CLAIMS

1. An isolated antibody comprising a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 317-474, 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 antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-158, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 159-316, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-158 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 159-316.

3. The antibody of claim 2, wherein the antibody comprises the CDR1, CDR2, and CDR3 of a heavy chain variable region (V_H) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 475-632.

4. The antibody of claim 3, wherein the antibody comprises the:

1) CDR1 of SEQ ID NO: 45, CDR2 of SEQ ID NO: 203, and CDR3 of SEQ ID NO: 361;
2) CDR1 of SEQ ID NO: 54, CDR2 of SEQ ID NO: 212, and CDR3 of SEQ ID NO: 370;
3) CDR1 of SEQ ID NO: 61, CDR2 of SEQ ID NO: 219, and CDR3 of SEQ ID NO: 377;
4) CDR1 of SEQ ID NO: 74, CDR2 of SEQ ID NO: 232, and CDR3 of SEQ ID NO: 390;
5) CDR1 of SEQ ID NO: 82, CDR2 of SEQ ID NO: 240, and CDR3 of SEQ ID NO: 398;
6) CDR1 of SEQ ID NO: 84, CDR2 of SEQ ID NO: 242, and CDR3 of SEQ ID NO: 400;
7) CDR1 of SEQ ID NO: 88, CDR2 of SEQ ID NO: 246, and CDR3 of SEQ ID NO: 404;
8) CDR1 of SEQ ID NO: 90, CDR2 of SEQ ID NO: 248, and CDR3 of SEQ ID NO: 406;
9) CDR1 of SEQ ID NO: 95, CDR2 of SEQ ID NO: 253, and CDR3 of SEQ ID NO: 411;
10) CDR1 of SEQ ID NO: 101, CDR2 of SEQ ID NO: 259, and CDR3 of SEQ ID NO: 417;
11) CDR1 of SEQ ID NO: 103, CDR2 of SEQ ID NO: 261, and CDR3 of SEQ ID NO: 419;

12) CDR1 of SEQ ID NO: 105, CDR2 of SEQ ID NO: 263, and CDR3 of SEQ ID NO: 421;
13) CDR1 of SEQ ID NO: 109, CDR2 of SEQ ID NO: 267, and CDR3 of SEQ ID NO: 425;
14) CDR1 of SEQ ID NO: 116, CDR2 of SEQ ID NO: 274, and CDR3 of SEQ ID NO: 432;
15) CDR1 of SEQ ID NO: 142, CDR2 of SEQ ID NO: 300, and CDR3 of SEQ ID NO: 458;
16) CDR1 of SEQ ID NO: 144, CDR2 of SEQ ID NO: 302, and CDR3 of SEQ ID NO: 460;
17) CDR1 of SEQ ID NO: 146, CDR2 of SEQ ID NO: 304, and CDR3 of SEQ ID NO: 462;
18) CDR1 of SEQ ID NO: 147, CDR2 of SEQ ID NO: 305, and CDR3 of SEQ ID NO: 463;
19) CDR1 of SEQ ID NO: 149, CDR2 of SEQ ID NO: 307, and CDR3 of SEQ ID NO: 465;
20) CDR1 of SEQ ID NO: 150, CDR2 of SEQ ID NO: 308, and CDR3 of SEQ ID NO: 466;
or
21) CDR1 of SEQ ID NO: 157, CDR2 of SEQ ID NO: 315, and CDR3 of SEQ ID NO: 473.

5. An isolated antibody comprising a V_H comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 475-632, wherein said antibody specifically binds to APC and minimally binds to PC.

6. The antibody of any one of claims 1-5, wherein said antibody binds to an exosite of APC.

7. The antibody of any one of claims 1-6, 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.

8. The antibody of any one of claims 1-6, wherein the antibody is a nanobody.

9. The antibody of claim 8, wherein the antibody is a V_HH antibody.

10. 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 APC-mediated protease-activated receptor 1 (PAR1) cleavage at residue R46;
d) enhances, minimally affects, or inhibits APC-mediated PAR1 cleavage at residue R41;
e) increases, minimally affects, or decreases the ratio of APC-mediated PAR1 cleavage at residue R46 to APC-mediated PAR1 cleavage at residue R41;
f) enhances, minimally affects, or inhibits the endothelial barrier protective activity of APC;
g) increases, minimally affects, or decreases the plasma half-life of APC; or
h) any combination thereof.

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

12. A nucleic acid encoding the antibody of any one of claims 1-11.

13. A vector comprising the nucleic acid of claim 12.

14. A host cell comprising the nucleic acid of claim 12 or the vector of claim 13.

15. A method of producing an antibody, the method comprising:
a) culturing the host cell of claim 14 under conditions that result in production of the antibody; and
b) isolating the antibody from the host cell.

16. A pharmaceutical composition comprising the antibody of any one of claims 1-11 and a pharmaceutically acceptable carrier.

17. Use of a therapeutically effective amount of the antibody of any one of claims 1-11 , the antibody of any one of claims 1-11 specifically bound to an exogenous APC protein or variant thereof, or the pharmaceutical composition of claim 16, 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.

18. The use of claim 17, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting the anticoagulant function of APC.

19. The use of claim 17, 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.

20. The use of claim 17, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting one or more cytoprotective function of APC.

21. The use of claim 20, 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.

22. The antibody of any one of claims 1-11 for use as a medicament for treating or preventing a condition.

23. The antibody of claim 22, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting the anticoagulant function of APC.

24. The antibody of claim 23, 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.

25. The antibody of claim 22, wherein the condition is a condition that can be treated or prevented by enhancing or inhibiting one or more cytoprotective function of APC.

26. The antibody of claim 25, 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.