

CLAIMS

What is claimed is:

1. An isolated antibody that specifically binds to a conformational epitope of an AS-SPIK protein, and does not specifically bind to a NS-SPIK protein, wherein the conformational epitope of the AS-SPIK protein comprises:
 - one or more amino acids selected from the group consisting of: L14, L15, S16, L17, D24 and S25 of SEQ ID NO: 2; and
 - one or more amino acids selected from the group consisting of: C58, V59, L60, C61, and F62 of SEQ ID NO: 2.
2. The isolated antibody of claim 1, wherein the conformational epitope comprises amino acids L14, L15, S16, and L17 of SEQ ID NO: 2.
3. The isolated antibody of claim 1, wherein the conformational epitope comprises amino acids L60 and C61 of SEQ ID NO: 2.
4. The isolated antibody of claim 1, wherein the conformational epitope comprises amino acids L14, L15, S16, L17, L60, and C61 of SEQ ID NO: 2.
5. The isolated antibody of claim 2, wherein the conformational epitope further comprises amino acids D24 and S25 of SEQ ID NO: 2.
6. The isolated antibody of claim 3, wherein the conformational epitope further comprises amino acids C58, V59 and F62 of SEQ ID NO: 2.
7. The isolated antibody of claim 1, wherein the conformational epitope comprises amino acids L14, L15, S16, L17, D24, S25, C58, V59, L60, C61 and F62 of SEQ ID NO: 2.
8. The isolated antibody of any one of claims 1-7, comprising:
 - a CDRH1 sequence comprising S6; and/or
 - a CDRH2 sequence comprising I2, G5, G6, Y10 and K16; and/or

- a CDRH3 sequence comprising G4 and Y7; and/or
 - a CDRL1 sequence comprising Q4 and S9; and/or
 - a CDRL2 sequence comprising A2, S3, T4 and S7; and/or
 - a CDRL3 sequence comprising Q1, Q2, Y4 and S5.
9. The isolated antibody of claim 8, comprising:
- a CDRH1 sequence comprising S6;
 - a CDRH2 sequence comprising I2, G5, G6, Y10 and K16;
 - a CDRH3 sequence comprising G4 and Y7;
 - a CDRL1 sequence comprising Q4 and S9;
 - a CDRL2 sequence comprising A2, S3, T4 and S7; and
 - a CDRL3 sequence comprising Q1, Q2, Y4 and S5.
10. An isolated antibody that specifically binds to a conformational epitope of an AS-SPIK protein, and does not specifically bind to a NS-SPIK protein, wherein the conformational epitope of the AS-SPIK protein comprises:
- one or more amino acids selected from the group consisting of: L36, N37, I42 and Y43 of SEQ ID NO: 2; and
 - one or more amino acids selected from the group consisting of: R67, Q68, I71 and L72 of SEQ ID NO: 2.
11. The isolated antibody of claim 10, wherein the conformational epitope comprises amino acids L36 and N37 of SEQ ID NO: 2.
12. The isolated antibody of claim 10, wherein the conformational epitope comprises amino acids I42 and Y43 of SEQ ID NO: 2.
13. The isolated antibody of claim 10, wherein the conformational epitope comprises amino acids L36, N37, I42 and Y43 of SEQ ID NO: 2.
14. The isolated antibody of claim 10, wherein the conformational epitope comprises amino acids R67, Q68, I71 and L72 of SEQ ID NO: 2.

15. The isolated antibody of claim 10, wherein the conformational epitope comprises amino acids L36, N37, I42, Y43, R67, Q68, I71 and L72 of SEQ ID NO: 2.
16. The isolated antibody of any one of claims 10-15, wherein the antibody comprises:
 - a CDRH1 sequence comprising Y3, S7 and W9; and/or
 - a CDRH2 sequence comprising A1, I2, G4, G6 and Y10; and/or
 - a CDRH3 sequence comprising R1 and D7; and/or
 - a CDRL1 sequence comprising A2, S3, Q4, I6, Y9, L10 and S11; and/or
 - a CDRL2 sequence comprising A2, S3, L5 and S7; and/or
 - a CDRL3 sequence comprising Q1, Q2, and T5.
17. The isolated antibody of claim 16, wherein the antibody comprises:
 - a CDRH1 sequence comprising Y3, S7 and W9;
 - a CDRH2 sequence comprising A1, I2, G4, G6 and Y10;
 - a CDRH3 sequence comprising R1 and D7;
 - a CDRL1 sequence comprising A2, S3, Q4, I6, Y9, L10 and S11;
 - a CDRL2 sequence comprising A2, S3, L5 and S7; and
 - a CDRL3 sequence comprising Q1, Q2, and T5.
18. The antibody of any one of claims 1-17, which is multi-specific.
19. The antibody of claim 18, which is bispecific.
20. The antibody of claim 19, having binding affinity to an effector cell.
21. The antibody of claim 19, having binding affinity to a T-cell antigen.
22. The antibody of claim 21, wherein the T-cell antigen comprises a CD3 protein.
23. The antibody of any one of claims 1-22, which is a monoclonal antibody.
24. The antibody of any one of claims 1-22, which is in a CAR-T format.

25. An immunoconjugate comprising an antibody according to any one of claims 1-23, covalently attached to a cytotoxic agent.
26. The immunoconjugate of claim 25, wherein the cytotoxic agent is selected from the group consisting of: a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope and a nucleolytic enzyme.
27. An immunoconjugate having the formula Ab-(L-D)_p, wherein:
- (a) Ab is an antibody according to any one of claims 1-23;
 - (b) L is a linker;
 - (c) D is a drug moiety; and
 - (d) p is an integer that ranges from 1 to 8.
28. The immunoconjugate of claim 27, wherein D is selected from the group consisting of: a maytansinoid, an auristatin and dolostatin.
29. The immunoconjugate of claim 27, wherein L comprises one or more linkers selected from the group consisting of 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio)pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1 carboxylate (SMCC), 4-(2-Pyridyldithio)butyric acid-N-hydroxysuccinimide ester (SPDB), and N-Succinimidyl (4-iodo-acetyl)aminobenzoate (SIAB).
30. A pharmaceutical composition comprising the antibody or immunoconjugate of any one of claims 1-29.
31. A method for the treatment of a disorder characterized by expression of AS-SPIK, comprising administering to a subject with said disorder an antibody or immunoconjugate of any one of claims 1-29, or the pharmaceutical composition of claim 30.
32. Use of an antibody or immunoconjugate of any one of claims 1-29, in the preparation of a medicament for the treatment of a disorder characterized by expression of AS-SPIK.

33. An antibody or immunoconjugate of any one of claims 1-29 for use in the treatment of a disorder characterized by expression of AS-SPIK.
34. The method or use of any one of claims 31-33, wherein the disorder is a liver disorder.
35. The method or use of claim 34, wherein the liver disorder is hepatocellular carcinoma.
36. The method or use of claim 34, wherein the liver disorder is intrahepatic cholangiocarcinoma.
37. The method or use of claim 34, wherein the liver disorder is a viral infection.
38. The method or use of claim 34, wherein the liver disorder is an inflammatory liver disorder.
39. The method or use of claim 38, wherein the inflammatory liver disorder is cirrhosis of the liver.
40. A polynucleotide encoding an antibody of any one of claims 1-24.
41. A vector comprising the polynucleotide of claim 40.
42. A host cell comprising the vector of claim 41.
43. A method of producing an antibody or immunoconjugate of any one of claims 1-29, comprising growing a host cell according to claim 42 under conditions permissive for expression of the antibody, and isolating the antibody from the cell.
44. A diagnostic method for determining whether a subject has or is at risk of developing a disorder characterized by expression of AS-SPIK, the method comprising:
- (a) contacting a biological test sample from the subject with an AS-SPIK antibody according to any one of claims 1-23 to generate an AS-SPIK-antibody complex;
 - (b) detecting a concentration of the AS-SPIK-antibody complex in the biological test sample;
- and
- (c) comparing the concentration of the AS-SPIK-antibody complex to a reference value to determine whether the subject has or is at risk of developing the disorder.

45. A diagnostic method for determining whether a subject has or is at risk of developing a disorder characterized by expression of AS-SPIK, the method comprising:

- (a) contacting a biological test sample from the subject with a first antibody or antigen-binding fragment that specifically binds to SPIK to form a SPIK-antibody complex;
- (b) contacting the SPIK-antibody complex with an AS-SPIK antibody or antigen-binding fragment according to any one of claims 1-23 to generate an AS-SPIK-antibody complex;
- (c) detecting a concentration of the AS-SPIK-antibody complex in the biological test sample; and
- (d) comparing the concentration of the AS-SPIK-antibody complex to a reference value to determine whether the subject has or is at risk of developing the disorder.

46. The diagnostic method according to claim 44 or 45, wherein the antibody or antigen-binding fragment comprises a detectable label.

47. The diagnostic method according to claim 44 or 45, wherein the disorder is a liver disorder.

48. The diagnostic method according to claim 47, wherein the liver disorder is selected from the group consisting of: hepatocellular carcinoma, intrahepatic cholangiocarcinoma, viral infection of the liver, inflammatory disorder of the liver, and cirrhosis of the liver.

49. A kit comprising an antibody or immunoconjugate according to any one of claims 1-29.

50. The kit according to claim 49, further comprising an antibody that specifically binds to SPIK.