Claims

1. An anti-Factor XII/XIIa monoclonal antibody or antigen-binding fragment thereof that has a more than 2 fold higher binding affinity to human Factor XIIa-beta than to human Factor XII and that is capable of completely inhibiting the amidolytic activity of human Factor XIIa.

2. The anti-Factor XII/XIIa monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the binding affinity is measured by surface plasmon resonance-based technology, and wherein completely inhibiting the amidolytic activity of human Factor XIIa means an inhibition of at least 80% of the activity observed in a control experiment without any inhibitor present.

~~2.~~3. An anti-Factor XII/XIIa monoclonal antibody or antigen-binding fragment thereof, that inhibits Factor XIIa-alpha by more than 50% when used at a molar ratio of FXIIa-alpha to antibody of 1:0.2.

~~3.~~4. The antibody or antigen-binding fragment thereof of any of claims 1 ~~or claim 2~~to 3, wherein the antibody binds murine FXII/FXIIa; and wherein the level of binding of the antibody to a polypeptide comprising SEQ ID NO: 2 in which (a) the asparagine residue at position 398 of SEQ ID NO: 2 is substituted for lysine; or (b) the isoleucine residue at position 438 of SEQ ID NO: 2 is substituted for alanine, is lower than the level of binding of the protein to the corresponding polypeptide comprising SEQ ID NO: 2 without said substitution.

~~4.~~5. The antibody or antigen-binding fragment thereof of any of claims 1 to ~~3~~4, wherein the antibody comprises a heavy chain variable (vH) region which is more than 85% identical to the sequence of SEQ ID NO: 4.

~~5.~~6. The antibody or fragment thereof of any of claims 1 to 45, wherein the antibody comprises a light chain variable (vL) region which is more than 85% identical to the sequence of SEQ ID NO: 5.

~~6.~~7. The antibody or fragment thereof of any of claims 1 to ~~5~~6, wherein the antibody comprises heavy chain CDR1 at least 80% identical to the sequence of SEQ ID NO: 6, heavy chain CDR2 at least 60% identical with SEQ ID NO: 7, and heavy chain CDR3 at least 80% identical to the sequence of SEQ ID NO: 9.

~~7.~~8. The antibody or fragment thereof of any of claims 1 to ~~6~~7, wherein the antibody comprises light chain CDR1 at least 50% identical with SEQ ID NO: 11, light chain CDR2 of SEQ ID NO: 12, and light chain CDR3 of SEQ ID NO: 14.

~~8.~~9. The antibody or fragment thereof of any previous claim, wherein it binds human Factor XIIa-beta with a K_D of better than 10^{-7}M.

~~9.~~10. The antibody or fragment thereof of any previous claim, wherein it competes with Infestin for binding to human Factor XIIa-beta.

~~10.~~11. The antibody or fragment thereof of any previous claim, wherein the antibody is a human IgG or variant thereof.

~~11.~~12. The antibody or fragment thereof of claim ~~10~~11, wherein the IgG is IgG4.

~~12.~~13. A nucleic acid encoding the antibody or fragment thereof of any previous claim.

~~13.~~14. A vector comprising the nucleic acid of claim ~~12~~13, operably linked to a suitable promoter sequence.

~~14.~~15. A cell line or yeast cell comprising the vector of claim ~~13~~14.

~~15.~~16. A method of producing the antibody or fragment thereof of any of claims 1 to ~~11~~12, comprising culturing the cell line or yeast cell of claim ~~14~~15 under appropriate conditions to express the antibody and purifying the antibody from the culture supernatant.

~~16.~~17. An antibody or antigen-binding fragment thereof of any of claims 1 to ~~11~~12 for medical use.

18. Use of an antibody or antigen-binding fragment thereof of any of claims 1 to 12 in the preparation of a medicament for medical use.

~~17.~~19. An antibody or antigen binding fragment thereof of any of claims 1 to ~~11~~ 12 or the use of claim 18, for ~~use in~~ preventing and/or treating a disorder selected from the group consisting of venous, arterial or capillary thrombus formation, thrombus formation in the heart, thromboembolism, thrombus formation during and/or after contacting blood of a human or animal subject with artificial surfaces, by preventing the formation and/or the stabilization of thrombi and thereby three-dimensional intraluminal thrombus growth, or by preventing and/or treating intraluminal thrombi; interstitial lung disease, inflammation, a neurological inflammatory disease, complement activation, fibrinolysis, angiogenesis and diseases related to FXII/ FXIIa-induced kinin formation or FXII/FXIIa-mediated complement activation.

~~18.~~20. The antibody or antigen-binding fragment thereof or the use of claim ~~17~~19, wherein the venous or arterial thrombus formation is stroke, myocardial infarction, deep vein thrombosis, portal vein thrombosis, thromboembolism, renal vein thrombosis, jugular vein thrombosis, cerebral venous sinus thrombosis, Budd-Chiari syndrome or Paget-Schroetter disease.

~~19.~~21. The antibody or antigen-binding fragment thereof or the use of of claim ~~17~~20, wherein the diseases related to FXII/FXIIa-induced kinin formation are selected from the group hereditary angioedema, bacterial infections of the lung, trypanosoma infections, hypotensive shock, pancreatitis, chagas disease, articular gout, arthritis, disseminated intravascular coagulation (DIC) and sepsis.

~~20.~~22. The antibody or antigen-binding fragment thereof or the use of of claim ~~17~~19, wherein the interstitial lung disease is fibroproliferative and/or idiopathic pulmonary fibrosis.

~~21.~~23. The antibody or antigen-binding fragment thereof or the use of claim ~~17~~19, wherein the thrombus formation during and/or after contacting blood with artificial surfaces occurs during and/or after a medical procedure performed on

said human or animal subject and, wherein said antibody is administered before and/or during and/or after said medical procedure, and further wherein

(i) the artificial surface is exposed to at least 80% of the blood volume of the subject and the artificial surface is at least 0.2 m^2 or

(ii) the artificial surface is a container for collection of blood outside the body of the subject or

(iii) the artificial surface is a stent, valve, intraluminal catheter, or a system for internal assisted pumping of blood.

~~22.~~24. A medical device coated with an antibody or antigen-binding fragment thereof of any of claims 1 to ~~11~~12, wherein the device is a cardiopulmonary bypass machine, an extracorporeal membrane oxygenation system for oxygenation of blood, a device for assisted pumping of blood, a blood dialysis device, a device for the extracorporeal filtration of blood, a repository for use in the collection of blood, an intraluminal catheter, a stent, an artificial heart valve, and/or accessories for any one of said devices including tubing, cannulae, centrifugal pump, valve, port, and/or diverter.

~~23.~~25. The antibody or antigen-binding fragment thereof of any of claims 1 to ~~11~~12 for administration in a patient receiving a medical procedure, wherein the medical procedure comprises contact with at least one of:

(a) heart,

(b) at least one blood vessel chosen from: the aorta, the aortic arch, a carotid artery, a coronary artery, brachiocephalic artery, vertebrobasilar circulation, intracranial arteries, renal artery, a hepatic artery, a mesenteric artery, and/or a blood vessel of the arterial system cranial to the heart,

(c) a venous blood vessel if the patient has a known septal defect;

and wherein the medical procedure comprises release of at least one embolus in at least one of said blood vessels in the body that could result in ischemia in at least one target organ and administration of the antibody or antigen-binding fragment thereof before, during, and/or after the medical procedure.

~~24.~~26. The antibody or antigen-binding fragment thereof of any of claims 1 to ~~11~~ 12 for the prevention or treatment of a condition associated with increased retinal vascular permeability, including progressive retinopathy, sight-threatening complication of retinopathy, macular edema, non-proliferative retinopathy, proliferative retinopathy, retinal edema, diabetic retinopathy, hypertensive retinopathy, and retinal trauma.

~~25.~~27. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any of claims 1 to ~~11~~12.

28. Use of the antibody or antigen-binding fragment thereof of any of claims 1 to 12 in the preparation of a medicament for the prevention or treatment of a condition associated with increased retinal vascular permeability, including progressive retinopathy, sight-threatening complication of retinopathy, macular edema, non-proliferative retinopathy, proliferative retinopathy, retinal edema, diabetic retinopathy, hypertensive retinopathy, and retinal trauma.