CLAIMS

1. An isolated antibody comprising a heavy chain variable region (V_H) comprising a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 118, wherein said antibody specifically binds to activated protein C (APC) and minimally binds to unactivated protein C (PC).

2. The antibody of claim 1, wherein the V_H further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 109-113, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8 and 114-117, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 109-113 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8 and 114-117.

3. The antibody of claim 2, wherein the V_H comprises the CDR1, CDR2, and CDR3 of a V_H having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-15 and 119-129.

4. An isolated antibody comprising a V_H comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-15 and 119-129, wherein said antibody specifically binds to APC and minimally binds to PC.

5. An isolated antibody comprising a light chain variable region (V_L) comprising a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23 and 138-140, wherein said antibody specifically binds to APC and minimally binds to PC.

6. The antibody of claim 5, wherein the V_L further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-19 and 130-131, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 21-22 and 132-137, or (c) both a CDR1 comprising an amino acid sequence selected from the

group consisting of SEQ ID NOs: 16-19 and 130-131 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 21-22 and 132-137.

7. The antibody of claim 6, wherein the V_L comprises the CDR1, CDR2, and CDR3 of a V_L having an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-35 and 141-151.

8. An isolated antibody comprising a V_L comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-35 and 141-151, wherein said antibody specifically binds to APC and minimally binds to PC.

9. The antibody of any one of claims 5-8 further comprising a V_H comprising a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 118.

10. The antibody of claim 9, wherein the V_H further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 109-113, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8 and 114-117, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 109-113 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8 and 114-117.

11. The antibody of claim 10, wherein the V_H comprises the CDR1, CDR2, and CDR3 of a V_H having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-15 and 119-129.

12. The antibody of claim 10, wherein the V_H comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-15 and 119-129.

13. An isolated antibody comprising:

1) the V_H of SEQ ID NO: 10 and the V_L of SEQ ID NO: 24;
2) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 25;
3) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 26;
4) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 27;
5) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 28;
6) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 29;
7) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 30;
8) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 31;
9) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 32;
10) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 33;
11) the V_H of SEQ ID NO: 12 and the V_L of SEQ ID NO: 28;
12) the V_H of SEQ ID NO: 13 and the V_L of SEQ ID NO: 34;
13) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 35;
14) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 34;
15) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 28;
16) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 31;
17) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 32;
18) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 33;
19) the V_H of SEQ ID NO: 15 and the V_L of SEQ ID NO: 28;
20) the V_H of SEQ ID NO: 15 and the V_L of SEQ ID NO: 29;
21) the V_H of SEQ ID NO: 14 and the V_L of SEQ ID NO: 29;
22) the V_H of SEQ ID NO: 15 and the V_L of SEQ ID NO: 33;
23) the V_H of SEQ ID NO: 119 and the V_L of SEQ ID NO: 29;
24) the V_H of SEQ ID NO: 120 and the V_L of SEQ ID NO: 29;
25) the V_H of SEQ ID NO: 121 and the V_L of SEQ ID NO: 29;
26) the V_H of SEQ ID NO: 122 and the V_L of SEQ ID NO: 29;
27) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 141;
28) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 142;
29) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 143;
30) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 144;

31) the V_H of SEQ ID NO: 123 and the V_L of SEQ ID NO: 29;
32) the V_H of SEQ ID NO: 124 and the V_L of SEQ ID NO: 29;
33) the V_H of SEQ ID NO: 125 and the V_L of SEQ ID NO: 29;
34) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 145;
35) the V_H of SEQ ID NO: 126 and the V_L of SEQ ID NO: 29;
36) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 146;
37) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 147;
38) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 148;
39) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 149;
40) the V_H of SEQ ID NO: 127 and the V_L of SEQ ID NO: 29;
41) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 150;
42) the V_H of SEQ ID NO: 11 and the V_L of SEQ ID NO: 151;
43) the V_H of SEQ ID NO: 128 and the V_L of SEQ ID NO: 29; or
44) the V_H of SEQ ID NO: 129 and the V_L of SEQ ID NO: 29.

14. The antibody of any one of claims 1-13, wherein said antibody binds to an exosite of APC.

15. The antibody of any one of claims 1-14, wherein the antibody is an antibody selected from the group consisting of an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, an IgM antibody, an IgA1 antibody, an IgA2 antibody, a secretory IgA antibody, an IgD antibody, an IgE antibody, and an antigen-binding fragment thereof.

16. The antibody of claim 15, wherein the antibody is an IgG4 antibody.

17. The antibody of any one of claims 1-9, wherein the antibody:
a) enhances, minimally affects, or inhibits the anticoagulant activity of APC;
b) enhances, minimally affects, or inhibits APC-mediated histone cleavage;
c) enhances, minimally affects, or inhibits the endothelial barrier protective activity of APC;
d) increases, minimally affects, or decreases the plasma half-life of APC; or
e) any combination thereof.

18. An isolated antibody that specifically binds to APC, minimally binds to PC, and competes with the antibody of claim 1 for binding to APC.

19. A nucleic acid encoding the antibody of any one of claims 1-18.

20. A vector comprising the isolated nucleic acid of claim 19.

21. A host cell comprising the nucleic acid of claim 19 or the vector of claim 20.

22. A method of producing an antibody, the method comprising:

a) culturing the host cell of claim 21 under conditions that result in production of the antibody; and
b) isolating the antibody from the host cell.

23. A pharmaceutical composition comprising the antibody of any one of claims 1-18 and a pharmaceutically acceptable carrier.

24. Use of a therapeutically effective amount of the antibody of any one of claims 1-18, the antibody of any one of claims 1-18 specifically bound to an exogenous APC protein or variant thereof, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating or preventing a condition in a subject, wherein said medicament is to be administered to the subject.

25. The use of claim 24, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting the anticoagulant function of APC.

26. The use of claim 25, wherein the condition is selected from the group consisting of a hemorrhage, a contusion, a burn, gastrointestinal bleeding, uncontrolled bleeding, bleeding due to a transplantation or resection procedure, bleeding due to a surgery, bleeding due to a traumatic

injury, variceal bleeding, bleeding in cirrhosis, thrombocytopenia, idiopathic thrombocytopenic purpura, hemophilia, aortic aneurysm, over-administration of an anticoagulant or antithrombotic, menorrhagia, deficiency of a clotting factor, Glanzmann's Thrombasthenia, and Bernard-Soulier syndrome.

27. The use of claim 24, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting one or more cytoprotective function of APC.

28. The use of claim 27, wherein the condition is selected from the group consisting of sepsis, inflammation in acute ischemic disease, coronavirus disease 2019 (COVID-19), diabetes, diabetic nephropathy, diabetic ulcers, wounds, amyotrophic lateral sclerosis (ALS), multiple sclerosis, central nervous system injury, ischemic stroke, Alzheimer's disease, acute kidney injury, a lung disorder, acute pancreatitis, a cancer, an inflammatory disease, and an autoimmune disease.

29. The antibody of any one of claims 1-18 for use as a medicament for treating or preventing a condition.

30. The antibody of claim 29, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting the anticoagulant function of APC.

31. The antibody of claim 30, wherein the condition is selected from the group consisting of a hemorrhage, a contusion, a burn, gastrointestinal bleeding, uncontrolled bleeding, bleeding due to a transplantation or resection procedure, bleeding due to a surgery, bleeding due to a traumatic injury, variceal bleeding, bleeding in cirrhosis, thrombocytopenia, idiopathic thrombocytopenic purpura, hemophilia, aortic aneurysm, over-administration of an anticoagulant or antithrombotic, menorrhagia, deficiency of a clotting factor, Glanzmann's Thrombasthenia, and Bernard-Soulier syndrome.

32. The antibody of claim 29, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting one or more cytoprotective function of APC.

33. The antibody of claim 32, wherein the condition is selected from the group consisting of sepsis, inflammation in acute ischemic disease, COVID-19, diabetes, diabetic nephropathy, diabetic ulcers, wounds, ALS, multiple sclerosis, central nervous system injury, ischemic stroke, Alzheimer's disease, acute kidney injury, a lung disorder, acute pancreatitis, a cancer, an inflammatory disease, and an autoimmune disease.