The role of Notch signaling in liver cancer is not well understood. Qi et al. report that Notch1 signaling inhibits growth of human hepatocellular carcinoma cells in vitro and in vivo by inducing cell cycle arrest and apoptosis (Qi et al., Cancer Res. 63:8323 (2003)) and Viatour et al. report that expression of Notch1 intracellular domain decreased proliferation and induced apoptosis in murine and human HCC cells (Viatour et al., J. Exp. Med. 208(10):1963 (2011)). Others report that Notch1 small interfering RNA (siRNA) reduced cell invasion and migration but not viability (Zhou et al. Dig. Dis. Sci.). Yet others report that inhibition of individual Notch pathway family members had no effect. Taken together, the Notch pathway's role in liver cancer was not well understood.

SUMMARY

Use of Notch2 signaling inhibitors for the treatment of patients having or at risk of having proliferative disorders of the liver is provided.

In one aspect, there is provided use of an anti-Jagged1 (anti-Jag1) antibody in the manufacture of a medicament for treating a liver cancer in an individual in need thereof, wherein the liver cancer comprises cells that express EpCAM.

~~In one aspect, there is provided use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating liver cancer.~~ Disclosed are methods of treating a liver cancer in an individual in need thereof , comprising the step of administering to the individual an effective amount of a Notch2 signaling inhibitor. In some embodiments, the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, or metastatic liver cancer. In some embodiments, the hepatocellular carcinoma comprises progenitor-like or cholangiocarcinoma-like liver tumor. In some embodiments, the liver cancer is a refractory cancer.

In some embodiments, the method further comprises administering at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to chemotherapeutic agent and an antibody.

In some embodiments, the liver cancer comprises cells that express EpCAM, AFP, Notch2, Jag1, Notch2 and Jag1, nuclear Notch2 ICD, Sox9, CK19, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul, or any combination thereof. In specific embodiments, the liver cancer comprises cells that are AFP^+ $EpCAM^+$. In some embodiments, the liver cancer comprises cells that are AFP^+ $EpCAM^-$, AFP^+ $EpCAM^+$ $SPP1^+$, AFP^- $EpCAM^+$, AFP^- $EpCAM^+$ $Notch2^+$, AFP^+ $EpCAM^-$ $Notch2^+$, AFP^+ $EpCAM^+$ $Sox9^+$ and AFP^+ $EpCAM^+$ $Sox9^+$ or AFP^- $EpCAM^+$ $SPP1^+$. Liver cancers that comprise cells with alternative combinations of marker expression are specifically contemplated.

In some embodiments, at least one of EpCAM, AFP, Notch2, Jag1, Sox9, CK19, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul protein expression was determined in a sample from the individual using immunohistochemistry (IHC). In some

embodiments, expression is nucleic acid expression. In some embodiments, expression is determined by a method selected from the group consisting of RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, gene expression profiling, polymerase chain reaction, SAGE, MassARRAY technique, fluorescent in situ hybridization and Western blotting.

In some embodiments, administering the Notch2 signaling inhibitor results in a decrease in the expression in the liver cancer of at least one of EpCAM, AFP, Notch2, Notch2 ICD, Jag1, Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb. In some embodiments, administering the Notch2 signaling inhibitor results in an increase in the expression in the liver cancer of at least one of Wnt2, Axin2 and Glul. In some embodiments, expression is determined by RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, and Western blotting.

Any of the antibodies of the above embodiments may be a full-length IgG1 or IgG2a antibody. In some embodiments, the antibody causes cancer cell death, e.g., liver cancer cell death. Any of the antibodies in the above embodiments may be conjugated to a growth inhibitory agent, e.g., a cytotoxic agent. Examples of cytotoxic agent include, but are not limited to, toxins, antibiotics, radioactive isotopes and nucleolytic enzymes. Any of the antibodies in the above embodiments may be produced by known methods in the art, e.g., in bacteria or in CHO cells.

~~In another aspect, there is provided use of an anti-Jag1 antibody in the manufacture of a medicament for preventing liver cancer in an individual at risk of having liver cancer.~~ Disclosed are methods for preventing liver cancer in an individual at risk of having liver cancer, comprising the step of administering to the individual an effective amount of a Notch2 signaling inhibitor. In some embodiments, the individual has a liver condition selected from the group consisting of hepatitis B or C, cirrhosis of the liver, non-viral/non-alcoholic steatohepatitis, benign liver tumors, hemangiomas, hepatic adenomas, and focal nodular hyperplasia. In some embodiments, the Notch2 signaling inhibitor is an anti-Jag1 antibody, e.g., an anti-Jag1 antagonist antibody.

Disclosed are methods for inhibiting growth of a cell that expresses secreted phosphoprotein1 (SPP1), comprising contacting the cell with a Notch2 signaling inhibitor, thereby inhibiting growth of the cell. ~~In one aspect, there is provided an *in vitro* method of inhibiting proliferation of a liver cancer cell that expresses secreted phosphoprotein1 (SPP1), the method comprising contacting the cell with a Notch2 signaling inhibitor, thereby inhibiting growth of the cell. In another aspect, there is provided use of a Notch2 signaling inhibitor in the manufacture of a medicament for inhibiting proliferation of a liver cancer cell, wherein the liver cancer cell is one that expresses a secreted phosphoprotein1 (SPP1).~~ In one embodiment, SPP1 protein comprises the amino acid sequence shown in FIG. 11. In one embodiment, contacting the cell with the Notch2 signaling inhibitor reduces SPP1 expression in the cell. For example, contacting the cell with the Notch2 signaling inhibitor reduces SPP1 expression in the cell by at least about 50%, 60%, 70%, 80%, 90%, or 100%. The expression of SPP1 mRNA or protein can be determined by any method in the art. In some embodiments, the Notch2 signaling inhibitor is

an anti-Notch2 antibody, e.g., an anti-Notch2 negative regulatory region (NRR) antibody, such as any anti-Notch2 NRR antibody disclosed herein. In some embodiments, the antibody is an anti-Jag1 antibody, such as any anti-Jag1 antibody disclosed herein. In some embodiments, the cell is a liver cancer cell. In some embodiments, the liver cancer cell expresses EpCAM, AFP, AFP and EpCAM, Notch2, Jag1, Notch2 and Jag1, nuclear Notch2 ICD, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul, or any combination thereof. In some embodiments, contacting the cell with the Notch2 signaling inhibitor results in a decrease in the expression in the cell of at least one of EpCAM, AFP, Notch2, Notch2 ICD, Jag1, Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb. In some embodiments, administering the Notch2 signaling inhibitor results in an increase in the expression in the cell of at least one of Wnt2, Axin2 and Glul. In some embodiments, expression is determined by RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, and Western blotting.

Disclosed are methods for inhibiting proliferation of a cell that expresses secreted phosphoprotein1 (SPP1), comprising contacting the cell with a Notch2 signaling inhibitor, thereby inhibiting proliferation of the cell.

~~In another aspect, there is provided use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating a liver cancer in a mammal, wherein the liver cancer in the mammal comprises cells that express an Spp1 gene encoding a peptide comprising an amino acid sequence having at least 90% identity to the polypeptide shown in FIG. 11.~~

Disclosed are methods for treating a mammal having a liver cancer comprising cells that express a Spp1 gene encoding a peptide comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% identity to the polypeptide shown in FIG. 11, comprising administering to the mammal an effective amount of a Notch2 signaling inhibitor, thereby effectively treating the mammal. In some embodiments, the cells express a SPP1 protein comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% identity to the polypeptide shown in FIG. 11.

In some embodiments, the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, or metastatic liver cancer. In some embodiments, the liver cancer is a refractory cancer. Any of the antibodies herein may be a full-length IgG1 or IgG2a antibody. In some embodiments, the antibody causes cancer cell death, e.g., liver cell death. Any of the herein may be conjugated to a growth inhibitory agent, e.g., a cytotoxic agent. Examples of cytotoxic agent include, but are not limited to, toxins, antibiotics, radioactive isotopes and nucleolytic enzymes. Any of the antibodies herein may be produced by known methods in the art, e.g., in bacteria or in CHO cells.

In some embodiments, the method further comprises administering at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to chemotherapeutic agent and an antibody.

In some embodiments, the liver cancer comprises cells that express EpCAM, AFP, AFP and EpCAM, Notch2, Jag1, Notch2 and Jag1, nuclear Notch2 ICD, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul, or any combination thereof. In some embodiments, administering the Notch2 signaling inhibitor results in a decrease in the expression in the liver cancer of at least one of EpCAM, AFP, Notch2, Notch2 ICD, Jag1, Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb. In some embodiments, administering the Notch2 signaling inhibitor results in an increase in the expression in the liver cancer of at least one of Wnt2, Axin2 and Glul. In some embodiments, expression is determined by RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, and Western blotting.

~~In another aspect, there is provided use of an anti-Jag1 antagonist antibody in the manufacture of a medicament for treating a liver cell proliferative disorder in an individual, wherein the liver cell proliferative disorder is associated with increased expression or activity of a protein having at least 90% amino acid sequence identity to the polypeptide shown in FIG. 8C.~~ Disclosed are methods for treating a liver cell proliferative disorder associated with increased expression or activity of a protein having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% amino acid sequence identity to the polypeptide shown in FIG. 8C, comprising administering to an individual in need of such treatment an effective amount of an anti-Jag1 antagonist antibody, thereby effectively treating the liver cell proliferative disorder. In some embodiments, the cell proliferative disorder is a cancer, such as liver cancer. In some embodiments the individual has a liver condition selected from the group consisting of hepatitis B or C, cirrhosis of the liver, benign liver tumors, hemangiomas, hepatic adenomas, and focal nodular hyperplasia.

In certain embodiments, the anti-Jag1 antibody is any of the anti-Jag1 antibodies described herein. In certain embodiments, the anti-Jag1 antibody is a human, humanized, or chimeric antibody. In certain embodiments, any of the antibodies of the above embodiments is an antibody fragment.

Disclosed are methods for treating a liver cell proliferative disorder associated with increased expression or activity of a protein having at least 90% amino acid sequence identity to the polypeptide shown in FIG. 11, comprising administering to an individual in need of such treatment an effective amount of an anti-Jag1 antagonist antibody, thereby effectively treating the liver cell proliferative disorder. In some embodiments, the cell proliferative disorder is a cancer, such as liver cancer. In some embodiments the individual has a liver condition selected from the group consisting of hepatitis B or C, cirrhosis of the liver, benign liver tumors, hemangiomas, hepatic adenomas, and focal nodular hyperplasia.

~~In another aspect, there is provided use of a Notch2 signaling inhibitor in the manufacture of a medicament for reducing serum SPP1 protein levels in an individual having liver cancer.~~ Disclosed are methods for reducing serum SPP1 protein levels in an individual, the method comprising administering to the individual an effective amount of a Notch2 signaling inhibitor thereby reducing serum SPP1 levels in the individual. In one embodiment, the individual has a liver cancer. In one embodiment, the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are at least about 80 ng/ml. In certain embodiments, the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are between about 80 ng/ml and about 500 ng/ml, between about 86 ng/ml and about 250 ng/ml, between about 120 ng/ml and about 170 ng/ml, or about 165 ng/ml. In some embodiments, administering the Notch2 signaling inhibitor to the individual results in serum SPP1 protein levels of less than 80 ng/ml. In specific embodiments, serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor are 24 hours prior to administering the Notch2 signaling inhibitor. Serum SPP1 protein levels prior to or following administration of the Notch2 signaling inhibitor may be determined by any appropriate method, such as enzyme-linked immunosorbent assay. In specific embodiments, serum SPP1 protein levels are reduced about one, two, three, six or 12 month after administering the Notch2 signaling inhibitor. In some embodiments, the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma or metastatic liver cancer. In some embodiments, the Notch2 signaling inhibitor is an siRNA, small-molecule inhibitor or antibody. In some embodiments, the antibody is an antagonist antibody.

In certain embodiments, any of the antibodies of the above embodiments is a monoclonal antibody. In certain embodiments, any of the antibodies of the above embodiments is a human, humanized, or chimeric antibody. In certain embodiments, any of the antibodies of the above embodiments is an antibody fragment.

In some embodiments, the method further comprises administering at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to chemotherapeutic agent and an antibody. In some embodiments, Sorafenib is an additional therapeutic agent.

In some embodiments, the liver cancer comprises cells that express EpCAM, AFP, AFP and EpCAM, Notch2, Jag1, Notch2 and Jag1, nuclear Notch2 ICD, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul, or any combination thereof. In some embodiments, Ras is a mutant Ras. In some embodiments, administering the Notch2 signaling inhibitor results in a decrease in the expression in the liver cancer of at least one of EpCAM, AFP, Notch2, Notch2 ICD, Jag1, Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb. In some

embodiments, administering the Notch2 signaling inhibitor results in an increase in the expression in the liver cancer of at least one of Wnt2, Axin2 and Glul. In some embodiments, expression is determined by RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, and Western blotting.

~~In another aspect, there is provided use of an antibody that binds to Notch2 or Jag1 in the manufacture of a medicament for treating a liver cancer in a mammal, wherein the medicament is to be contacted with a tumor that is at least in part dependent upon a growth potentiating effect of Notch2 signaling.~~ Disclosed are methods for treating a liver tumor in a mammal, wherein the growth of the liver tumor is at least in part dependent upon a growth potentiating effect of Notch2 signaling, comprising contacting the tumor with an antibody that binds to Notch2 or Jag1. In one embodiment, binding of the antibody to the tumor antagonizes the growth-potentiating activity of Notch2. In some embodiments, the mammal is a human.

Disclosed are methods for treating of liver cancer comprising administering to an individual who has elevated serum SPP1 protein levels an effective amount of a Notch2 signaling inhibitor. In one embodiment, the serum SPP1 protein levels of the individual are at least about 80 ng/ml. In certain embodiments, the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are between about 80 ng/ml and about 500 ng/ml, between about 86 ng/ml and about 250 ng/ml, between about 120 ng/ml and about 170 ng/ml, or about 165 ng/ml. In some embodiments, administering the Notch2 signaling inhibitor to the individual results in serum SPP1 protein levels of less than 80 ng/ml. In specific embodiments, serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor are 24 hours prior to administering the Notch2 signaling inhibitor. Serum SPP1 protein levels prior to or following administration of the Notch2 signaling inhibitor may be determined by any appropriate method, such as enzyme-linked immunosorbent assay. In specific embodiments, serum SPP1 protein levels are reduced in the individual about one, two, three, six or 12 month after administering the Notch2 signaling inhibitor. In some embodiments, the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma or metastatic liver cancer. In some embodiments, the Notch2 signaling inhibitor is an siRNA, small-molecule inhibitor or antibody. In some embodiments, the antibody is an antagonist antibody, such as an anti-Notch2 antagonist antibody or an anti-Jag1 antagonist antibody.

~~In another aspect, there is provided use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating an individual having a liver cancer, wherein a decrease in Notch2 signaling determined following treatment, compared to Notch2 signaling prior to treatment, is indicative of reduction of liver cancer in the individual.~~ Disclosed are methods for treating an individual having a liver cancer, comprising the steps of administering to the individual a Notch2 signaling inhibitor; and determining Notch2 signaling, wherein a decrease in Notch2 signaling following treatment, compared to Notch2 signaling prior to treatment, is indicative of reduction of liver cancer in the individual. In some embodiments, Notch2 signaling is determined by measuring Notch2 ICD nuclear localization, e.g., by immunohistochemical analysis of a liver cancer sample from

the individual. In some embodiments, Notch2 signaling is determined by measuring expression of a gene selected from the group consisting of Notch2, Jag1, Hes and Hey1. Expression can be determined by any method, e.g., RT-PCR, microarray, and RNAseq analysis. In some embodiments, the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer. In some embodiments, the Notch2 signaling inhibitor is an siRNA, small-molecule inhibitor or antibody. In some embodiments, the antibody is an antagonist antibody, such as an anti-Notch2 antagonist antibody or an anti-Jag1 antagonist antibody.

~~In another aspect, there is provided use of an antibody to Notch2 or Jag1 in the manufacture of a medicament for inhibiting cellular proliferation in mammalian liver cancer cells. In another aspect, there is provided a method of inhibiting cellular proliferation comprising treating mammalian liver cancer cells with an antibody to Notch2 or Jag1, wherein the cell is in a culture medium.~~ Disclosed are methods for inhibiting cellular proliferation comprising treating mammalian liver cancer cells with an antibody to Notch2 or Jag1, whereby proliferation of the liver cancer cell is inhibited. In certain embodiments, the cell is in a patient. In certain embodiments, the cell is in a culture medium. In certain embodiments, the cell is a liver cancer cell. In certain embodiments, the antibody is an anti-Notch2 or anti-Jag1 antagonist antibody is as described herein. In certain embodiments, the antibody is a human, humanized, or chimeric antibody. In certain embodiments, any of the antibodies of the above embodiments is an antibody fragment.

In any of the methods herein, Notch2 signaling inhibitors may be the following inhibitors. In some embodiments, the Notch2 signaling inhibitor is a siRNA, small-molecule inhibitor or antibody. In some embodiments, the antibody is an antagonist antibody. In some embodiments, the antibody is an anti-Notch2 antibody, e.g., an anti-Notch2 negative regulatory region (NRR) antibody. In some embodiments, the antibody does not significantly bind to a Notch family member other than Notch2. In some embodiments, the antibody binds to mouse Notch2 NRR and human Notch2 NRR, e.g., with a Kd of $\leq$ 10 nM. In some embodiments, the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;
(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;
(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and
(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

comprising, in order, the amino acid sequence of huMAb4D5-8 heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 of FIG. 18.

In a further embodiment, any antibody of the embodiments herein further comprises a light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 of FIG. 19.

In a further embodiment, any antibody of the embodiments herein further comprises a heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 of FIG. 19.

In certain embodiments, the antibody is an isolated antibody that binds to Jag1, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:94; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:97; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:94. In some embodiments, the antibody comprises a VL sequence of SEQ ID NO:97. In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO:97. In some embodiments, the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:95; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:98; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:95. In some embodiments, the antibody comprises a VL sequence of SEQ ID NO:98. In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:95 and a VL sequence of SEQ ID NO:98.

In certain embodiments, the antibody is an isolated antibody that binds to Jag1, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:93; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:96; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:93. In some embodiments, the antibody comprises a VL sequence of SEQ ID NO:96. In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:93 and a VL sequence of SEQ ID NO:96.

~~In one aspect, there is provided~~Disclosed is an article of manufacture comprising (a) a container; (b) a composition of matter contained within the container comprising an anti-Notch2 antibody or an

anti-Jagged1 antibody and a carrier for the treatment of liver cancer; and (c) a label affixed to the container, or a package insert included with the container, referring to the use of the composition of matter for the therapeutic treatment of or the diagnostic detection of a liver cancer. ~~In another aspect, there is provided use of an article of manufacture as described herein in the preparation of a medicament for treatment of a liver cancer. In another aspect, there is provided use of an article of manufacture as described herein in the preparation of a medicament for treatment of a liver cell proliferative disorder.~~

~~In one aspect,~~Disclosed is an anti-Notch2 antibody for use in the treatment of a liver cancer is provided. In certain embodiments, the liver cancer is hepatocellular carcinoma. In certain embodiments, the antibody is an anti-Notch2 NRR antagonist antibody. ~~In one aspect,~~Disclosed is an anti-Jag1 antibody for use in the treatment of a liver cancer is provided. In certain embodiments, the liver cancer is hepatocellular carcinoma. In certain embodiments, the antibody is an anti-Jag1 antagonist antibody.

~~In one aspect, there is provided~~Disclosed is use of an anti-Notch2 antibody in the preparation of a medicament treating a liver cancer. ~~In one aspect, there is provided~~Disclosed is use of an anti-Jagged1 antibody in the preparation of a medicament for treating a liver cancer.

Disclosed is use of an article of manufacture described herein in the preparation of a medicament for the therapeutic treatment of a liver cancer. Disclosed is use of an article of manufacture as described herein in the preparation of a medicament for treatment or prevention of a liver cell proliferative disorder.

BRIEF DESCRIPTION OF THE FIGURES

FIGs. 1A-F illustrate characterization of liver cancer marker expression in the AKT/Ras HTV liver cancer model. FIGs. 1A-C depict immunohistochemical staining of tumors that are $AFP^{+}EpCAM^{-}$(FIG. 1A), $AFP^{+}EpCAM^{+}$(FIG. 1B) and $AFP^{-}EpCAM^{+}$(FIG. 1C). FIG. 1D depicts the prevalence of marker expression, expressed in percentage of total cells. FIG. 1F depicts immunohistochemical staining of activation of Notch2 signaling indicated by localization of the Notch2 protein in the nucleus. FIG. 1E depicts the percent cells with nuclear Notch2 staining.

FIGs. 2A-D illustrate reduced tumor burden in Ras/AKT HTV mice treated with anti-Notch2 or anti-Jag1 antagonist antibodies. FIG. 2A depicts isolated livers from HTV mice treated with an isotype control antibody (upper left), an anti-Notch2 antibody (upper right) or an anti-Jag1 antibody (lower left) beginning on the day of the HTV. FIG. 2B depicts Ras/AKT HTV mice liver weight following antibody treatment administered at the time of HTV injection, expressed in percent body weight. FIG. 2C depicts Ras/AKT HTV mice liver weight

WHAT IS CLAIMED IS:

1. Use of an anti-Jagged1 (anti-Jag1) antibody in the manufacture of a medicament for treating a liver cancer in an individual in need thereof, wherein the liver cancer comprises cells that express EpCAM.

2. The use of claim 1, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

3. The use of claim 1, wherein the anti-Jag1 antibody is a monoclonal antibody.

4. The use of claim 3, wherein the anti-Jag1 antibody is an IgG1 or IgG2a antibody.

5. The use of claim 3, wherein the anti-Jag1 antibody is a chimeric antibody, a humanized antibody, or a human antibody.

6. The use of claim 1, wherein the anti-Jag1 antibody comprises:

a) heavy chain hypervariable region 1 (HVR-H1) comprising the amino acid sequence of SEQ ID NO:81; heavy chain hypervariable region 2 (HVR-H2) comprising the amino acid sequence of SEQ ID NO:84; heavy chain hypervariable region 3 (HVR-H3) comprising the amino acid sequence of SEQ ID NO:87; light chain hypervariable region 1 (HVR-L1) comprising the amino acid sequence of SEQ ID NO:88; light chain hypervariable region 2 (HVR-L2) comprising the amino acid sequence of SEQ ID NO:89; and light chain hypervariable region 3 (HVR-L3) comprising the amino acid sequence of SEQ ID NO:92; or

b) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81; HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; HVR-H3 comprising the amino acid sequence of SEQ ID NO:85; HVR-L1 comprising the amino acid sequence of SEQ ID NO:88; HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and HVR-L3 comprising the amino acid sequence of SEQ ID NO:90; or

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81; HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; HVR-H3 comprising the amino acid sequence of SEQ ID NO:86; HVR-L1 comprising the amino acid sequence of SEQ ID NO:88; HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and HVR-L3 comprising the amino acid sequence of SEQ ID NO:91; or

d) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81; HVR-H2 comprising the amino acid sequence of SEQ ID NO:83; HVR-H3 comprising the amino acid sequence of SEQ ID NO:85; HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

7. The use of claim 1, wherein the anti-Jag1 antibody comprises:

a) a heavy chain variable region(VH) sequence of SEQ ID NO:93 and a light chain variable region (VL) sequence of SEQ ID NO:96; or

b) a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO:97; or

c) a VH sequence of SEQ ID NO:95 and a VL sequence of SEQ ID NO:98.

8. The use of claim 1, wherein the anti-Jag1 antibody is conjugated to a cytotoxic agent.

9. The use of claim 8, wherein the cytotoxic agent is selected from toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

10. The use of claim 1, wherein the liver cancer comprises cells that express at least one of AFP, Notch2, Jag1, Sox9, CK19, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul.

11. The use of claim 1, wherein the liver cancer comprises cells having nuclear Notch2.

12. The use of claim 1, wherein the liver cancer comprises cells having activated Ras.

13. The use of claim 1, wherein administration of the anti-Jag1 antibody results in a decrease in EpCAM expression in the cells.

14. The use of claim 1, wherein the liver cancer comprises cells that express AFP and wherein administration of the anti-Jag1 antibody results in a decrease in AFP expression in the cells.

15. The use of claim 1, wherein administration of the anti-Jag1 antibody results in a decrease in expression, compared to expression prior to administration of the inhibitor, in the liver cancer of at least one of Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

16. The use of claim 1, wherein administration of the anti-Jag1 antibody results in an increase in expression in the liver cancer of at least one of Wnt2, Axin2 and Glul.

17. The use of claim 1, wherein the liver cancer is at least in part dependent upon a growth potentiating effect of Notch2 signaling.

WHAT IS CLAIMED IS:

1. Use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating liver cancer.

2. The use of claim 1, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

3. The use of claim 1, wherein the Notch2 signaling inhibitor is selected from the group consisting of antibody, siRNA and small-molecule inhibitor.

4. The use of claim 3, wherein the antibody is a monoclonal antibody.

5. The use of claim 3, wherein the antibody is an antagonist antibody.

6. The use of claim 3, wherein the antibody is an anti-Notch2 antibody.

7. The use of claim 6, wherein the antibody is an anti-Notch2 NRR antibody.

8. The use of claim 6, wherein the antibody does not significantly bind to a Notch family member other than Notch2.

9. The use of claim 6, wherein the antibody binds to mouse Notch2 NRR and human Notch2 NRR.

10. The use of claim 6, wherein the antibody binds to a Notch2 NRR with a Kd of $\leq$ 10 nM.

11. The use of claim 6, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

12. The use of claim 3, wherein the antibody is an anti-Jag1 antibody.

13. The use of claim 12, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

14. The use of claim 12, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

15. The use of claim 12, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

16. The use of claim 12, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

17. The use of any of claims 13-16, wherein the antibody further comprises light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 of FIG. 18.

18. The use of any of claims 13-16, wherein the antibody further comprises heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 of FIG. 18.

19. The use of any of claims 13-16, wherein the antibody further comprises light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 light chain variable domain framework LC-FR1, LC-FR2, LC-FR3, and LC-FR4 of FIG. 19.

20. The use of any of claims 13-16, wherein the antibody further comprises heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 comprising, in order, the amino acid sequence of huMAb4D5-8 heavy chain variable domain framework HC-FR1, HC-FR2, HC-FR3, and HC-FR4 of FIG. 19.

21. The use of claim 3, wherein the antibody is an isolated antibody that binds to Jag1, comprising

(a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:93;

(b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:96; or

(c) a VH sequence as in (a) and a VL sequence as in (b).

22. The use of claim 21, wherein the antibody comprises a VH sequence of SEQ ID NO:93.

23. The use of claim 21, wherein the antibody comprises a VL sequence of SEQ ID NO:96.

24. The use of claim 21, wherein the antibody comprises a VH sequence of SEQ ID NO:93 and a VL sequence of SEQ ID NO:96.

25. The use of claim 3, wherein the antibody is an isolated antibody that binds to Jag1, comprising:

(a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:94;

(b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:97; or

(c) a VH sequence as in (a) and a VL sequence as in (b).

26. The method of claim 25, wherein the antibody comprises a VH sequence of SEQ ID NO:94.

27. The use of claim 25, wherein the antibody comprises a VL sequence of SEQ ID NO:97.

28. The use of claim 25, wherein the antibody comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO:97.

29. The use of claim 3, wherein the antibody is an isolated antibody that binds to Jag1, comprising:

(a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:95;

(b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:98; or

(c) a VH sequence as in (a) and a VL sequence as in (b).

30. The use of claim 29, wherein the antibody comprises a VH sequence of SEQ ID NO:95.

31. The use of claim 29, wherein the antibody comprises a VL sequence of SEQ ID NO:98.

32. The use of claim 29, wherein the antibody comprises a VH sequence of SEQ ID NO:95 and a VL sequence of SEQ ID NO:98.

33. The use of any one of claims 1-32, wherein the antibody is a full-length IgG1 or IgG2a antibody.

34. The use of any one of claims 1-32, wherein the antibody is an antibody fragment.

35. The use of any one of claims 1-32, wherein the antibody is a human, humanized or chimeric antibody.

36. The use of any one of claims 1-32, wherein the antibody is conjugated to a growth inhibitory agent.

37. The use of claim 36, wherein the antibody is conjugated to a cytotoxic agent.

38. The use of claim 37, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

39. The use of any one of claims 1-32, wherein the antibody is produced in bacteria.

40. The use of any one of claims 1-32, wherein the antibody is produced in CHO cells.

41. The use of any one of claims 1-32, wherein the antibody causes cancer cell death.

42. The use of any one of claims 1-32, wherein the medicament is to be administered with at least one additional therapeutic agent.

43. The use of claim 42, wherein the additional therapeutic agent is a chemotherapeutic agent.

44. The use of claim 42, wherein the additional therapeutic agent is an antibody.

45. The use of any one of claims 1-32, wherein the liver cancer comprises cells that express at least one of EpCAM, AFP, Notch2, Jag1, Sox9, CK19, Ras, Prom1, Spp1, FoxM1, Plk1, ccnb1, Aurkb, Wnt2, Axin2, or Glul.

46. The use of claim 45, wherein the liver cancer comprises cells having nuclear Notch2.

47. The use of claim 45, wherein the liver cancer comprises cells having activated Ras.

48. The use of claim 45, wherein the liver cancer comprises cells that express EpCAM and wherein administering the Notch2 signaling inhibitor results in a decrease in EpCAM expression in the cells.

49. The use of claim 45, wherein the liver cancer comprises cells that express AFP and wherein administering the Notch2 signaling inhibitor results in a decrease in AFP expression in the cells.

50. The use of claim 45, wherein administering the Notch2 signaling inhibitor results in a decrease in expression, compared to expression prior to administering the inhibitor, in the liver cancer of at least one of Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

51. The use of claim 45, wherein administering the Notch2 signaling inhibitor results in an increase in expression in the liver cancer of at least one of Wnt2, Axin2 and Glul.

52. Use of an anti-Jag1 antibody in the manufacture of a medicament for preventing liver cancer in an individual at risk of having liver cancer.

53. The use of claim 52, wherein the antibody is a monoclonal antibody.

54. The use of claim 52, wherein the antibody is an antagonist antibody.

55. The use of claim 52, wherein the antibody is an antibody fragment.

56. The use of claim 52, wherein the antibody is a human, humanized or chimeric antibody.

57. The use of claim 52, wherein the antibody is conjugated to a growth inhibitory agent.

58. The use of claim 52, wherein the antibody is conjugated to a cytotoxic agent.

59. The use of claim 52, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

60. The use of claim 52, wherein the antibody is produced in bacteria.

61. The use of claim 52, wherein the antibody is produced in CHO cells.

62. The use of claim 52, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

63. The use of claim 62, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

64. The use of claim 62, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

65. The use of claim 62, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

66. The use of any one of claims 52-65, wherein the medicament is to be administered with at least one additional therapeutic agent.

67. The use of claim 66, wherein the additional therapeutic agent is an antibody.

68. The use of claim 67, wherein the additional therapeutic agent is an anti-Notch2 antagonist antibody.

69. The use of claim 52, wherein the individual has a liver condition selected from the group consisting of hepatitis B or C, cirrhosis of the liver, benign liver tumors, hemangiomas, hepatic adenomas, and focal nodular hyperplasia.

70. An *in vitro* method of inhibiting proliferation of a liver cancer cell that expresses secreted phosphoprotein1 (SPP1), the method comprising contacting the cell with a Notch2 signaling inhibitor, thereby inhibiting growth of the cell.

71. Use of a Notch2 signaling inhibitor in the manufacture of a medicament for inhibiting proliferation of a liver cancer cell, wherein the liver cancer cell is one that expresses a secreted phosphoprotein1 (SPP1).

72. The method or use of claim 70-71, wherein administering the antibody reduces SPP1 expression in the liver cancer cell.

73. The method or use of claim 72, wherein administering the antibody reduces SPP1 expression in the liver cancer cell by at least about 50%, 60%, 70%, 80%, 90%, 95% or 100%.

74. The method or use of claim 70-71, wherein expression was determine using polymerase chain reaction analysis.

75. The method or use of claim 70-71, wherein the SPP1 protein comprises the amino acid sequence shown in FIG. 11.

76. The method or use of claim 70-71, wherein the Notch2 signaling inhibitor is an antibody that binds to a protein selected from the group consisting of Notch2 and Jag1

77. The method or use of claim 76, wherein the antibody is an anti-Notch2 antibody.

78. The method or use of claim 77, wherein the antibody is an anti-Notch2 NRR antibody.

79. The method or use of claim 78, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;
(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;
(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and
(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

80. The method or use of claim 76, wherein the antibody is an anti-Jag1 antibody.

81. The method or use of claim 80, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;
(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;
(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

82. The method or use of claim 81, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

83. The method or use of claim 81, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

84. The method or use of claim 81, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

85. The method or use of any one of claims 70-84, wherein the antibody is a monoclonal antibody.

86. The method or use of any one of claims 70-84, wherein the antibody is an antagonist antibody.

87. The method or use of any one of claims 70-84, wherein the antibody is an antibody fragment.

88. The method or use of any one of claims 70-84, wherein the antibody is a human, humanized or chimeric antibody.

89. The method or use of any one of claims 70-84, wherein the antibody is conjugated to a growth inhibitory agent.

90. The method or use of claim 89, wherein the antibody is conjugated to a cytotoxic agent.

91. The method or use of any one of claims 70-84, wherein the antibody is produced in bacteria.

92. The method or use of any one of claims 70-84, wherein the antibody is produced in CHO cells.

93. The method or use of any one of claims 70-84, wherein the antibody induces cell death.

94. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses EpCAM.

95. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses AFP.

96. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses AFP and EpCAM.

97. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses Notch2.

98. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses cell expresses Jag1.

99. The method or use of any one of claims 70-84, wherein the liver cancer cell expresses Notch2 and Jag1.

100. The method or use of any one of claims 70-84, wherein the liver cancer cell comprises nuclear Notch2.

101. The method or use of any one of claims 70-84, wherein the liver cancer cell comprises activated Ras.

102. The method or use of any one of claims 70-84, wherein contacting the cell with the antibody results in a decrease in expression by the cell of at least one of EpCAM, AFP, Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

103. The method or use of any one of claims 70-84, wherein contacting the cell with the antibody results in an increase in expression by the cell of at least one of Wnt2, Axin2 and Glul.

104. The use of any one of claims 71-84, wherein the cell is in an individual.

105. Use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating a liver cancer in a mammal, wherein the liver cancer in the mammal comprises cells that express an Spp1 gene encoding a peptide comprising an amino acid sequence having at least 90% identity to the polypeptide shown in FIG. 11.

106. The use of claim 105, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

107. The use of claim 105, wherein the mammal is a human.

108. The use of claim 105, wherein the Notch2 signaling inhibitor is selected from the group consisting of antibody, siRNA and small-molecule inhibitor.

109. The use of claim 108, wherein the antibody is an anti-Notch2 antibody.

110. The use of claim 109, wherein the antibody is an anti-Notch2 NRR antibody.

111. The use of claim 110, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

112. The use of claim 108, wherein the antibody is an anti-Jag1 antibody.

113. The use of claim 112, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

114. The use of claim 113, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

115. The use of claim 113, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

116. The use of claim 113, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

117. The use of any one of claims 105-116, wherein the antibody is a monoclonal antibody.

118. The use of any one of claims 105-116, wherein the antibody is an antagonist antibody.

119. The use of any one of claims 105-116, wherein the antibody is an antibody fragment.

120. The use of any one of claims 105-116, wherein the antibody is a human, humanized or chimeric antibody.

121. The use of any one of claims 105-116, wherein the antibody is conjugated to a growth inhibitory agent.

122. The use of any one of claims 105-116, wherein the antibody is conjugated to a cytotoxic agent.

123. The use of claim 122, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

124. The use of any one of claims 105-116, wherein the antibody is produced in bacteria.

125. The use of any one of claims 105-116, wherein the antibody is produced in CHO cells.

126. The use of any one of claims 105-116, wherein the antibody causes cancer cell death.

127. The use of any one of claims 105-116, wherein the medicament is to be administered with at least one additional therapeutic agent.

128. The use of claim 127, wherein the additional therapeutic agent is a chemotherapeutic agent.

129. The use of claim 128, wherein the additional therapeutic agent is an antibody.

130. The use of any one of claims 105-116, wherein the liver cancer comprises cells that express EpCAM.

131. The use of any one of claims 105-116, wherein the liver cancer comprises cells that express AFP.

132. The use of claim 131, wherein the liver cancer comprises cells that express EpCAM.

133. The use of any one of claims 105-116, wherein the liver cancer comprises cells that express Notch2.

134. The use of any one of claims 105-116, wherein the liver cancer comprises cells that express Jag1.

135. The use of any one of claims 105-116, wherein the liver cancer comprises cells that express Notch2 and Jag1.

136. The use of any one of claims 105-116, wherein the liver cancer comprises cells having nuclear Notch2.

137. The use of any one of claims 105-116, wherein the liver cancer comprises cells having activated Ras.

138. The use of any one of claims 105-116, wherein administering the Notch2 signaling inhibitor results in a decrease in EpCAM expression in the liver cancer.

139. The use of any one of claims 105-116, wherein administering the Notch2 signaling inhibitor results in a decrease in AFP expression in the liver cancer.

140. The use of any one of claims 105-116, wherein administering the Notch2 signaling inhibitor results in a decrease in expression in the liver cancer of at least one of Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

141. The use of any one of claims 105-116, wherein administering the Notch2 signaling inhibitor results in a decrease in SPP1 expression in the liver cancer.

142. The use of any one of claims 105-116, wherein administering the Notch2 signaling inhibitor results in an increase in expression in the liver cancer of at least one of Wnt2, Axin2 and Glul.

143. The use of claim 105-116, wherein expression is determined by a method selected from the group consisting of RNAseq, microarray analysis, immunohistochemistry, enzyme-linked immunosorbent assay, gene expression profiling, polymerase chain reaction, SAGE, MassARRAY technique, fluorescent in situ hybridization and Western blotting.

144. Use of an anti-Jag1 antagonist antibody in the manufacture of a medicament for treating a liver cell proliferative disorder in an individual, wherein the liver cell proliferative disorder is associated with increased expression or activity of a protein having at least 90% amino acid sequence identity to the polypeptide shown in FIG. 8C.

145. The use of Claim 144, wherein the cell proliferative disorder is cancer.

146. The use of claim 144, wherein the individual has a liver condition selected from the group consisting of hepatitis B or C, cirrhosis of the liver, benign liver tumors, hemangiomas, hepatic adenomas, and focal nodular hyperplasia.

147. The use of claim 144, wherein the antibody is an antibody fragment.

148. The use of claim 144, wherein the antibody is a human, humanized or chimeric antibody.

149. The use of claim 144, wherein the antibody is conjugated to a growth inhibitory agent.

150. The use of claim 144, wherein the antibody is conjugated to a cytotoxic agent.

151. The use of claim 150, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

152. The use of claim 144, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

153. The use of claim 152, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

154. The use of claim 152, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

155. The use of claim 152, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

156. Use of a Notch2 signaling inhibitor in the manufacture of a medicament for reducing serum SPP1 protein levels in an individual having liver cancer.

157. The use of claim 156, wherein the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are at least about 80 ng/ml.

158. The use of claim 157, wherein the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are between about 80 ng/ml and about 500 ng/ml.

159. The use of claim 158, wherein the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are between about 86 ng/ml and about 250 ng/ml.

160. The use of claim 159, wherein the serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor to the individual are between about 120 ng/ml and about 170 ng/ml.

161. The use of claim 156, wherein administering the Notch2 signaling inhibitor to the individual results in serum SPP1 protein levels of less than 80 ng/ml.

162. The use of claim 156, wherein serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor are 24 hours prior to administering the Notch2 signaling inhibitor.

163. The use of claim 156, wherein serum SPP1 protein levels prior to administering the Notch2 signaling inhibitor are determined by enzyme-linked immunosorbent assay.

164. The use of claim 156, wherein serum SPP1 protein levels are reduced about one month after administering the Notch2 signaling inhibitor.

165. The use of claim 156, wherein serum SPP1 protein levels are reduced about two months after administering the Notch2 signaling inhibitor.

166. The use of claim 156, wherein serum SPP1 protein levels are reduced about three months after administering the Notch2 signaling inhibitor.

167. The use of claim 156, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

168. The use of claim 156, wherein the Notch2 signaling inhibitor is selected from the group consisting of antibody, siRNA and small-molecule inhibitor.

169. The use of claim 168, wherein the antibody is an anti-Notch2 antibody.

170. The use of claim 169, wherein the antibody is an anti-Notch2 NRR antibody.

171. The use of claim 170, wherein the antibody binds to mouse Notch2 NRR and human Notch2 NRR.

172. The use of claim 170, wherein the antibody binds to a Notch2 NRR with a Kd of ≤ 10 nM.

173. The use of claim 170, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

174. The use of claim 168, wherein the antibody is an anti-Jag1 antibody.

175. The use of claim 174, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

176. The use of claim 175, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

177. The use of claim 175, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

178. The use of claim 175, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

179. The use of claim 168, wherein the antibody is a monoclonal antibody.

180. The use of claim 168, wherein the antibody is an antagonist antibody.

181. The use of claim 168, wherein the antibody is an antibody fragment.

182. The use of claim 168, wherein the antibody is a human, humanized or chimeric antibody.

183. The use of claim 168, wherein the antibody is conjugated to a growth inhibitory agent.

184. The use of claim 168, wherein the antibody is conjugated to a cytotoxic agent.

185. The use of claim 184, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

186. The use of claim 168, wherein the antibody is produced in bacteria.

187. The use of claim 168, wherein the antibody is produced in CHO cells.

188. Use of an antibody that binds to Notch2 or Jag1 in the manufacture of a medicament for treating a liver cancer in a mammal, wherein the medicament is to be contacted with a tumor that is at least in part dependent upon a growth potentiating effect of Notch2 signaling.

189. The use of claim 188, wherein the binding of the antibody to the cancer antagonizes the growth-potentiating activity of Notch2.

190. The use of claim 188, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

191. The use of claim 188, wherein the antibody is an anti-Notch2 antibody.

192. The use of claim 191, wherein the antibody is an anti-Notch2 NRR antibody.

193. The use of claim 192, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

194. The use of claim 188, wherein the antibody is an anti-Jag1 antibody.

195. The use of claim 194, wherein the antibody comprises:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

196. The use of claim 195, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

197. The use of claim 195, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

198. The use of claim 195, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

199. The use of any one of claims 188-198, wherein the antibody is a monoclonal antibody.

200. The use of any one of claims 188-198, wherein the antibody is an antagonist antibody.

201. The use of any one of claims 188-198, wherein the antibody is an antibody fragment.

202. The use of any one of claims 188-198, wherein the antibody is a human, humanized or chimeric antibody.

203. The use of any one of claims 188-198, wherein the antibody is conjugated to a growth inhibitory agent.

204. The use of any one of claims 188-198, wherein the antibody is conjugated to a cytotoxic agent.

205. The use of claim 204, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

206. The use of any one of claims 188-198, wherein the antibody is produced in bacteria.

207. The use of any one of claims 188-198, wherein the antibody is produced in CHO cells.

208. The use of any one of claims 188-198, wherein the antibody causes cancer cell death.

209. The use of any one of claims 188-198, wherein the medicament is to be administered with at least one additional therapeutic agent.

210. The use of claim 209, wherein the additional therapeutic agent is a chemotherapeutic agent.

211. The use of claim 209, wherein the additional therapeutic agent is an antibody.

212. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express EpCAM.

213. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express AFP.

214. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express AFP and EpCAM.

215. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express Notch2.

216. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express Jag1.

217. The use of any one of claims 188-198, wherein the liver cancer comprises cells that express Notch2 and Jag1.

218. The use of any one of claims 188-198, wherein the liver cancer comprises cells having nuclear Notch2.

219. The use of any one of claims 188-198, wherein the liver cancer comprises cells having activated Ras.

220. The use of any one of claims 188-198, wherein administering the antibody results in a decrease in EpCAM expression in the liver cancer.

221. The use of any one of claims 188-198, wherein administering the antibody results in a decrease in AFP expression in the liver cancer.

222. The use of any one of claims 188-198, wherein administering the antibody results in a decrease in expression in the liver cancer of at least one of Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

223. The use of any one of claims 188-198, wherein administering the antibody results in a decrease in SPP1 expression in the liver cancer.

224. The use of any one of claims 188-198, wherein administering the antibody results in an increase in expression in the liver cancer of at least one of Wnt2, Axin2 and Glul.

225. Use of a Notch2 signaling inhibitor in the manufacture of a medicament for treating an individual having a liver cancer, wherein

a decrease in Notch2 signaling determined following treatment, compared to Notch2 signaling prior to treatment, is indicative of reduction of liver cancer in the individual.

226. The use of claim 225, wherein Notch2 signaling is determined by measuring Notch2 ICD nuclear localization.

227. The use of claim 225, wherein Notch2 signaling is determined by measuring expression of a gene selected from the group consisting of Notch2, Jag1, Hes and Hey1.

228. The use of claim 225, wherein the liver cancer is selected from the group consisting of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, and metastatic liver cancer.

229. The use of claim 225, wherein the Notch2 signaling inhibitor is selected from the group consisting of antibody, siRNA and small-molecule inhibitor.

230. The use of claim 229, wherein the antibody is an anti-Notch2 antibody.

231. The use of claim 230, wherein the antibody is an anti-Notch2 NRR antibody.

232. The use of claim 231, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

233. The use of claim 229, wherein the antibody is an anti-Jag1 antibody.

234. The use of claim 233, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

235. The use of claim 234, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

236. The use of claim 234, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

237. The use of claim 234, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

238. The use of any one of claims 225-237, wherein the antibody is a monoclonal antibody.

239. The use of any one of claims 225-237, wherein the antibody is an antagonist antibody.

240. The use of any one of claims 225-237, wherein the antibody is an antibody fragment.

241. The use of any one of claims 225-237, wherein the antibody is a human, humanized or chimeric antibody.

242. The use of any one of claims 225-237, wherein the antibody is conjugated to a growth inhibitory agent.

243. The use of any one of claims 225-237, wherein the antibody is conjugated to a cytotoxic agent.

244. The use of any one of claims 225-237, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

245. The use of any one of claims 225-237, wherein the antibody is produced in bacteria.

246. The use of any one of claims 225-237, wherein the antibody is produced in CHO cells.

247. The use of any one of claims 225-237, wherein the antibody causes cancer cell death.

248. The use of any one of claims 225-237, wherein the medicament is to be administered with at least one additional therapeutic agent.

249. The use of claim 248, wherein the additional therapeutic agent is a chemotherapeutic agent.

250. The use of claim 248, wherein the additional therapeutic agent is an antibody.

251. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express EpCAM.

252. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express AFP.

253. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express AFP and EpCAM.

254. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express Notch2.

255. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express Jag1.

256. The use of any one of claims 225-237, wherein the liver cancer comprises cells that express Notch2 and Jag1.

257. The use of any one of claims 225-237, wherein the liver cancer comprises cells having nuclear Notch2.

258. The use of any one of claims 225-237, wherein the liver cancer comprises cells having activated Ras.

259. The use of any one of claims 225-237, wherein administering the Notch2 signaling inhibitor results in a decrease in EpCAM expression in the liver cancer.

260. The use of any one of claims 225-237, wherein administering the Notch2 signaling inhibitor results in a decrease in AFP expression in the liver cancer.

261. The use of any one of claims 225-237, wherein administering the Notch2 signaling inhibitor results in a decrease in expression in the liver cancer of at least one of Prom1, Spp1, FoxM1, Plk1, ccnb1 and Aurkb.

262. The use of any one of claims 225-237, wherein administering the Notch2 signaling inhibitor results in a decrease in SPP1 expression in the liver cancer.

263. The use of any one of claims 225-237, wherein administering the Notch2 signaling inhibitor results in an increase in expression in the liver cancer of at least one of Wnt2, Axin2 and Glul.

264. Use of an antibody to Notch2 or Jag1 in the manufacture of a medicament for inhibiting cellular proliferation in mammalian liver cancer cells.

265. The use of claim 264, wherein the cell is in a human.

266. A method of inhibiting cellular proliferation comprising treating mammalian liver cancer cells with an antibody to Notch2 or Jag1, wherein the cell is in a culture medium.

267. An article of manufacture comprising (a) a container; (b) a composition of matter contained within the container comprising an anti-Notch2 antibody or an anti-Jag1 antibody and a carrier for the treatment of liver cancer; and (c) a label affixed to the container, or a package insert included with the container, referring to the use of the composition of matter for the therapeutic treatment of or the diagnostic detection of a liver cancer.

268. An anti-Notch2 antibody for use in the treatment of a liver cancer.

269. The anti-Notch2 antibody of claim 268, wherein the liver cancer is hepatocellular carcinoma.

270. The anti-Notch2 antibody of claim 269, wherein the antibody is an anti-Notch2 antagonist antibody

271. The anti-Notch2 antibody of claim 270, wherein the antibody is an anti-Notch2 NRR antibody.

272. An anti-Jag1 antibody for use in the treatment of a liver cancer.

273. The anti-Jag1 antibody of claim 272, wherein the liver cancer is hepatocellular carcinoma.

274. The anti-Jag1 antibody of claim 272, wherein the antibody is an anti-Jag1 antagonist antibody.

275. The anti-Jag1 antibody of claim 272, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;
(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;
(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;
(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;
(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and
(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

276. The antibody of claim 275, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

277. The antibody of claim 275, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

278. The antibody of claim 275, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

279. Use of an anti-Notch2 antibody in the preparation of a medicament for treating a liver cancer.

280. The use of claim 279, wherein the liver cancer is hepatocellular carcinoma.

281. The use of claim 279, wherein the antibody is an anti-Notch2 antagonist antibody

282. The use of claim 279, wherein the antibody is an anti-Notch2 NRR antibody

283. The use of claim 279, wherein the antibody binds to a Notch2 NRR with a Kd of $\leq$ 10 nM.

284. The use of claim 281, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:3;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:4;

(d) an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:9;

(e) an HVR-L2 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:14; and

(f) an HVR-L3 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO:19.

285. Use of an anti-Jagged1 antibody in the preparation of a medicament for treating a liver cancer.

286. The use of claim 285, wherein the cancer is hepatocellular carcinoma.

287. The use of claim 285, wherein the antibody is an anti-Jag1 antagonist antibody.

288. The use of claim 285, wherein the antibody comprises at least one, two, three, four, five, or six HVRs selected from:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) HVR-H2 comprising an amino acid sequence of SEQ ID NO:84;

(c) HVR-H3 comprising an amino acid sequence of SEQ ID NO:87;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:92.

289. The use of claim 287, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

290. The use of claim 287, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:82;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:91.

291. The use of claim 287, wherein the antibody comprises:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:81;

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:83;

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:85;

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:88;

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:89; and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:90.

292. Use of an article of manufacture as claimed in claim 267 in the preparation of a medicament for treatment of a liver cancer.

293. Use of an article of manufacture as claimed in claim 267 in the preparation of a medicament for treatment of a liver cell proliferative disorder.