6C
B6C
C6C
C9C
D4C
D5C
E11C
F4C
G6C
JG1H7
control mAb

FIG. 6

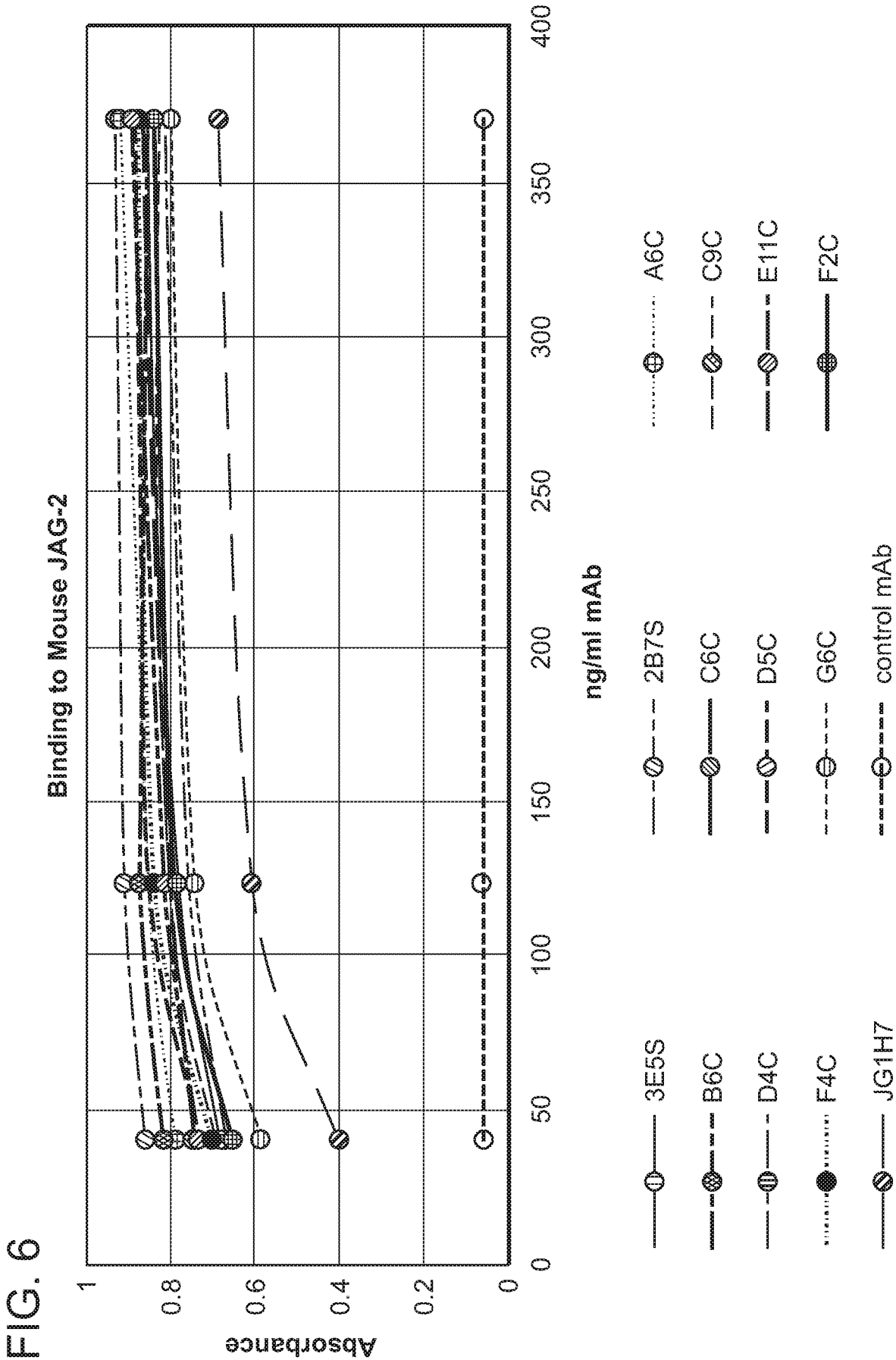

Binding to Mouse JAG-2
Absorbance
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
250
300
350
400
ng/ml mAb
3E5S
B6C
D4C
F4C
JG1H7
2B7S
C6C
D5C
G6C
control mAb
A6C
C9C
E11C
F2C

FIG. 7A

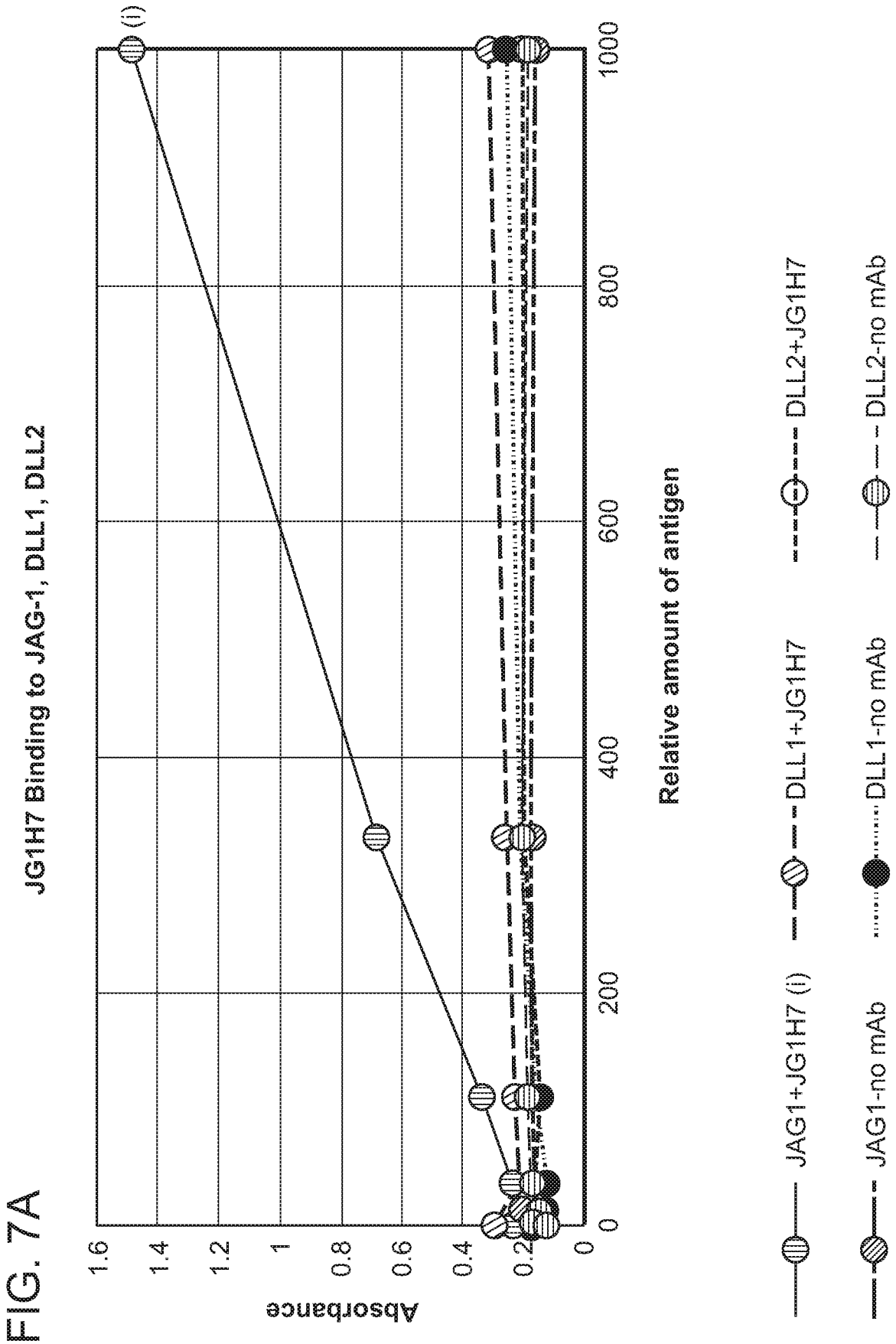
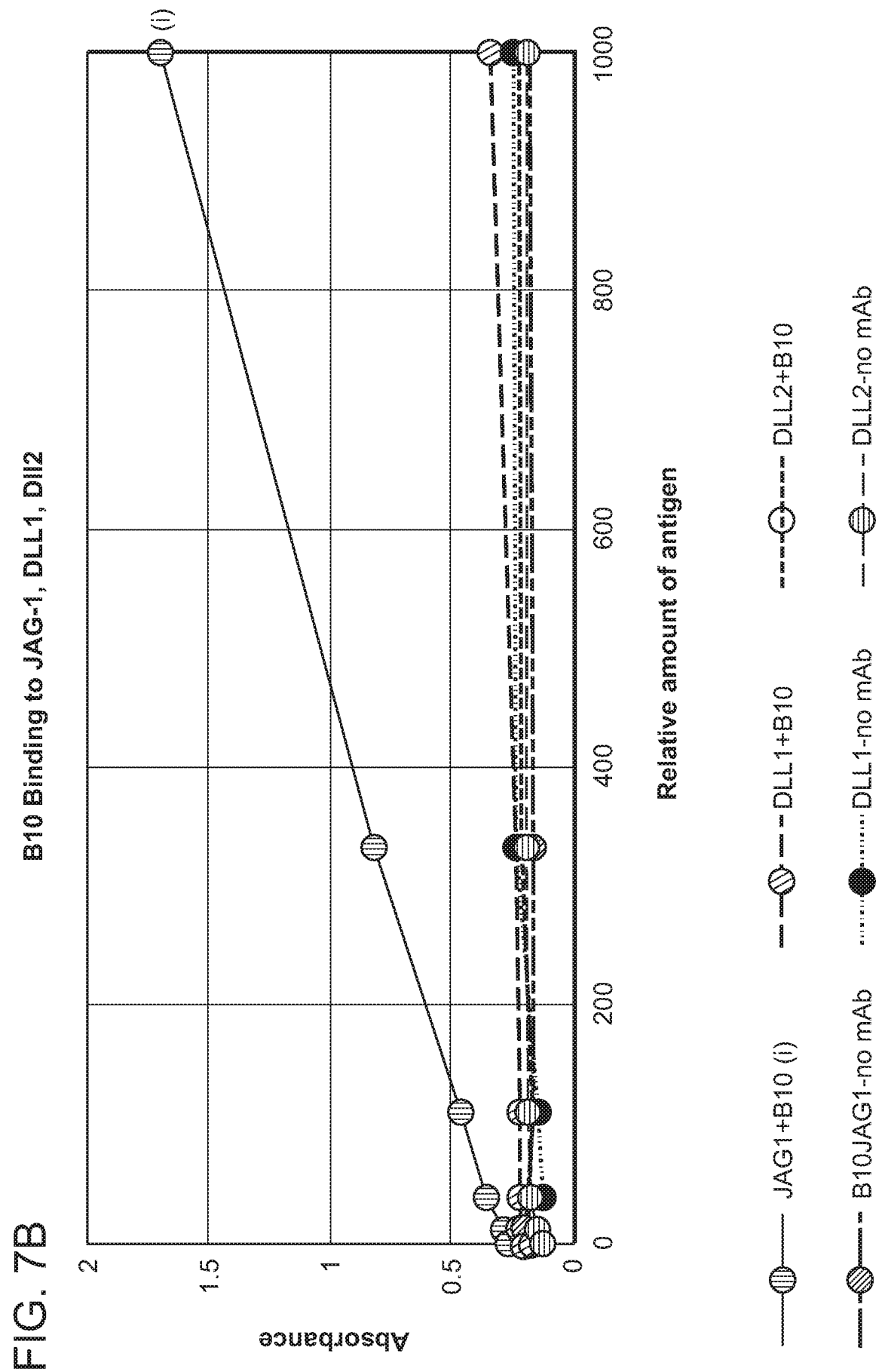

JG1H7 Binding to JAG-1, DLL1, DLL2
Absorbance
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
200
400
600
800
1000
Relative amount of antigen
(i)
JAG1+JG1H7 (i)
DLL1+JG1H7
DLL2+JG1H7
JAG1-no mAb
DLL1-no mAb
DLL2-no mAb

FIG. 7B


B10 Binding to JAG-1, DLL1, DII2
Absorbance
Relative amount of antigen
0
0.5
1
1.5
2
0
200
400
600
800
1000
(i)
JAG1+B10 (i)
DLL1+B10
DLL2+B10
B10JAG1-no mAb
DLL1-no mAb
DLL2-no mAb