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(54) Title: PROTEINACEOUS MOLECULES BINDING FACTOR IXA AND FACTOR X

(57) Abstract: The present invention provides proteinaceous molecules that bind to Factor IXa and Factor X for enhancing a proco-  
agulant activity.



## Proteinaceous molecules binding Factor IXa and Factor X

### Technical Field

The present invention provides therapeutics for the treatment and/or prevention of bleeding disorders such as hemophilia A. In particular, the present invention provides proteinaceous molecules that bind to Factor IXa and Factor X.

### Background art

Hemophilia A is a severe X-chromosome-linked recessive disorder caused by mutations in the factor VIII (FVIII) gene. FVIII is involved in the intrinsic pathway of blood coagulation, and FVIII deficiency leads to blood either coagulating poorly, or barely at all. FVIII deficiency, alternatively known as hemophilia A, is one of the most common hemorrhagic disorders, and affects one in about 10,000 males (Stonebraker et al. (2012) Haemophilia 18(3):e91-4). Hemophilia A has three grades of severity defined by factor FVIII plasma levels of 1% or less ("severe"), 2 to 5% ("moderate"), and 6 to 30% ("mild") (White et al. (2001) Thromb. Haemost. 85:560) or 5-<40% according to WFH "Guidelines for the Management of Hemophilia" 2nd edition Haemophilia; Epub 6 JUL 2012. DOI: 10.1111/j.1365-2516.2012.02909.x. In severe forms of the disorder, the first bleeds typically appear at 5 to 6 months of age, whereas the first bleeds are delayed until about 1 to 2 years of age in the moderate form. A bleed can appear spontaneously, or following minimum trauma. Approximately half of all patients with hemophilia A are classified as having the severe form of the disease. These patients experience severe bleeding starting in early childhood, and frequent episodes of spontaneous or excessive bleeding later in life. Bleeding commonly occurs into joints and muscles, and without appropriate treatment, recurrent bleeding can lead to irreversible hemoarthropathy (Manco-Johnson et al. (2007) N. Engl. J. Med. 357(6):535-44).

An important goal of hemophilia A treatment is maintenance of FVIII plasma levels >1%, which reduces bleeding risk. To achieve this, intravenous recombinant or plasma-derived FVIII is administered frequently as prophylactic therapy. However, this current standard of treatment of hemophilia A is difficult, has several drawbacks, and incurs a considerable physical and mental burden on patients and their families.

The most common hindrance in FVIII treatment is the production of alloantibodies against FVIII, which act as FVIII inhibitors. As many as 30% of severely affected patients develop such alloantibodies, and once development has occurred, the effective use of FVIII for treating on-going bleeds is restricted (Kempton & White (2009) Blood 113(1): 11-7). In such

cases, alternative bypassing agents are used to control bleeding. However, these agents typically have shorter half-lives and are not always effective. Furthermore, frequent administration of FVIII is required due to its short plasma half-life (an average of about 12 hours in adults, and even shorter in children). Such a regimen can be difficult, particularly in young children. Since available treatments are associated with complications and side effects, there is no single treatment that optimally and effectively treats hemophilia. Thus, there remains an unmet need for new and effective treatments that resolve the drawbacks of treating hemophilia A with FVIII.

## **Figures**

**Figure 1:** Diagrams of bispecific multivalent proteinaceous molecules. The “3 by 1” topology is characterized by having three antigen-binding sites that bind to Factor IXa and one antigen-binding site that binds to Factor X. The “1 by 3” topology is characterized by having three antigen-binding sites that bind to Factor X and one antigen-binding site that binds to Factor IXa. The “2 by 2” topology is characterized by having two antigen-binding sites that bind to Factor X and two antigen-binding sites that binds to Factor IXa. The antigen-binding sites that bind to Factor IXa and the antigen-binding sites that bind to Factor X may be switched around for the “2 by 2” constructs. Further, the binding modules of the “1 by 3” and “3 by 1” constructs are not limited to being attached to the C-terminus of the heavy chain, but may also be attached to the N-terminus of the heavy chain or the N- or C-terminus of the light chain. All binding modules depicted here are attached to the scaffold module through linkers.

**Figure 2:** Diagram of trispecific multivalent proteinaceous molecule. In particular, a trispecific multivalent proteinaceous molecule comprising a “IXa/X”-type scaffold. The topology of this molecule can be characterized in that the molecule comprises an antigen-binding site that binds to Factor IXa, an antigen-binding site that binds to Factor X, and a third and fourth antigen-binding site that can bind to another target that enhances the procoagulant activity of the molecule. The binding modules labeled “Z” may be any binding module that comprises an antigen-binding site that binds to anything other than Factor IXa or Factor X. Further, the binding modules are not limited to being attached to the C-terminus of the heavy chain, but may also be attached to the N-terminus of the heavy chain or the N- or C-terminus of the light chain. All binding modules depicted here are attached to the scaffold module through linkers.

**Figure 3:** Diagram of trispecific multivalent proteinaceous molecule. In particular, a trispecific multivalent proteinaceous molecule comprising the features of a “2 by 2” topology with two

additional binding modules comprising an antigen-binding site each. The two additional antigen-binding sites bind to another target that enhances the procoagulant activity of the molecule. The binding modules labeled "Z" may be any binding module that comprises an antigen-binding site that binds to anything other than Factor IXa or Factor X. Further, the antigen-binding sites that bind to Factor IXa and the antigen-binding sites that bind to Factor X may be switched around for any of the constructs depicted in Figure 3. All binding modules depicted here are attached to the scaffold module through linkers.

**Figure 4:** Diagrams of different topologies which are possible and encompassed by the present invention. The binding modules labeled "Z" are optional and may be replaced by any binding module that comprises an antigen-binding site that binds to anything other than Factor IXa or Factor X. Further, the antigen-binding sites that bind to Factor IXa and the antigen-binding sites that bind to Factor X may be switched around for any of the constructs depicted in Figure 4. A) In this embodiment, two binding modules are attached to the N-terminus of the heavy chains through a linker, two binding modules are attached to the C-terminus of the light chains through a linker and two binding modules are attached to the C-terminus of the heavy chains through a linker. B) In this embodiment, two binding modules are attached to the C-terminus of the light chains through a linker and two binding modules in tandem are attached to the C-terminus of each heavy chain. C) This embodiment is a permutation of (A). It is clear that the binding modules may be interchangeable as discussed herein. D) This embodiment is a permutation of (A) and (C). It is clear that the binding modules may be interchangeable as discussed herein. E) In this embodiment, two binding modules are attached to the C-terminus of the light chains through a linker and three binding modules in tandem are attached to the C-terminus of each heavy chain. F) In this embodiment, two binding modules that are Fabs or scFabs are attached to the N-terminus of the light chains through a linker. G) In this embodiment, two binding modules that are scFvs are inserted between the CH1 and CH2 domain of the scaffold module.

**Figure 5:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of constructs that comprise similar antigen-binding site sequences but comprise different linkers.

**Figure 6:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of constructs that comprise similar antigen-binding site sequences but comprise different linkers.

**Figure 7:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of trispecific constructs that comprise bavituximab.

5 **Figure 8:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of trispecific constructs that comprise domain V of  $\beta$ 2-glycoprotein I.

10 **Figure 9:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of constructs that are bispecific and multivalent.

15 **Figure 10:** Peak thrombin values of different proteinaceous molecules at a concentration of 100 nM. This Figure provides a comparison between a number of different constructs with a 2 by 2 topology.

**Figure 11:** Results of the  $\beta$ 2-glycoprotein I ELISA described in Example 9. These results show that constructs comprising bavituximab are still able to bind domain II of  $\beta$ 2-glycoprotein I. Lex#4 is used as a negative control. Lex#4 is a bispecific KL-body that comprises the VL domain of V217, the VL domain of W83 and a VH domain, wherein the VH domain is SEQ ID NO: 4. SIA is a purified, bispecific, bivalent anti-FIX(a), anti-FX(a) antibody produced in HEK293 cells with identical sequence as Hemlibra, based on the published amino acid sequence (WHO Drug Information Vol. 29, No. 2, 2015 - Proposed International Nonproprietary Names, List 113. World Health Organization).

25 **Figure 12:** Results of the Phospholipid ELISA described in Example 9. These results show that constructs comprising domain V of  $\beta$ 2-glycoprotein I are still able to bind to phosphatidylserine. Lex#4 is used as a control. Lex#4 is a bispecific KL-body that comprises the VL domain of V217, the VL domain of W83 and a VH domain, wherein the VH domain is SEQ ID NO: 4. SIA is a purified, bispecific, bivalent anti-FIX(a), anti-FX(a) antibody produced in HEK293 cells with identical sequence as Hemlibra, based on the published amino acid sequence (WHO Drug Information Vol. 29, No. 2, 2015 - Proposed International Nonproprietary Names, List 113. World Health Organization).

35 **Figure 13:** Results of the GPIIb/IIIa ELISA described in Example 9. These results show that constructs comprising anti-LIBS are still able to bind to GPIIb/IIIa. Lex#1 is used as a

negative control. Lex#1 is identical to Lex#36 except that Lex#1 does not comprise a binding module.

### **Summary of the invention**

5 The present invention provides a proteinaceous molecule comprising (i) a scaffold module comprising a first antigen-binding site and a second antigen-binding site, and (ii) at least a first binding module comprising a third antigen-binding site; wherein at least one of the antigen-binding sites binds to Factor IXa and at least one of the antigen-binding sites binds to Factor X. In this embodiment, the remaining antigen-binding site(s) (i.e. the ones whose  
10 function has not been specified yet) can bind to a target (e.g. phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker) in order to enhance procoagulant activity as measured e.g. in a thrombin generation assay.

In some embodiments, any of the proteinaceous molecules described herein has a  
15 procoagulant activity. Those proteinaceous molecules that have a high procoagulant activity are particularly preferred.

The present invention also provides a nucleic acid encoding the proteinaceous molecule of the present invention. Further, the present invention provides a cell (preferably a mammalian  
20 cell) comprising a nucleic acid of the present invention and/or a proteinaceous molecule of the present invention.

A method for producing the proteinaceous molecule of the present invention comprising expressing the proteinaceous molecule according to the present invention in a cell and  
25 purifying the proteinaceous molecule is also provided by the present invention.

The present invention also provides a pharmaceutical composition comprising the proteinaceous molecules of the present invention and a pharmaceutically acceptable carrier and/or diluent.  
30

The present invention also provides the molecule or pharmaceutical composition of the present invention for use as a medicament. Further, the present invention provides the molecule or pharmaceutical composition of the present invention for use in a method of treating and/or preventing a bleeding disorder, wherein a patient or animal is administered a  
35 therapeutically effective amount of the molecule.

A method of treating and/or preventing a bleeding disorder wherein the patient or animal is administered a therapeutically effective amount of the molecule or pharmaceutical composition of the present invention is also provided. Further, the present invention provides the use of the molecule or pharmaceutical composition of the present invention for the manufacture of a medicament for the treatment and/or prevention of a bleeding disorder.

### **Detailed description of the invention**

#### **Definitions**

The term "affibody" refers to a protein that is derived from the Z domain of protein A and that been engineered to bind to a specific target (see Frejd & Kim, 2017. Exp Mol Med. 49(3): e306).

The term "animal", as used in the present application, refers to any multicellular eukaryotic heterotroph which is not a human. In some embodiments, the animal is selected from a group consisting of cats, dogs, pigs, ferrets, rabbits, gerbils, hamsters, guinea pigs, horses, rats, mice, cows, sheep, goats, alpacas, camels, donkeys, llamas, yaks, giraffes, elephants, meerkats, lemurs, lions, tigers, kangaroos, koalas, bats, monkeys, chimpanzees, gorillas, bears, dugongs, manatees, seals and rhinoceroses.

The term "antibody" refers to a molecule comprising at least one immunoglobulin domain that binds to, or is immunologically reactive with, a particular target. The term includes whole antibodies and any antigen binding portion or single chains thereof and combinations thereof; for instance, the term "antibody" in particular includes bivalent antibodies and bivalent bispecific antibodies.

A typical type of antibody comprises at least two heavy chains ("HC") and two light chains ("LC") interconnected by disulfide bonds.

Each "heavy chain" comprises a "heavy chain variable domain" (abbreviated herein as "VH") and a "heavy chain constant domain" (abbreviated herein as "CH"). The heavy chain constant domain typically comprises three constant domains, CH1, CH2, and CH3.

Each "light chain" comprises a "light chain variable domain" (abbreviated herein as "VL") and a "light chain constant domain" ("CL"). The light chain constant domain (CL) can be of the kappa type or of the lambda type. The VH and VL domains can be further subdivided into regions of hypervariability, termed Complementarity Determining Regions ("CDR"), interspersed with regions that are more conserved, termed "framework regions" ("FW").

Each VH and VL is composed of three CDRs and four FWs, arranged from amino-terminus to carboxy-terminus in the following order: FW1, CDR1, FW2, CDR2, FW3, CDR3, FW4. The present disclosure inter alia presents VH and VL sequences as well as the subsequences  
5 corresponding to CDR1, CDR2, and CDR3.

Accordingly, a person skilled in the art would understand that the sequences of FW1, FW2, FW3 and FW4 are equally disclosed. For a particular VH, FW1 is the subsequence between the N-terminus of the VH and the N-terminus of H-CDR1, FW2 is the subsequence between  
10 the C-terminus of H-CDR1 and the N-terminus of H-CDR2, FW3 is the subsequence between the C-terminus of H-CDR2 and the N-terminus of H-CDR3, and FW4 is the subsequence between the C-terminus of H-CDR3 and the C-terminus of the VH. Similarly, for a particular VL, FW1 is the subsequence between the N-terminus of the VL and the N-terminus of L-CDR1, FW2 is the subsequence between the C-terminus of L-CDR1 and the  
15 N-terminus of L-CDR2. FW3 is the subsequence between the C-terminus of L-CDR2 and the N-terminus of L-CDR3, and FW4 is the subsequence between the C-terminus of L-CDR3 and the C-terminus of the VL.

The variable domains of the heavy and light chains contain a region that interacts with a binding target, and this region interacting with a binding target is also referred to as an  
20 "antigen-binding site" or "antigen binding site" herein. The constant domains of the antibodies can mediate the binding of the antibody to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system. Exemplary antibodies of the present disclosure include typical  
25 antibodies, but also bivalent fragments and variations thereof such as a  $F(ab')_2$ .

As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, bivalent antibody fragments (such as  $F(ab')_2$ ), multispecific antibodies such as bispecific antibodies, chimeric antibodies, humanized antibodies, human antibodies,  
30 and any other modified immunoglobulin molecule comprising two antigen binding sites.

An antibody can be of any the five major classes (isotypes) of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta,  
35 epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies

can be naked or conjugated to other molecules such as therapeutic agents or diagnostic agents to form immunoconjugates.

The term “anticalin” refers to a protein that is derived from the lipocalin and that been engineered to bind to a specific target (see Skerra, 2008. FEBS J. 275(11):2677-83).

The term “antigen-binding fragment” or “Fab” refers to an antibody fragment comprising one constant and one variable domain of each of the heavy and light chain. A Fab fragment may be obtained by digesting an intact monoclonal antibody with papain.

The term “antigen-binding site” refers to a region of a scaffold module or binding module that allows for a non-covalent binding interaction with an intended target. An “antigen-binding site” may be, for example, a binding site comprising three complementary determining regions such as in the case of an antibody, scFv or scFab or a binding interface such as the phospholipid-binding interface of  $\beta$ 2-glycoprotein I.

The term “binding module” refers to any substance that binds to Factor IXa, Factor X, or any other target, which may enhance a pro-coagulating activity of the proteinaceous molecule of the present invention in comparison to the scaffold module per se. Non-limiting examples of binding modules include anticalin, repebody, monobody, scFv, Fab, scFab, affibody, fynomer, DARPin, nanobody, peptide aptamer, and nucleic acid aptamer.

The term “bispecific molecule” refers to a molecule that is able to bind to at least two different targets through two different antigen binding sites. The bispecific molecules of the present invention are able to bind to Factor IXa and Factor X. It follows that a “trispecific molecule” is a molecule that is able to bind to at least three different targets through three different antigen binding sites. The trispecific molecules of the present invention are able to bind to Factor IXa, Factor X and a further target in order to enhance a procoagulant activity. The term “multispecific molecule” refers to a molecule that is able to bind more than two different targets through more than two different antigen binding sites.

The term “designed ankyrin repeat proteins” or “DARPin” refers to a protein that is derived from an ankyrin repeat that has been engineered to bind to a specific target (see Plückthun, 2015. Annu Rev Pharmacol Toxicol. 55:489-511).

As used herein, the term "effective amount" of an agent, e.g., a therapeutic agent such as an antibody, is that amount sufficient to effect beneficial or desired results, for example, clinical

results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering a therapeutic agent that treats bleeding, an effective amount of an agent is, for example, an amount sufficient to reduce or decrease in bleeding occurrences, as compared to the response obtained without administration of the agent. The term "effective amount" can be used interchangeably with "effective dose,"  
5 "therapeutically effective amount," or "therapeutically effective dose."

The term "Factor IX" or "FIX" refers to a protein that is synthesized by liver hepatocytes as a pre-prozymogen that requires extensive posttranslational modification. The pre-prozymogen  
10 contains a pre-peptide (hydrophobic signal peptide) at its amino terminal that transports the growing polypeptide into the lumen of the Endoplasmic Reticulum. Once inside the ER, this signal peptide is cleaved by a signal peptidase. A pro-peptide functions as a recognition element for a vitamin K-dependent carboxylase ( $\gamma$ -glutamyl carboxylase) which modifies 12 glutamic acid residues to gammacarboxyglutamyl (Gla) residues. These residues are  
15 required for the association with the anionic phospholipid surface through  $\text{Ca}^{2+}$ -dependent binding. After the cleavage of the signal peptide and the propeptide, FIX is in a zymogen form. FIX zymogen thus circulates as a 415 amino acid, single chain polypeptide.

The zymogen of FIX is activated by FXIa or by the tissue factor/FVIIa complex. The first  
20 cleavage is at Arg 191 (Arg 145 in the mature FIX sequence), generating an inactive FIX-alpha. The second cleavage at Arg226 (Arg 180 in the mature FIX sequence) removes 35 amino acids of the FIX activation peptide and results in a catalytically active molecule FIXa-beta. This catalytically active FIXa not associated with FVIIIa is also called herein as free FIXa. This resulting heterodimer is held by a disulfide bridge at Cys178-Cys335. The serine  
25 protease contains a catalytic triad of His267, Asp315, and Ser411. Upon cleavage at Arg226, Val227 can form a salt bridge with Asp410, which is a characteristic of active serine proteases. Data concerning a non-limiting example of Factor IX has been deposited in UniProtKB under accession number P00740. In some embodiments, an antigen-binding site of the proteinaceous molecule of the present invention preferentially binds to free Factor IXa  
30 over the zymogen of Factor IX.

The term "Factor X" or "FX" refers to a vitamin-K dependent glycoprotein with a molecular weight of 58.5 kDa, which is secreted from liver cells into the plasma as a zymogen. Initially Factor X is produced as a prepropeptide with a signal peptide consisting in total of 488 amino  
35 acids.

The signal peptide is cleaved off by signal peptidase during export into the endoplasmic reticulum. The propeptide sequence is cleaved off after gamma carboxylation took place at the first 11 glutamic acid residues at the N-terminus of the mature N-terminal chain. A further processing step occurs by cleavage between Arg 182 and Ser 83. This processing step also leads concomitantly to the deletion of the tripeptide Arg180-Lys181-Arg182. The resulting secreted factor X zymogen consists of an N-terminal light chain of 139 amino acids (M, 16,200) and a C-terminal heavy chain of 306 amino acids (M, 42,000) which are covalently linked via a disulfide bridge between Cys172 and Cys342. The Factor X zymogen can be cleaved in its heavy chain by Factor IXa and consequently become activated after the release of an activation peptide resulting in a protein referred to as "Factor Xa" or "FXa". Data concerning a non-limiting example of Factor X has been deposited in UniProtKB under accession number P00742. In some embodiments, an antigen-binding site of the proteinaceous molecule of the present invention preferentially binds to the zymogen of Factor X over Factor Xa.

The term "fynomer" refers to a protein that is derived from the SH3 domain of human Fyn kinase that has been engineered to bind to a specific target (see Bertschinger et al., 2007. Protein Eng Des Sel. 20(2):57-68).

The terms "individual", "patient" or "subject" are used interchangeably in the present application to designate a human being and are not meant to be limiting in any way. The "individual", "patient" or "subject" can be of any age, sex and physical condition.

The term "linker" refers to at least one atom that forms a covalent bond between two chemical entities. The term "linker" may refer to at least one atom that forms a covalent bond between the scaffold module and another covalent bond to the binding module. If the scaffold module and binding module is linked solely through peptide bonds, the linker is referred to as a "peptide linker". Otherwise, the linker is referred to as a "chemical linker". Further, a "flexible peptide linker" comprises mostly small, non-polar or polar amino acids whereas a "rigid peptide linker" comprises alpha-helix forming sequences and/or are rich in proline residues (Chen et al., 2013. Adv Drug Deliv Rev. 65(10):1357-1369).

The term "monobody" refers to a protein that is derived from a fibronectin type III domain that has been engineered to bind to a specific target (see Koide et al., 2013. J Mol Biol. 415(2):393-405).

The term “nanobody” refers to a protein comprising the soluble single antigen-binding V-domain of a heavy chain antibody, preferably a camelid heavy chain antibody (see Bannas et al., 2017. Front Immunol. 8:1603).

- 5 The term “nucleic acid aptamer” refers to a short synthetic single-stranded oligonucleotide that specifically binds to various molecular targets (see Ni et al., 2011. Curr Med Chem. 18(27):4206-4214).

- 10 The term “peptide aptamer” refers to a short, 5-20 amino acid residue sequence that can bind to a specific target. Peptide aptamers are typically inserted within a loop region of a stable protein scaffold (see Reverdatto et al., 2015. Curr Top Med Chem. 15(12):1082-101).

- 15 The term “phosphatidylserine” may refer to both phosphatidyl-L-serine and phosphatidyl-D-serine. In some embodiments, the term “phosphatidylserine” refers to phosphatidyl-L-serine.

- 20 The term “phosphatidylserine-binding protein” refers to a protein that is capable of binding to phosphatidylserine. Non-limiting examples include Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Factor IX, Factor IXa, Factor X, Factor Xa, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, and  $\beta_2$ -glycoprotein I (Apo-H).

- 25 The term “platelet surface marker” refers to a molecule that can be found on the surface of a platelet which can be used to co-localize the proteinaceous molecule of the present invention to the surface of the platelet. Non-limiting examples include CD61, GPIb-IX, CD69, CD40, collagen chaperone HSP47, ephrin B1, thiol isomerase protein ERP5, Hematopoietic progenitor kinase 1-interacting protein of 55 (HIP-55), glycoprotein VI, platelet glycoprotein 1b, platelet-derived growth factor receptor, platelet endothelial aggregation receptor I, CD36, CD31, MARKS, multimerin, integrin alpha IIb/beta 3, triggering receptor expressed on  
30 myeloid cells (TREM) like transcript-1 (TLT-1), integrin-linked kinase (ILK), zyxin, collagen, P-selectin, Factor XIII, P-selectin glycoprotein ligand-1, integrin alpha 6 beta 1, thrombospondin, von Willebrand factor, G6B, CD42b, syntaxin binding protein 2, phosphatidylethanolamine, fibrinogen/fibrin, filamin, stomatin, sphingolipid, CD63, CD41, CD49b, CD107a, CD107b, CD42c, CD42, CD109, CD62P, CD154, PECAM-1, and ERPS.

- 35 The term “prevention”, as used in the present application, refers to a set of hygienic, pharmacological, surgical and/or physical means used to prevent the onset and/or

development of a disease and/or symptoms. The term “prevention” encompasses prophylactic methods, since these are used to maintain the health of an animal or individual.

The term “procoagulant activity” is used herein to define an activity that can promote coagulation, e.g. by promoting any process or reaction that contributes to coagulation (or by inhibiting any process or reaction that reduces coagulation). Accordingly, the term “procoagulant activity” encompasses (but is not limited to) one or more of the activities listed below:

- a Factor-VIIIa-like activity, i.e. an activity that corresponds to an activity of activated Factor VIII (Factor VIIIa).
- Enhancing Factor-IXa-mediated Factor X activation, as measured by a amidolytic (chromogenic or fluorogenic) assay based on FIXa-mediated FX activation. The assay measures FXa through cleavage of an FXa specific peptide substrate. The substrate is produced, giving a color that can be measured photometrically by absorbance.
- Shortening of clotting times, as measured by clotting assays such as Activated partial thromboplastin time (APTT) measure the activity of the intrinsic and common pathways of coagulation. Plasma is preincubated with an APTT reagent containing a contact activator, e.g. ellagic acid or kaolin, and phospholipid. Calcium chloride is added to promote fibrin clot formation. Possible readouts are clotting time or clot wave form.
- Enhancing thrombin generation, as measured in a thrombin generation assay such as Calibrated Automated Thrombography (CAT). The thrombogram describes the concentration of thrombin in clotting plasma and is therefore a functional test of the hemostatic system. The assay is based on the measurement of fluorescence that is generated by the cleavage of the fluorogenic substrate Z G G R AMC by thrombin over time.
- Enhancing global visco-elastic properties of clot formation as measured by viscoelastic hemostatic methods e.g. in whole blood under shear stress by assays such as ROTEM (Rotational thromboelastometry). In the instrument, a ball-bearing pin rotates in a stationary cup. The fibrin strands in the sample form between the wall of the cup and the pin during coagulation and the strength of the strands will affect the movement of the pin, which is detected.
- Improved thrombus formation under flow, as measured by flow chamber systems such as the t-TAS (Total Thrombus-formation Analysis System). This assay is used for the quantitative assessment of the thrombus formation process under variable flow. Blood flows through the analytical path of a microchip, platelets adhere and

aggregate on the surface of collagen-coated capillaries, eventually resulting in an increase of flow pressure.

- Shortening of the whole blood closure time (WBCT), as measured by a platelet function analyzer, which is based on Von Willebrand Factor (VWF)-mediated platelet adhesion to collagen after platelet activation. High shear stress is produced which leads to platelet adhesion and platelet aggregation. The time from the beginning to end of blood flow is measured.
- Aggregation of human platelets in platelet rich plasma (PRP) using e.g. an aggregometer. The aggregometer works on the basic principle of light transmission. As platelets aggregate, the light transmission of the sample increases.

All methods described above can be applied to human blood-related specimen, as well as specimen of different animal species. Therefore, they are analytical tools that can be used to analyze ex vivo the procoagulant activity of samples for e.g. assessing the pharmacodynamic properties of antibodies in animal studies.

- The present invention provides in-vivo methods and means for identifying a proteinaceous molecule with favorably characteristics typical of a therapeutic drug as well as in-vivo methods for selecting the most qualified proteinaceous molecule and/or the preclinical testing of the therapeutic proteinaceous molecule.
- In general an animal model is a living animal used during the research and development of human drugs, or for the purpose of better understanding the human disease mirrored by the animal model. The animal model chosen will usually recapitulate the human pathophysiology, and the pharmacology, exaggerated pharmacology, safety, and/or toxicity of the administered drug candidate while the efficacy of the treatment is reflected in modifications of a prevalent disease state or when challenging healthy animals with an artificial disease inducing insult (trauma). The drug candidate is administered either prophylactic or acutely through oral or parenteral routes including the intravenous and subcutaneous routes. Animal models have been proven valuable and predictive in the selection and development of human treatments for hemophilia including factor replacement therapies or bispecific antibody mimicking factor activity.
- Animal models refer to any animal classified including but not limited to rodents such as mouse, rat, guinea pig, hamster, rabbit, dog, cat, pig, cow, sheep, goat, horse, non-human primates. These include laboratory, domestic and farm animals, and also veterinary patients. Animal models make use of pharmacologic depletion or inhibition of procoagulant factors (Factor VIII), and naturally occurring or genetically engineered

modifications that are characterized by loss or gain of function of particular disease related genes and their encoded proteins. As an example animal models recapitulate the causative human loss of function of components in haemostatic regulation (Factor VIII, Factor IX, VWF, APC). In some cases, the rodent is mouse or rat, guinea pig, or hamster. The non-human model can be a rabbit, or more weight bearing animals like dog, sheep or a non-human primate such as *Cynomolgus* macaque or Rhesus macaque. In a further animal model setting, like the non-human primate, the test-article shows pharmacokinetic behavior, specific target engagement and a pharmacologic profile that closely reflects those in human.

- In particular, animal models in this invention can monitor for endpoints related to arterial or venous thrombosis, microvascular thrombosis, thrombolysis. As an example thrombosis/thrombolysis models apply ferric chloride, photochemicals, venous stasis, mechanical trauma, systemic epinephrine-collagen infusion, laser injury, spontaneous lysis of pulmonary embolism or microemboli and pharmacologic arterial thrombolysis. The vascular site of investigation includes but is not limited to carotid or femoral arteries, jugular or femoral veins, mesenteric or cremasteric arterioles, small ear veins and arteries, muscle arterioles, tail veins, blood vessels of the nail.
- In particular animal models in this invention monitor for endpoints related to hemostasis and pharmacologic changes thereof after spontaneous or induced bleeding episodes. Assessments can include those collected through spontaneous bleeds and when challenged by tail vein transection, tail-tip bleeding, vein puncture bleeding, cremaster injury model, ferric chloride carotid artery occlusion, nail-clipping, cutaneous injury (Surgicut), intramuscular injury, subcutaneous exfoliation, or injury models inducing mechanical trauma to the joint or by spontaneous hemarthrosis. Monitoring of disease modification includes but is not limited to endpoints assessing clinical signs, incidence and frequency of limping episodes, bleeding time, blood volume, measurements of bruised areas, joint swelling, blood hemoglobin levels, urinary hemoglobin; ex-vivo analyses of coagulation (ROTEM), APTT, factor-activity and thrombin generation; survival, re-bleeds, as well as pathological findings and changes in joint tissues, and internal bleeds in other tissues.
- Murine thrombosis models. Day SM, Reeve JL, Myers DD, Fay WP. *Thromb Haemost.* 2004;92(3):486-94
- Animal Models of Hemophilia. Denise E. Sabatino, Timothy C. Nichols, Elizabeth Merricks, Dwight A. Bellinger, Roland W. Herzog, and Paul E. Monahan *Prog Mol Biol Transl Sci.* 2012; 105: 151–209.

The term “repebody” refers to a protein that is derived from a leucine-rich repeat module and that been engineered to bind to a specific target (see Lee et al., 2012. PNAS. 109(9): 3299-3304).

- 5     The term “scaffold module” refers to a proteinaceous entity which comprises two antigen-binding sites and may act as a support structure for one or more binding modules. The binding modules may be attached to the scaffold module through a linker and/or the binding modules may be incorporated into any loop regions present in the scaffold module.
- 10    The term “single-chain antigen-binding fragment” or “scFab” refers to a fusion protein comprising one variable and one constant domain of the light chain of an antibody attached to one variable and one constant domain of the heavy chain of an antibody, wherein the heavy and light chains are linked together through a short peptide.
- 15    The term “single-chain variable fragment” or “scFv” refers to a fusion protein comprising the variable domains of the heavy chain and light chain of an antibody linked to one another with a peptide linker. In some embodiments, the scFv is a disulfide stabilized Fv (dsFv). Methods of stabilizing scFvs with disulfide bonds are disclosed in Reiter et al., 1996. Nat Biotechnol. 14(10):1239-45.
- 20    The terms “treatment” and “therapy”, as used in the present application, refer to a set of hygienic, pharmacological, surgical and/or physical means used with the intent to cure and/or alleviate a disease and/or symptoms with the goal of remediating the health problem. The terms “treatment” and “therapy” include preventive and curative methods, since both are directed to the maintenance and/or reestablishment of the health of an individual or animal. Regardless of the origin of the symptoms, disease and disability, the administration of a suitable medicament to alleviate and/or cure a health problem should be interpreted as a form of treatment or therapy within the context of this application.
- 25    The term “valent” as used within the current application denotes the presence of a specified number of antigen-binding sites in a proteinaceous molecule. As such, the terms “bivalent”, “trivalent”, “tetraivalent”, and “hexavalent” denote the presence of two antigen-binding sites, four antigen-binding sites, and six antigen-binding sites, respectively, in a proteinaceous molecule. The bispecific proteinaceous molecules disclosed herein are at least “trivalent” and may be, for example, “tetraivalent” or “hexavalent”. The term “multivalent” refers to a molecule that has at least three antigen-binding sites.
- 30    The term “valent” as used within the current application denotes the presence of a specified number of antigen-binding sites in a proteinaceous molecule. As such, the terms “bivalent”, “trivalent”, “tetraivalent”, and “hexavalent” denote the presence of two antigen-binding sites, four antigen-binding sites, and six antigen-binding sites, respectively, in a proteinaceous molecule. The bispecific proteinaceous molecules disclosed herein are at least “trivalent” and may be, for example, “tetraivalent” or “hexavalent”. The term “multivalent” refers to a molecule that has at least three antigen-binding sites.
- 35    The term “valent” as used within the current application denotes the presence of a specified number of antigen-binding sites in a proteinaceous molecule. As such, the terms “bivalent”, “trivalent”, “tetraivalent”, and “hexavalent” denote the presence of two antigen-binding sites, four antigen-binding sites, and six antigen-binding sites, respectively, in a proteinaceous molecule. The bispecific proteinaceous molecules disclosed herein are at least “trivalent” and may be, for example, “tetraivalent” or “hexavalent”. The term “multivalent” refers to a molecule that has at least three antigen-binding sites.

### Proteinaceous molecules of the present invention

The present invention provides a proteinaceous molecule comprising (i) a scaffold module comprising a first antigen-binding site and a second antigen-binding site, and (ii) at least a first binding module comprising a third antigen-binding site; wherein at least one of the antigen-binding sites binds to Factor IXa and at least one of the antigen-binding sites binds to Factor X. In this embodiment, the remaining antigen-binding site(s) can bind to a target (e.g. phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker) in order to enhance procoagulant activity as measured e.g. in a thrombin generation assay and/or to a target associated with a site of injury (e.g. von Willebrand factor (VWF), fibrinogen or collagen) in order to localize the proteinaceous molecule to the site of injury.

In some embodiments, the first binding module is attached to the scaffold module through a linker, or the first binding module is inserted within a loop region of the scaffold module. In some embodiments, the first binding module is attached to the scaffold module through a linker.

As is apparent from Figures 1-4 all of the binding modules may be attached to the scaffold module through one or more linkers. The binding modules may be in tandem such as in Figure 4B and 4E. In some embodiments, each individual binding module is attached to the scaffold module separately through a linker such as in, for example, Figures 1-3 as well as Figure 4A, C, D and F.

### *Scaffold module*

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof. In some embodiments, the scaffold module is an IgD, IgE or IgG. In some embodiments, the scaffold module is an IgG or a bivalent fragment thereof. In some embodiments, the scaffold module is an IgG. In some embodiments, IgG refers to IgG1.

In some embodiments, the scaffold module is an IgG that comprises a mutation that reduces FcγR and C1q binding (see Wang et al., 2018. Protein Cell. 9(1): 63–73). In some embodiments, the mutation is a LALA mutation (see Xu et al., 2000. Cell Immunol. 200(1): 16-26).

In some embodiments, the scaffold module is an IgG that comprises a mutation that improves FcRn-mediated transport in human systems.

In some embodiments, the scaffold module is an IgG that comprises a mutation that increases its serum half-life in humans (see, for example, the mutations disclosed in WO 02/060919 A2). In some embodiments, the mutation is a YTE mutation (see Robbie et al., 2013. Antimicrob Agents Chemother. 57(12):6147-53).

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In some embodiments, the scaffold module is an IgG that comprises a further antigen-binding site. In some embodiments, the further antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker. The further antigen-binding site may be introduced by modifying loop regions in the CH3 domain (see Wozniak-Knopp et al., 2010. Protein Eng Des Sel. 23(4):289-97).

10

The scaffold modules of the present invention can be divided into two groups:

- 1) the scaffold module is bispecific and binds to Factor IXa and Factor X; or
- 2) the scaffold module is monospecific and binds to Factor IXa or Factor X.

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Thus, in some embodiments, the first antigen-binding site binds to Factor IXa, and the second antigen-binding site binds to Factor X. In an alternative embodiment, each of the first antigen-binding site and the second antigen-binding site binds to Factor IXa, or each of the first antigen-binding site and the second antigen-binding site binds to Factor X.

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*Scaffold module – bispecific*

The bispecific scaffold module may be, for example, obtained through chemical crosslinking of two monospecific antibodies, the scaffold module may be a quadroma or any recombinant bispecific antibody disclosed herein.

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In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises two heavy chains with identical HCDRs. In some embodiments, the scaffold module comprises two heavy chains comprising identical HCDRs, wherein HCDR1 is GFTFSSYA (SEQ ID NO: 1), HCDR2 is ISGSGGST (SEQ ID NO: 2) and HCDR3 is AKSYGAFDY (SEQ ID NO: 3).

30

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises two heavy chains with identical VH domains. In some embodiments, the scaffold module comprises two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4.

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SEQ ID NO 4:

EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAISGSGGSTYY  
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSS

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that  
comprises two identical heavy chains. In some embodiments, the scaffold module comprises  
two identical heavy chains comprising SEQ ID NO: 5.

SEQ ID NO: 5

EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAISGSGGSTYY  
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSSASTK  
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL  
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLF  
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV  
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS  
LTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFS  
CSVMHEALHNHYTQKSLSLSPG

In some embodiments, the scaffold module comprises two identical heavy chains comprising  
SEQ ID NO: 405.

SEQ ID NO: 405

EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAISGSGGSTYY  
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSSASTK  
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL  
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLF  
PPKPKDTLYITREPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS  
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT  
CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCS  
VMHEALHNHYTQKSLSLSPG (YTE mutation is highlighted)

In some embodiments, the scaffold module comprises two light chains. In one embodiment,  
one light chain variable domain is fused to a Kappa constant domain and the other variable  
light chain domain is fused to a Lambda constant domain. This allows for the purification of  
scaffold modules that comprise two antigen binding sites wherein one antigen binding site  
binds to one target and the other binds to another.

In some embodiments, the Lambda constant domain comprises SEQ ID NO: 165 and the Kappa constant domain comprises SEQ ID NO: 166.

SEQ ID NO: 165:

5 GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSSPVKAGVETTTPSKQ  
SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO: 166:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS  
10 KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises two identical heavy chains as well as two light chains wherein one light chain variable domain is fused to a Kappa constant domain and the other variable light chain  
15 domain is fused to a Lambda constant domain (referred to as a “κλ-body”). In this embodiment the scaffold module comprises two antigen-binding sites, wherein one antigen-binding site binds to Factor IXa and the other antigen-binding site binds to Factor X.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that  
20 comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;
- (ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and
- 25 (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a;

In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W83, W88, W128, W127 or W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V198, V202,  
30 V204, V212, or V217 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR 3 of (ii) and (iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83  
35 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2a.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

5 (ii) one light chain comprising the LCDR1, LCDR2 and LDR3 of any one of the Factor X binding light chains disclosed in Table 1; and

(iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2b;

10 In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W206, W83, W88, W128, W127 or W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V245, V43, V90, V141, V149, V198, V202, V204, V212, V305, V320 or V217 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR 3 of (ii) and (iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W206 and V245, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2b.

20

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

25 (ii) one light chain comprising the LCDR1, LCDR2 and LDR3 of any one of the Factor X binding light chains disclosed in Table 1; and

(iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a;

30 In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W83 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W88 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some

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LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W206 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W207 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W140 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W196 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2a.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;
- (ii) one light chain comprising the LCDR1, LCDR2 and LDR3 of any one of the Factor X binding light chains disclosed in Table 1; and
- (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2b;

In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W83 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W88 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245,

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V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W204 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W206 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W207 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W140 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V245, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W196 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W206 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, V320, V305, V90, V141, V149, V155, V198, V202, V204, V212, V217, V241, V242, V245, V249, V281, V282, V283, V284, V285, V286, V287, V288, V289, V290, V296 or V196 disclosed in Table 2b.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (ii) and (iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V245, VL of V305, VL of V320, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some embodiments, the VL of (ii) and (iii) are the VL of W206 and V245, VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W83 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in

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V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W198 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W204 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W206 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W207 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W140 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a. In some embodiments, the VL of (ii) is the VL of W196 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4a.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W83 disclosed in

Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W88

disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of

W122 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the

VL of W127 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the

VL of W128 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W133 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some

embodiments, the VL of (ii) is the VL of W159 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245,

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VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W196 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b. In some embodiments, the VL of (ii) is the VL of W206 disclosed in Table 3, and the VL of (iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V155, VL of V198, VL of V202, VL of V204, VL of V212, VL of V217, VL of V241, VL of V242, VL of V245, VL of V249, VL of V281, VL of V282, VL of V283, VL of V284, VL of V285, VL of V286, VL of V287, VL of V288, VL of V289, VL of V290, VL of V296 or VL of V196 disclosed in Table 4b.

#### *Scaffold module – monospecific*

The monospecific scaffold module may comprise two identical light chains and two identical heavy chains. This allows for the expression of a single symmetrical molecular entity to be affinity purified from a culture media as one would with a monoclonal antibody.

In some embodiments, the scaffold module is an antibody or bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and
- (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a.

In some embodiments, the scaffold module is an antibody or bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

(ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V320, LCDR1, LCDR2 and LCDR3 of V305, LCDR1, LCDR2 and LCDR3 of V155, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a. In some embodiments, the VL of each of the two light chains is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of each of the two light chains is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a.

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b. In some embodiments, the VL of each of the two light chains is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of each of the two light chains is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V320, VL of V305, VL of V155, VL of V245, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b.

**Table 1: LCDRs of Factor X binding light chains**

| Identifier | LCDR1                         | LCDR2                   | LCDR3                             |
|------------|-------------------------------|-------------------------|-----------------------------------|
| W83        | SSNILTNNK<br>(SEQ ID NO: 9)   | AIS<br>(SEQ ID NO: 10)  | QSYDTSGHTLTAV<br>(SEQ ID NO: 11)  |
| W88        | QSVTTGY<br>(SEQ ID NO: 12)    | EAS<br>(SEQ ID NO: 13)  | QQVTRRSPWT<br>(SEQ ID NO: 14)     |
| W122       | SSNILTHRN<br>(SEQ ID NO: 15)  | GVS<br>(SEQ ID NO: 16)  | QSYDTSVKPMSAV<br>(SEQ ID NO: 17)  |
| W127       | SGSINNY<br>(SEQ ID NO: 18)    | NHN<br>(SEQ ID NO: 19)  | QSWTWSGEKV<br>(SEQ ID NO: 20)     |
| W128       | SGSINNY<br>(SEQ ID NO: 21)    | NHN<br>(SEQ ID NO: 22)  | QSWTWEGLKV<br>(SEQ ID NO: 23)     |
| W133       | SGSINNY<br>(SEQ ID NO: 24)    | NHN<br>(SEQ ID NO: 25)  | QSWSWEGLRV<br>(SEQ ID NO: 26)     |
| W159       | SGSINNY<br>(SEQ ID NO: 27)    | NHN<br>(SEQ ID NO: 28)  | QSWTWEGLKV<br>(SEQ ID NO: 29)     |
| W162       | SGSINNY<br>(SEQ ID NO: 30)    | NHN<br>(SEQ ID NO: 31)  | QSWTWEGLDV<br>(SEQ ID NO: 32)     |
| W189       | QSVTTGY<br>(SEQ ID NO: 33)    | DIS<br>(SEQ ID NO: 34)  | QQVTRRSPWT<br>(SEQ ID NO: 35)     |
| W198       | SGSINNY<br>(SEQ ID NO: 36)    | NHN<br>(SEQ ID NO: 37)  | QSWTWEGLKV<br>(SEQ ID NO: 38)     |
| W204       | SSNILTNNK<br>(SEQ ID NO: 39)  | AIS<br>(SEQ ID NO: 40)  | QSYDTGRRALTAV<br>(SEQ ID NO: 41)  |
| W206       | SGSINNY<br>(SEQ ID NO: 42)    | NHN<br>(SEQ ID NO: 43)  | QSWTWSGEKV<br>(SEQ ID NO: 44)     |
| W207       | HGSINNY<br>(SEQ ID NO: 45)    | NHN<br>(SEQ ID NO: 46)  | QSWTWEGLDV<br>(SEQ ID NO: 47)     |
| W140       | SSNILTNRN<br>(SEQ ID NO: 364) | GVS<br>(SEQ ID NO: 365) | QSYDIGGRSMTAV<br>(SEQ ID NO: 366) |
| W196       | SSNILTNRN<br>(SEQ ID NO: 367) | GVS<br>(SEQ ID NO: 368) | QSYDTGRRALTAV<br>(SEQ ID NO: 369) |

**Table 2a: LCDRs of Factor IXa binding light chains**

| Identifier | LCDR1                      | LCDR2                  | LCDR3                             |
|------------|----------------------------|------------------------|-----------------------------------|
| V43        | QAIHAH<br>(SEQ ID NO: 48)  | DNS<br>(SEQ ID NO: 49) | QQATFGHALST<br>(SEQ ID NO: 50)    |
| V90        | NIEAES<br>(SEQ ID NO: 51)  | TDS<br>(SEQ ID NO: 52) | QVRDSNDDRAV<br>(SEQ ID NO: 53)    |
| V141       | QKVDDDE<br>(SEQ ID NO: 54) | RAS<br>(SEQ ID NO: 55) | QQYNDPDLGYEDYT<br>(SEQ ID NO: 56) |
| V149       | QEVDDNE<br>(SEQ ID NO: 60) | GAS<br>(SEQ ID NO: 61) | QQYNDPDLGYDGYT<br>(SEQ ID NO: 62) |
| V155       | QSVDDDE<br>(SEQ ID NO: 63) | GAS<br>(SEQ ID NO: 64) | QQYNDPDLGYEGYT<br>(SEQ ID NO: 65) |
| V198       | NIEAET<br>(SEQ ID NO: 66)  | SDS<br>(SEQ ID NO: 67) | QVRDSVDDLIV<br>(SEQ ID NO: 68)    |
| V202       | NIEAET<br>(SEQ ID NO: 69)  | RDS<br>(SEQ ID NO: 70) | QVRDSVDDKAV<br>(SEQ ID NO: 71)    |
| V204       | NIEAET<br>(SEQ ID NO: 72)  | NDN<br>(SEQ ID NO: 73) | QVRDSNDDLIV<br>(SEQ ID NO: 74)    |
| V212       | NIEAES<br>(SEQ ID NO: 75)  | NDN<br>(SEQ ID NO: 76) | QVLLNDADEGV<br>(SEQ ID NO: 77)    |
| V217       | QNIVNH<br>(SEQ ID NO: 78)  | DNS<br>(SEQ ID NO: 79) | QQAPYGHALST<br>(SEQ ID NO: 80)    |
| V241       | NIEAET                     | NDS                    | QVRDSNDDKIV                       |

|      |                            |                         |                                  |
|------|----------------------------|-------------------------|----------------------------------|
|      | (SEQ ID NO: 81)            | (SEQ ID NO: 82)         | (SEQ ID NO: 83)                  |
| V242 | NIEAET<br>(SEQ ID NO: 84)  | NDN<br>(SEQ ID NO: 85)  | QVRDSVDDLAV<br>(SEQ ID NO: 86)   |
| V245 | NIEAET<br>(SEQ ID NO: 87)  | SDS<br>(SEQ ID NO: 88)  | QVRDSIDDLIV<br>(SEQ ID NO: 89)   |
| V249 | NIEAET<br>(SEQ ID NO: 90)  | SDS<br>(SEQ ID NO: 91)  | GVLLNDADEGF<br>(SEQ ID NO: 92)   |
| V281 | NIEAET<br>(SEQ ID NO: 93)  | SDN<br>(SEQ ID NO: 94)  | TLRDSNDDRAL<br>(SEQ ID NO: 95)   |
| V282 | NIEAET<br>(SEQ ID NO: 96)  | SDS<br>(SEQ ID NO: 97)  | GVRDSNDDRAL<br>(SEQ ID NO: 98)   |
| V283 | NIEAET<br>(SEQ ID NO: 99)  | RDN<br>(SEQ ID NO: 100) | SIRDSNDDRAL<br>(SEQ ID NO: 101)  |
| V284 | NIEAET<br>(SEQ ID NO: 102) | SDN<br>(SEQ ID NO: 103) | QVRDSNDDRRAV<br>(SEQ ID NO: 104) |
| V285 | NIEAET<br>(SEQ ID NO: 105) | SDS<br>(SEQ ID NO: 106) | QVRDSNDDRRAV<br>(SEQ ID NO: 107) |
| V286 | NIEAET<br>(SEQ ID NO: 108) | NDN<br>(SEQ ID NO: 109) | GTRDSNDDRRAV<br>(SEQ ID NO: 110) |
| V287 | NIEAET<br>(SEQ ID NO: 111) | SDN<br>(SEQ ID NO: 112) | GLRDSNDDRRAV<br>(SEQ ID NO: 113) |
| V288 | NIEAET<br>(SEQ ID NO: 114) | SDS<br>(SEQ ID NO: 115) | QVRDSNDDRRAV<br>(SEQ ID NO: 116) |
| V289 | NIEAET<br>(SEQ ID NO: 117) | SDS<br>(SEQ ID NO: 118) | SVRDSNDDRRAV<br>(SEQ ID NO: 119) |
| V290 | NIEAET<br>(SEQ ID NO: 120) | SDN<br>(SEQ ID NO: 121) | TVRDSNDDRRAV<br>(SEQ ID NO: 122) |
| V296 | NIEAET<br>(SEQ ID NO: 123) | NDN<br>(SEQ ID NO: 124) | YLRDSVDDLAR<br>(SEQ ID NO: 125)  |
| V196 | NIEAET<br>(SEQ ID NO: 287) | RDS<br>(SEQ ID NO: 288) | QVRDSNDDRRAV<br>(SEQ ID NO: 289) |

**Table 2b: LCDRs of Factor IXa binding light chains**

| Identifier | LCDR1                      | LCDR2                  | LCDR3                             |
|------------|----------------------------|------------------------|-----------------------------------|
| V43        | QAIHAH<br>(SEQ ID NO: 48)  | DNS<br>(SEQ ID NO: 49) | QQATFGHALST<br>(SEQ ID NO: 50)    |
| V90        | NIEAES<br>(SEQ ID NO: 51)  | TDS<br>(SEQ ID NO: 52) | QVRDSNDDRRAV<br>(SEQ ID NO: 53)   |
| V141       | QKVDDDE<br>(SEQ ID NO: 54) | RAS<br>(SEQ ID NO: 55) | QQYNPDPLGYEDYT<br>(SEQ ID NO: 56) |
| V149       | QEVDDNE<br>(SEQ ID NO: 60) | GAS<br>(SEQ ID NO: 61) | QQYNPDPLGYDGYT<br>(SEQ ID NO: 62) |
| V155       | QSVDDDE<br>(SEQ ID NO: 63) | GAS<br>(SEQ ID NO: 64) | QQYNPDPLGYEGYT<br>(SEQ ID NO: 65) |
| V198       | NIEAET<br>(SEQ ID NO: 66)  | SDS<br>(SEQ ID NO: 67) | QVRDSVDDLIV<br>(SEQ ID NO: 68)    |
| V202       | NIEAET<br>(SEQ ID NO: 69)  | RDS<br>(SEQ ID NO: 70) | QVRDSVDDKAV<br>(SEQ ID NO: 71)    |
| V204       | NIEAET<br>(SEQ ID NO: 72)  | NDN<br>(SEQ ID NO: 73) | QVRDSNDDLIV<br>(SEQ ID NO: 74)    |
| V212       | NIEAES<br>(SEQ ID NO: 75)  | NDN<br>(SEQ ID NO: 76) | QVLLNDADEGV<br>(SEQ ID NO: 77)    |
| V217       | QNIVNH<br>(SEQ ID NO: 78)  | DNS<br>(SEQ ID NO: 79) | QQAPYGHALST<br>(SEQ ID NO: 80)    |
| V241       | NIEAET<br>(SEQ ID NO: 81)  | NDS<br>(SEQ ID NO: 82) | QVRDSNDDKIV<br>(SEQ ID NO: 83)    |

|      |                            |                         |                                  |
|------|----------------------------|-------------------------|----------------------------------|
| V242 | NIEAET<br>(SEQ ID NO: 84)  | NDN<br>(SEQ ID NO: 85)  | QVRDSVDDLAV<br>(SEQ ID NO: 86)   |
| V245 | NIEAET<br>(SEQ ID NO: 87)  | SDS<br>(SEQ ID NO: 88)  | QVRDSIDDLIV<br>(SEQ ID NO: 89)   |
| V249 | NIEAET<br>(SEQ ID NO: 90)  | SDS<br>(SEQ ID NO: 91)  | GVLLNDADEGF<br>(SEQ ID NO: 92)   |
| V281 | NIEAET<br>(SEQ ID NO: 93)  | SDN<br>(SEQ ID NO: 94)  | TLRDSNDDRAL<br>(SEQ ID NO: 95)   |
| V282 | NIEAET<br>(SEQ ID NO: 96)  | SDS<br>(SEQ ID NO: 97)  | GVRDSNDDRAL<br>(SEQ ID NO: 98)   |
| V283 | NIEAET<br>(SEQ ID NO: 99)  | RDN<br>(SEQ ID NO: 100) | SIRDSNDDRAL<br>(SEQ ID NO: 101)  |
| V284 | NIEAET<br>(SEQ ID NO: 102) | SDN<br>(SEQ ID NO: 103) | QVRDSNDDRRAV<br>(SEQ ID NO: 104) |
| V285 | NIEAET<br>(SEQ ID NO: 105) | SDS<br>(SEQ ID NO: 106) | QVRDSNDDRRAV<br>(SEQ ID NO: 107) |
| V286 | NIEAET<br>(SEQ ID NO: 108) | NDN<br>(SEQ ID NO: 109) | GTRDSNDDRRAV<br>(SEQ ID NO: 110) |
| V287 | NIEAET<br>(SEQ ID NO: 111) | SDN<br>(SEQ ID NO: 112) | GLRDSNDDRRAV<br>(SEQ ID NO: 113) |
| V288 | NIEAET<br>(SEQ ID NO: 114) | SDS<br>(SEQ ID NO: 115) | QVRDSNDDRRAV<br>(SEQ ID NO: 116) |
| V289 | NIEAET<br>(SEQ ID NO: 117) | SDS<br>(SEQ ID NO: 118) | SVRDSNDDRRAV<br>(SEQ ID NO: 119) |
| V290 | NIEAET<br>(SEQ ID NO: 120) | SDN<br>(SEQ ID NO: 121) | TVRDSNDDRRAV<br>(SEQ ID NO: 122) |
| V296 | NIEAET<br>(SEQ ID NO: 123) | NDN<br>(SEQ ID NO: 124) | YLRDSVDDLAR<br>(SEQ ID NO: 125)  |
| V196 | NIEAET<br>(SEQ ID NO: 287) | RDS<br>(SEQ ID NO: 288) | QVRDSNDDRRAV<br>(SEQ ID NO: 289) |
| V305 | NIEAES<br>(SEQ ID NO: 370) | NDN<br>(SEQ ID NO: 371) | QVLLNDADQGV<br>(SEQ ID NO: 372)  |
| V320 | NIEAES<br>(SEQ ID NO: 373) | NDN<br>(SEQ ID NO: 374) | QVLLNDADQGV<br>(SEQ ID NO: 375)  |

**Table 3: VL of Factor X binding light chains**

| Identifier | VL                                                                                                                                    |
|------------|---------------------------------------------------------------------------------------------------------------------------------------|
| W83        | QSVLTQPPSVSGAPGQRTISCTGSSSNILTNKNVHWYQQLPGTAPKLLIYAIRRPSGVPDR<br>FSGSKSGTSASLAITGLQAEDEADYYCQSYDTSGLTLTAVFGGGTKLTVL (SEQ ID NO: 126)  |
| W88        | EIVLTQSPGTLSPGERATLSCRASQSVTTGYLAWYQQKPGQAPRLIYEASKRATGIPDRFS<br>GSGSGTDFTLTISRLEPEDFAVYYCQQVTRRSPWTFGGGTKVEIK (SEQ ID NO: 127)       |
| W122       | QSVLTQPPSVSGAPGQRTISCTGSSSNILTHRNHWYQQLPGTAPKLLIYGVS KRPSGVPDR<br>FSGSKSGTSASLAITGLQAEDEADYYCQSYDTSVKPMSAVFGGGTKLTVL (SEQ ID NO: 128) |
| W127       | NFMLTQPHSVSESPGKTVTISCTRSSGSINYYYQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWSGEKVFVGGGTKLTVL (SEQ ID NO: 129)   |
| W128       | NFMLTQPHSVSESPGKTVTISCTRSSGSINYYYQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWEGKLVFVGGGTKLTVL (SEQ ID NO: 130)   |
| W133       | NFMLTQPHSVSESPGKTVTISCTRSSGSINYYYQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWEGRLVFVGGGTKLTVL (SEQ ID NO: 131)   |
| W159       | NFMLTQPHSVSESPGKTVTISCTRSSGSINYYYQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWEGAKLVFVGGGTKLTVL (SEQ ID NO: 132)  |
| W162       | NFMLTQPHSVSESPGKTVTISCTRSSGSINYYYQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWEGDLVFVGGGTKLTVL (SEQ ID NO: 133)   |
| W189       | EIVLTQSPGTLSPGERATLSCRASQSVTTGYLAWYQQKPGQAPRLIYDISRRATGIPDRFS<br>GSGSGTDFTLTISRLEPEDFAVYYCQQVTRRSPWTFGGGTKVEIK (SEQ ID NO: 134)       |

|      |                                                                                                                                       |
|------|---------------------------------------------------------------------------------------------------------------------------------------|
| W198 | NFMLTQPHSVSESPGKTVTISCTRSSGSIISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEADYYCQSWTWEGLKVFGGGTKLTVL (SEQ ID NO: 135)     |
| W204 | QSVLTQPPSVSGAPGQRVTISCTGSSSNILTNKNVHWYQQLPGTAPKLLIYASRRPSGVPDR<br>FSGSKSGTSASLAITGLQAEDADYYCQSYDTGRRALTAVFGGGTKLTVL (SEQ ID NO: 136)  |
| W206 | NFMLTQPHSVSESPGKTVTISCTRSSGSIISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEADYYCQSWTWSGEKVFGGGTKLTVL (SEQ ID NO: 137)     |
| W207 | NFMLTQPHSVSESPGKTVTISCTRPHGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEADYYCQSWTWEGLVFGGGTKLTVL (SEQ ID NO: 138)       |
| W140 | QSVLTQPPSVSGAPGQRVTISCTGSSSNILTNKNVHWYQQLPGTAPKLLIYGVSNRPSGVPDR<br>FSGSKSGTSASLAITGLQAEDADYYCQSYDIGGRSMTAVFGGGTKLTVL (SEQ ID NO: 290) |
| W196 | QSVLTQPPSVSGAPGQRVTISCTGSSSNILTNKNVHWYQQLPGTAPKLLIYGVSNRPSGVPDR<br>FSGSKSGTSASLAITGLQAEDADYYCQSYDTGRRALTAVFGGGTKLTVL (SEQ ID NO: 291) |

**Table 4a: VL of Factor IXa binding light chains**

| Identifier | VL                                                                                                                                  |
|------------|-------------------------------------------------------------------------------------------------------------------------------------|
| V43        | DIQLTQSPSFLSASVGDRTITCRASQAIHAHLRWYQQKPGKAPKLLIYDNSPLQSGVPSRFS<br>GSGSGTEFTLTISLQPEDFATYYCQATFGHALSTFGQGTKEIK (SEQ ID NO: 139)      |
| V90        | SYVLTQPPSVSVAPGKTAILTCGGDNIEAESVHWYQQKPDQAPLLVYTDYSRPSGIPERFSG<br>SNSGNTATLTITRVEVGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 140)    |
| V141       | EIVLTQSPGTLSPGERATLSCRASQKVDDELAWYQQKPGQAPRLIYASNRATGIPDRF<br>SGSGSGTDFLTISRLEPEDFAVYYCQYNDPDLGYEDYTFGQGTKEIK (SEQ ID NO: 141)      |
| V149       | EIVLTQSPGTLSPGERATLSCRASQEVDDNELAWYQQKPGQAPRLIYGASSRATGIPDRF<br>SGSGSGTDFLTISRLEPEDFAVYYCQYNDPDLGYDGYTFGQGTKEIK (SEQ ID NO: 143)    |
| V155       | EIVLTQSPGTLSPGERATLSCRASQSVDDDELAWYQQKPGQAPRLIYGASSRATGIPDRF<br>SGSGSGTDFLTISRLEPEDFAVYYCQYNDPDLGYEGYTFGQGTKEIK (SEQ ID NO: 144)    |
| V198       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSIRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSVDDLYVFGGGTKLTVL (SEQ ID NO: 145)   |
| V202       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSVDDKAVFGGGTKLTVL (SEQ ID NO: 146)    |
| V204       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDLIVFGGGTKLTVL (SEQ ID NO: 147)   |
| V212       | SYVLTQPPSVSVAPGKTARITCGGDNIEAESVHWYQQKPGQAPVLVIYNDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVLLNDADEGVFGGGTKLTVL (SEQ ID NO: 148)   |
| V217       | DIQLTQSPSFLSASVGDRTITCRASQIVNHLRWYQQKPGKAPKLLIYDNSPLQSGVPSRFS<br>GSGSGTEFTLTISLQPEDFATYYCQAPYGHALSTFGQGTKEIK (SEQ ID NO: 149)       |
| V241       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNTPTGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDKIVFGGGTKLTVL (SEQ ID NO: 150)   |
| V242       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNIWETGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSVDDLAVFGGGTKLTVL (SEQ ID NO: 151)   |
| V245       | SYVLTQPPSVSVAPGKTARITCRGDNIEAETVGWYQQKPGQAPVLVIYSDSVRMSGIPERFSG<br>SNSWNTATLTISRVEAGDEADYYCQVRDSIDDLIVFGGGTKLTVL (SEQ ID NO: 152)   |
| V249       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGVLLNDADEGFFFGGGTKLTVLG (SEQ ID NO: 153) |
| V281       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCTLRDSNDDRALFGGGTKLTVL (SEQ ID NO: 154)   |
| V282       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGVRDSNDDRALFGGGTKLTVL (SEQ ID NO: 155)   |
| V283       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRDNIIRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCSIRDSNDDRALFGGGTKLTVL (SEQ ID NO: 156)  |
| V284       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRFVIGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 157)  |
| V285       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSILTVGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 158)   |
| V286       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGTRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 159)   |
| V287       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG                                                                     |

|      |                                                                                                                                   |
|------|-----------------------------------------------------------------------------------------------------------------------------------|
|      | SNSGNTATLTISRVEAGDEADYYCGLRDSNDDRAMFGGGTKLTVL (SEQ ID NO: 160)                                                                    |
| V288 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRNLGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 161) |
| V289 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCSVRDSNDDRAMFGGGTKLTVL (SEQ ID NO: 162) |
| V290 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCTVRDSNDDRASFGGGTKLTVL (SEQ ID NO: 163) |
| V296 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCYLRDSVDDLARFGGGTKLTVL (SEQ ID NO: 164) |
| V196 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 292)  |

**Table 4b: VL of Factor IXa binding light chains**

| Identifier | VL                                                                                                                                   |
|------------|--------------------------------------------------------------------------------------------------------------------------------------|
| V43        | DIQLTQSPSFLSASVGDRTITCRASQAIHAHLRWYQQKPGKAPKLLIYDNSPLQSGVPSRFS<br>GSGSGTEFTLTISLQPEDFATYYCQATFGHALSTFGQGTKEIK (SEQ ID NO: 139)       |
| V90        | SYVLTQPPSVSVAPGKTAILTCGGDNIEAESVHWYQQKPDQAPLLVYTDYSRPSGIPERFSG<br>SNSGNTATLTITRVEVGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 140)     |
| V141       | EIVLTQSPGTLISLSPGERATLSCRASQKVDDDELAWYQQKPGQAPRLIYRASNRATGIPDRF<br>SGSGSGTDFTLTISRLEPEDFAVYYCQYNDPDLGYEDYTFGQGTKEIK (SEQ ID NO: 141) |
| V149       | EIVLTQSPGTLISLSPGERATLSCRASQEVDDNELAWYQQKPGQAPRLIYGASSRATGIPDRF<br>SGSGSGTDFTLTISRLEPEDFAVYYCQYNDPDLGYDGYTFGQGTKEIK (SEQ ID NO: 143) |
| V155       | EIVLTQSPGTLISLSPGERATLSCRASQSVDDDELAWYQQKPGQAPRLIYGASSRATGIPDRF<br>SGSGSGTDFTLTISRLEPEDFAVYYCQYNDPDLGYEGYTFGQGTKEIK (SEQ ID NO: 144) |
| V198       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSIRPSGIPERFSGS<br>NSGNTATLTISRVEAGDEADYYCQVRDSVDDLYVFGGGTKLTVL (SEQ ID NO: 145)    |
| V202       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSVDDKAVFGGGTKLTVL (SEQ ID NO: 146)     |
| V204       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDLIVFGGGTKLTVL (SEQ ID NO: 147)    |
| V212       | SYVLTQPPSVSVAPGKTARITCGGDNIEAESVHWYQQKPGQAPVLVIYNDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVLLNDADEGVFGGGTKLTVL (SEQ ID NO: 148)    |
| V217       | DIQLTQSPSFLSASVGDRTITCRASQNIWNHLRWYQQKPGKAPKLLIYDNSPLQSGVPSRFS<br>GSGSGTEFTLTISLQPEDFATYYCQAPYGHALSTFGQGTKEIK (SEQ ID NO: 149)       |
| V241       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYDNSNTPTGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDKIVFGGGTKLTVL (SEQ ID NO: 150)    |
| V242       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNIWETGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSVDDLAVFGGGTKLTVL (SEQ ID NO: 151)    |
| V245       | SYVLTQPPSVSVAPGKTARITCRGDNIEAETVGWYQQKPGQAPVLVIYSDSVRMSGIPERFSG<br>SNSWNTATLTISRVEAGDEADYYCQVRDSIDDLIVFGGGTKLTVL (SEQ ID NO: 152)    |
| V249       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGVLLNDADEGFFGGGKLTVLG (SEQ ID NO: 153)    |
| V281       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCTLRDSNDDRALFGGGTKLTVL (SEQ ID NO: 154)    |
| V282       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGVRDSNDDRALFGGGTKLTVL (SEQ ID NO: 155)    |
| V283       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRDNIRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCSIRDSNDDRALFGGGTKLTVL (SEQ ID NO: 156)    |
| V284       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRVFGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 157)    |
| V285       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSILTVGIPERFSGS<br>NSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 158)    |
| V286       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCGTRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 159)    |
| V287       | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG                                                                      |

|      |                                                                                                                                   |
|------|-----------------------------------------------------------------------------------------------------------------------------------|
|      | SNSGNTATLTISRVEAGDEADYYCGLRDSNDDRAMFGGGTKLTVL (SEQ ID NO: 160)                                                                    |
| V288 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRNLGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 161) |
| V289 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDSNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCSVRDSNDDRAMFGGGTKLTVL (SEQ ID NO: 162) |
| V290 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYSDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCTVRDSNDDRASFGGGTKLTVL (SEQ ID NO: 163) |
| V296 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYNDNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCYLRDSVDDLARFGGGTKLTVL (SEQ ID NO: 164)  |
| V196 | SYVLTQPPSVSVAPGKTARITCGGDNIEAETVHWYQQKPGQAPVLVIYRSDRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSNDDRAVFGGGTKLTVL (SEQ ID NO: 292)  |
| V305 | SYVLTQPPSVSVAPGKTARITCGGDNIEAESVHWYQQKPGQAPVLVIYNDNNRPSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVLLNDADQGVFGGGTKLTVL (SEQ ID NO: 376) |
| V320 | SYVLTQPPSVSVAPGKTARITCRGDNIEAETVGWYQQKPGQAPVLVIYSDSVRMSGIPERFSG<br>SNSGNTATLTISRVEAGDEADYYCQVRDSIDDLIVFGGGTKLTVL (SEQ ID NO: 377) |

In some embodiments, the scaffold module is an antibody or a bivalent fragment thereof that comprises a modified hinge domain wherein a linker is inserted between the CH1 and CH2 domain of the antibody. In some embodiments, the scaffold module comprises two identical heavy chains comprising SEQ ID NO: 5 wherein a linker is inserted between residue C219 and D220 of SEQ ID NO: 5. In some embodiments, the scaffold module comprises two identical heavy chains comprising SEQ ID NO: 5 wherein a flexible linker is inserted between residue C219 and D220 of SEQ ID NO: 5.

In some embodiments, the scaffold module comprises two identical heavy chains comprising SEQ ID NO: 5 wherein 1, 2, 3 or 4 repeats of GGGGS (SEQ ID NO: 6) or GSAGSAAGSGEF (SEQ ID NO: 7) is inserted between residue C219 and D220 of SEQ ID NO: 5. In some embodiments, the scaffold module comprises two identical heavy chains comprising SEQ ID NO: 5 wherein GGGSGGGSGGGSGGGGS (SEQ ID NO: 8) or GSAGSAAGSGEF (SEQ ID NO: 7) is inserted between residue C219 and D220 of SEQ ID NO: 5.

### Linker

In some embodiments, the first and, optionally, any further binding module is attached to the scaffold module. Any linker can be employed to attach the one or more binding module(s) to the scaffold module. The skilled person is aware of a number of different linkers which could be used.

In some embodiments, the linker is a chemical linker or a peptide linker. In some embodiments, the linker is a peptide linker.

Methods of designing a suitable peptide linker are known in the art (Chen et al., 2013. Adv Drug Deliv Rev. 65(10):1357-1369). In particular, peptide linkers can be classified as flexible or rigid depending on the sequence and structure of the linker. In some embodiments, at

least one or all of the linker(s) is or are a flexible peptide linker. According to the findings of the present invention, flexible linkers provide an advantage in a thrombin generation assay in comparison to more rigid linkers.

- 5 In some embodiments, the linker is cleavable. For example, the linker may comprise a disulfide bond or a protease cleavage site. In some embodiments, the linker comprises a thrombin or Factor Xa cleavage site.

In some embodiments, the linker is selected from Table 5. In some embodiments, the linker  
10 is a flexible linker selected from Table 5.

**Table 5: Linker sequences**

| Linker type | SEQ ID NO | Sequence                              |
|-------------|-----------|---------------------------------------|
| Flexible    | 167       | GGGGS                                 |
| Flexible    | 168       | GGG                                   |
| Flexible    | 169       | GGGGG                                 |
| Flexible    | 170       | GGGSGGGGS                             |
| Flexible    | 171       | GGGSGGGSGGGGS                         |
| Flexible    | 8         | GGGSGGGSGGGSGGGGS                     |
| Flexible    | 7         | GSAGSAAGSGEF                          |
| Rigid       | 172       | AEAAAKEAAAKEAAKALEAEAAAKEAAAKEAAKA    |
| Rigid       | 173       | GGGAEEAAKEAAAKEAAKALEAEAAAKEAAAKEAAKA |
| Rigid       | 174       | EAAAKEAAAKEAAAK                       |
| Rigid       | 175       | GGGEAAAKEAAAKEAAAK                    |
| Rigid       | 176       | APAPAPAPAPAPAPAPAPAP                  |
| Rigid       | 177       | GGGAPAPAPAPAPAPAPAPAPAP               |

In some embodiments, the linker comprises SEQ ID NO: 8.

15 In some embodiments, the linker comprises or consists of SEQ ID NO: 168 or SEQ ID NO: 169. This may be preferable because a short linker which cannot be post-translationally modified during protein expression would result in a reduced heterogeneity and improve the developability of the proteinaceous molecule as a drug.

### *Binding modules*

20 The proteinaceous molecules of the present invention may comprise one or more binding modules. The binding modules may increase the number of antigen-binding sites on the proteinaceous molecule that bind to Factor IXa/Factor X, or they may add a further specificity  
25 making the proteinaceous molecule multispecific, e.g. trispecific.

In some embodiments, the antigen-binding site of the binding module binds to Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C,

Protein S, Factor II (prothrombin), Factor V, Factor VII, Factor IX, Factor IXa, Factor X, Factor Xa, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin,  $\beta_2$ -glycoprotein I, CD61, GPIb-IX, CD69, CD40, collagen chaperone HSP47, ephrin B1, thiol isomerase protein ERP5, Hematopoietic progenitor kinase 1-interacting protein of 55 (HIP-55), glycoprotein VI, platelet glycoprotein 1b, platelet-derived growth factor receptor, platelet endothelial aggregation receptor I, CD36, CD31, MARKS, multimerin, integrin alpha IIb/beta 3, triggering receptor expressed on myeloid cells (TREM) like transcript-1 (TLT-1), integrin-linked kinase (ILK), zyxin, collagen, P-selectin, Factor XIII, P-selectin glycoprotein ligand-1, integrin alpha 6 beta 1, thrombospondin, von Willebrand factor, G6B, CD42b, syntaxin binding protein 2, phosphatidylethanolamine, fibrinogen/fibrin, filamin, stomatin, sphingolipid, CD63, CD41, CD49b, CD107a, CD107b, CD42c, CD42, CD109, CD62P, CD154, PECAM-1, or ERPS.

Thus, in some embodiments, the antigen-binding site of the binding module binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

In some embodiments, the phosphatidylserine-binding protein is Protein C, Protein Z, Protein S, Tissue Factor, Factor II (prothrombin), Factor V, Factor VII, Factor VIII, Factor IX, Factor IXa, Factor X, Factor Xa, Mer, LOX-1,  $\alpha_5\beta_3$  integrin, lactadherin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an oxysterol binding protein, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I.

In some embodiments, the binding module binds to a platelet surface marker, wherein the platelet surface marker is CD61, GPIb-IX, CD69, CD40, collagen chaperone HSP47, ephrin B1, thiol isomerase protein ERP5, Hematopoietic progenitor kinase 1-interacting protein of 55 (HIP-55), glycoprotein VI, platelet glycoprotein 1b, platelet-derived growth factor receptor, platelet endothelial aggregation receptor I, CD36, CD31, MARKS, multimerin, integrin alpha IIb/beta 3, triggering receptor expressed on myeloid cells (TREM) like transcript-1 (TLT-1), integrin-linked kinase (ILK), zyxin, collagen, P-selectin, Factor XIII, P-selectin glycoprotein ligand-1, integrin alpha 6 beta 1, thrombospondin, von Willebrand factor, G6B, CD42b, syntaxin binding protein 2, phosphatidylethanolamine, fibrinogen/fibrin, filamin, stomatin, sphingolipid, CD63, CD41, CD49b, CD107a, CD107b, CD42c, CD42, CD109, CD62P, CD154, PECAM-1, or ERPS.

The binding module may be linked to the scaffold module through a linker or may be inserted into a loop region present in the scaffold module. In some embodiments, the scaffold module is an IgG or bivalent fragment thereof and the binding module is attached to the C- or N-

terminus of a light or heavy chain. In some embodiments, the binding module is inserted between the CH1 and CH2 domain, i.e. around the hinge region. In some embodiments, the scaffold module is an antibody or bivalent fragment thereof comprising a heavy and a light chain and the binding module is attached to the C- or N-terminus of the light or heavy chain.

- 5 In some embodiments, the scaffold module is an antibody or bivalent fragment thereof comprising two heavy and two light chains and the binding module is attached to the C- or N-terminus of a light or heavy chain.

*Binding modules that bind to Factor IXa or Factor X*

- 10 In some embodiments, the antigen-binding site of the binding module binds to Factor IXa or Factor X.

In some embodiments, the binding module is an anticalin, repebody, monobody, scFv, Fab, scFab, affibody, fynomer, DARPin, nanobody, peptide aptamer, or nucleic acid aptamer. In

- 15 some embodiments, the binding module is a scFv or scFab. In some embodiments, the binding module is a scFv.

In some embodiments, the binding module is a scFv or scFab that comprises (i) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or  
20 the Factor IXa binding light chains disclosed in Table 2a, and (ii) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3. In some embodiments, the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

- 25 In some embodiments, the binding module is a scFv or scFab that comprises (i) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and (ii) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3. In some embodiments, the LCDR1, LCDR2 and LCDR3 are that of V198, W206,  
30 W198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

In some embodiments, the binding module is a scFv or scFab that comprises (i) the VL of any one of the Factor X binding light chains disclosed in Table 3 or the Factor IXa binding light chains disclosed in Table 4a, and (ii) SEQ ID NO: 4 (VH domain). In some  
35 embodiments, (i) is the VL of V198, V202, W128, W88, W127, V212 or W162 of Tables 3 and 4a.

In some embodiments, the binding module is a scFv or scFab that comprises (i) the VL of any one of the Factor X binding light chains disclosed in Table 3 or the Factor IXa binding light chains disclosed in Table 4b, and (ii) SEQ ID NO: 4 (VH domain). In some embodiments, (i) is the VL of V198, W206, W198, V202, W128, W88, W127, V212, or W162 of Tables 3 and 4b.

In some embodiments, the binding module is a scFv that comprises (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SYVLTQPPSVSVAPGKTARITCGGD (SEQ ID NO: 179), FW2 is VHWHYQQKPGQAPVLIY (SEQ ID NO: 180), FW3 is DRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYC (SEQ ID NO: 181) and FW4 is FGCGTKLTVL (SEQ ID NO: 182), and (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183. In some embodiments, the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

In some embodiments, the binding module is a scFv that comprises (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SYVLTQPPSVSVAPGKTARITCGGD (SEQ ID NO: 179), FW2 is VHWHYQQKPGQAPVLIY (SEQ ID NO: 180), FW3 is DRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYC (SEQ ID NO: 181) and FW4 is FGCGTKLTVL (SEQ ID NO: 182), and (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183. In some embodiments, the LCDR1, LCDR2 and LCDR3 are that of V198, W206, W198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

SEQ ID NO: 183

EVQLLESQGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWWSAISGSGGSTYY  
ADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSS

#### *Binding modules that bind to other targets*

In some embodiments, the binding module binds to phosphatidylserine, a platelet surface marker, or a phosphatidylserine-binding protein, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin,

the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta$ 2-glycoprotein I.

In some embodiments, the binding module binds to a target associated with a site of injury (e.g. von Willebrand factor (VWF), fibrinogen or collagen) in order to localize the proteinaceous molecule to the site of injury, instead of or in addition to binding to phosphatidylserine, a platelet surface marker or a phosphatidylserine-binding protein as mentioned above.

10 In some embodiments, the binding module is an anticalin, repebody, monobody, scFv, Fab, scFab, affibody, fynomer, DARPin, nanobody, peptide aptamer, or nucleic acid aptamer. In some embodiments, the binding module is a scFv or scFab. In some embodiments, the binding module is a scFv.

15 In some embodiments, the binding module is a scFv or scFab that comprises a VL domain and a VH domain, wherein the VL domain comprises LCDR1, LCDR2 and LCDR3 and the VH domain comprises HCDR1, HCDR2 and HCDR3, wherein:

- (i) LCDR1 is QDIGSS (SEQ ID NO: 293), LCDR2 is ATS (SEQ ID NO: 294), LCDR3 is LQYVSSPPT (SEQ ID NO: 295), HCDR1 is GYSFTGYN (SEQ ID NO: 296), HCDR2 is IDPYYGDT (SEQ ID NO: 297) and HCDR3 is VKGGYYGHWYFDV (SEQ ID NO: 298);
- 20 (ii) LCDR1 is SLRSYY (SEQ ID NO: 299), LCDR2 is GKN (SEQ ID NO: 300), LCDR3 is NSSKIPRRMVV (SEQ ID NO: 301), HCDR1 is GFTFSSYA (SEQ ID NO: 302), HCDR2 is INGSGGST (SEQ ID NO: 303) and HCDR3 is AKTRRKVFDY (SEQ ID NO: 304); or
- (iii) LCDR1 is GNIHNY (SEQ ID NO: 305), LCDR2 is NAK (SEQ ID NO: 306), LCDR3 is QHFWSTPYT (SEQ ID NO: 307), HCDR1 is GFTFSSYI (SEQ ID NO: 308), HCDR2 is IRSGGDNT (SEQ ID NO: 309) and HCDR3 is AIYYGNYGGLAY (SEQ ID NO: 310).
- 25

In some embodiments, the binding module is a scFv or scFab that comprises a VL domain and a VH domain, wherein the VL domain is selected from SEQ ID NO: 184, SEQ ID NO: 185 or SEQ ID NO: 186 and the VH domain is selected from SEQ ID NO: 187, SEQ ID NO: 188 or SEQ ID NO: 189. In some embodiments, the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187, the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

35

SEQ ID NO: 184 (VL of bavituximab)

DIQMTQSPSSLSASLGERVSLTCRASQDIGSSLNWLQQGPDGTIKRLIYATSSLD SGV PKRF  
SGSRSGSDYSLTISSLESEDFVDYYCLQYVSSPPTFGCGTKLELKRADAAP

SEQ ID NO: 185 (VL of PS72)

5 SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLLVIYGKNNRPSGIPDRF  
SGSSSGNTASLTITGAQAEDEADYYCNSSKIPRRMVVFGCGTKLTVL

SEQ ID NO: 186 (VL of anti-LIBS)

DILMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQKSPQLLVYNAKTLADGVPSRF  
10 SGSGSGTQYSLKINSLQPEDFGSYQCQHFWSPTYTFGCGTKLEIKRADAAP

SEQ ID NO: 187 (VH of bavituximab)

EVQLQQSGPELEKPGASVKLSCKASGYSFTGYNMNWWKQSHGKCLEWIGHIDPYYGDTSY  
NQKFRGKATLTVDKSSSTAYMQLKSLTSEDSAVYYCVKGGYYGHWFYFDVWGAGTTTVTVSS  
15

SEQ ID NO: 188 (VH of PS72)

EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWWSAINGSGGSTYY  
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKTRRKVFDYWGQGTLVTVSS

20 SEQ ID NO: 189 (VH of anti-LIBS)

QVQLQQSGGGLVKPGGSLKLSCAASGFTFSSYIMSWVRQTPEKCLEWWATIRSGGDNTYY  
PDSVKGRFTISRDN AKNKLYLQMSSLRSED TALYYCAIYYGNYGGLAYWGQGTLVTVSA

In some embodiments, the binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID  
25 NO: 192.

Bavituximab:

EVQLQQSGPELEKPGASVKLSCKASGYSFTGYNMNWWKQSHGKCLEWIGHIDPYYGDTSY  
NQKFRGKATLTVDKSSSTAYMQLKSLTSEDSAVYYCVKGGYYGHWFYFDVWGAGTTTVTVSS  
30 GGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASLGERVSLTCRASQDIGSSLNWLQQ  
GPDGTIKRLIYATSSLD SGV PKRFSGSRSGSDYSLTISSLESEDFVDYYCLQYVSSPPTFGC  
GTKLELKRADAAP (SEQ ID NO: 190)

PS72

35 EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWWSAINGSGGSTYY  
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKTRRKVFDYWGQGTLVTVSSGGG  
GSGGGGSGGGGSGGGGSSSEL TQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQ

APVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSSSKIPRRMVVFSGGT  
KLTVL (SEQ ID NO: 191)

#### Anti-LIBS

- 5 QVQLQQSGGGLVKPGGSLKLSAASGFTFSSYIMSWVRQTPEKCLEWVATIRSGGDNTYY  
PDSVKGRFTISRDNANKLYLQMSSLRSEDALYYCAIYYGNYGGGLAYWGQGTLVTVSAGG  
GGSGGGGSGGGGSGGGGSDILMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQG  
KSPQLLVYNAKTLADGVPSRFSGSGSGTQYSLKINSLQPEDFGSYQCQHFWSPTPYTFGCGT  
KLEIK (SEQ ID NO: 192)

10

In some embodiments, the binding module is a scFv, scFab or Fab comprising the VH and VL domain of any one of 1-13 according to Table 6.

**Table 6: VL and VH sequences of humanized bavituximab constructs**

|   | VH sequence                                                                                                                                        | VL sequence                                                                                                                            |
|---|----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 1 | EVQLQQSGPELEKPGASVKLSCKASGYSTGYNMNW<br>VKQSHGKSLEWIGHIDPYGDTSYNQKFRGKATLTV<br>KSSSTAYMQLKSLTSEDSAVYYCVKGGYYGHWYFDV<br>WGAGTTVTVSS (SEQ ID NO: 311) | DIQMTQSPSSLSASLGERVSLTCRASQDIGSSLN<br>WLQQGPDGTIKRLIYATSSLDGVPKRFSGSRSG<br>SDYSLTISSLESEDFDYCLQYVSSPPTFGAGTK<br>LEIK (SEQ ID NO: 312)  |
| 2 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYNQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 313)  | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>SDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 314) |
| 3 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYNQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 315)  | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>TDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 316) |
| 4 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYNQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 317)  | EIVMTQSPGTLSPGERATLSCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSRATGIPDRFSGSRSG<br>SDYTLTISRLEPEDFAVYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 318)  |
| 5 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYAQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 319)  | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>SDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 320) |
| 6 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYAQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 321)  | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>TDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 322) |
| 7 | QVQLVQSGAEVKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTSYAQKFQGRVTMTV<br>DKSTSTVYMELSSLRSEDATVYYCVKGGYYGHWYFD<br>VWGQGTMTVSS (SEQ ID NO: 323)  | EIVMTQSPGTLSPGERATLSCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSRATGIPDRFSGSRSG<br>SDYTLTISRLEPEDFAVYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 324)  |
| 8 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTTNNQGTGRFVFSV<br>DKSVSTAYLQISSLAEDTAVYYCVKGGYYGHWYFDV<br>WGQGTMTVSS (SEQ ID NO: 325)    | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>SDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 326) |
| 9 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYGDTTNNQGTGRFVFSV<br>DKSVSTAYLQISSLAEDTAVYYCVKGGYYGHWYFDV                                   | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQQKPGKAIRLIYATSSLQSGVPSRFSGSRSG<br>TDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK                          |

|    |                                                                                                                                                      |                                                                                                                                         |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
|    | WGQGTMTVTVSS (SEQ ID NO: 327)                                                                                                                        | LEIK (SEQ ID NO: 328)                                                                                                                   |
| 10 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYYGDTTYAQGFTGRFVFSV<br>DKSVSTAYLQISSLKAEDTAVYYCVKGGYYGHWYFDV<br>WGQGTMTVTVSS (SEQ ID NO: 329) | EIVMTQSPGTLSPGERATLSCRASQDIGSSLN<br>WLQKKPGQAIKRLIYATSSRATGIPDRFSGSRSG<br>SDYTLTISRLEPEDFAVYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 330)  |
| 11 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYYGDTTYAQGFTGRFVFSV<br>DKSVSTAYLQISSLKAEDTAVYYCVKGGYYGHWYFDV<br>WGQGTMTVTVSS (SEQ ID NO: 331) | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQKKPGKAIKRLIYATSSLQSGVPSRFSGSRSG<br>SDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 332) |
| 12 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYYGDTTYAQGFTGRFVFSV<br>DKSVSTAYLQISSLKAEDTAVYYCVKGGYYGHWYFDV<br>WGQGTMTVTVSS (SEQ ID NO: 333) | DIQMTQSPSSLSASVGDRTITCRASQDIGSSLN<br>WLQKKPGKAIKRLIYATSSLQSGVPSRFSGSRSG<br>TDYTLTISSLQPEDFATYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 334) |
| 13 | EVQLVQSGSELKKPGASVKVSCASGYSTGYNMNW<br>VRQAPGQGLEWMGHIDPYYGDTTYAQGFTGRFVFSV<br>DKSVSTAYLQISSLKAEDTAVYYCVKGGYYGHWYFDV<br>WGQGTMTVTVSS (SEQ ID NO: 335) | EIVMTQSPGTLSPGERATLSCRASQDIGSSLN<br>WLQKKPGQAIKRLIYATSSRATGIPDRFSGSRSG<br>SDYTLTISRLEPEDFAVYYCLQYVSSPPTFGQGTK<br>LEIK (SEQ ID NO: 336)  |

In some embodiments, the binding module is a scFv, scFab or Fab comprising the VH and VL domain of any one of 1-13 according to Table 7.

#### 5 Table 7: VL and VH sequences of humanized anti-LIBS constructs

|   | VH sequence                                                                                                                                           | VL sequence                                                                                                                              |
|---|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | QVQLQQSGGGLVKPGGSLKLSAASGFTFSSYIMSWV<br>RQTPEKRLIEWVATIRSGGDNTYYPDSVKGRFTISRDN<br>AKNKLYLQMSSLRSEDALYYCAIYYGNYGGLAYWGQ<br>GTLVTVSA (SEQ ID NO: 337)   | DILMTQSPASLSASVGETVTITCRASGNIHNYLAW<br>YQQKQKGKSPQLLVYNAKTADGVPSRFSGSGSG<br>TQYSLKINSLQPEDFGSYQCQHFWSPTYTFGGGT<br>KLEIK (SEQ ID NO: 338) |
| 2 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 339) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 340)  |
| 3 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 341) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 342)  |
| 4 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 343) | EIVMTQSPATLSVSPGERATLSCRASGNIHNYLA<br>WYQQKPGQAPRLVYNAKTATGIPARFSGSGS<br>GTEYTLTISSLQSEDFAVYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 344)   |
| 5 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 345) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 346)  |
| 6 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 347) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 348)  |
| 7 | EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYIMSWV<br>RQAPGKGLEWVSTIRSGGDNTYYPDSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAIYYGNYGGLAYWGQ<br>GTLVTVSS (SEQ ID NO: 349) | EIVMTQSPATLSVSPGERATLSCRASGNIHNYLA<br>WYQQKPGQAPRLVYNAKTATGIPARFSGSGS<br>GTEYTLTISSLQSEDFAVYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 350)   |
| 8 | QVQLVQSGAEVKKPGASVKVSCASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYPDKFQGRVTITRD<br>NSANTAYMELSSLRSEDALYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 351)    | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSPTYTFGGG<br>TKLEIK (SEQ ID NO: 352)  |

|    |                                                                                                                                                      |                                                                                                                                          |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 9  | QVQLVQSGAEVKKPGASVKVSCKASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYPDKFQGRVTITRD<br>NSANTAYMELSSLRSEDTAVYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 353) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLLYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSSTPYTFGGG<br>TKLEIK (SEQ ID NO: 354) |
| 10 | QVQLVQSGAEVKKPGASVKVSCKASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYPDKFQGRVTITRD<br>NSANTAYMELSSLRSEDTAVYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 355) | EIVMTQSPATLSVSPGERATLSCRASGNIHNYLA<br>WYQQKPGQAPRLLVYNKTRATGIPARFSGSGS<br>GTEYTLTISSLQSEDFAVYYCQHFWSSTPYTFGGG<br>TKLEIK (SEQ ID NO: 356) |
| 11 | QVQLVQSGAEVKKPGASVKVSCKASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYSQKFQGRVTITRD<br>NSANTAYMELSSLRSEDTAVYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 357) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLVYNKLTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSSTPYTFGGG<br>TKLEIK (SEQ ID NO: 358) |
| 12 | QVQLVQSGAEVKKPGASVKVSCKASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYSQKFQGRVTITRD<br>NSANTAYMELSSLRSEDTAVYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 359) | DIQMTQSPSSLSASVGDRTITCRASGNIHNYLA<br>WYQQKPGKAPKLLLYNAKTLESQVPSRFSGSGS<br>GTDYTLTISSLQPEDFATYYCQHFWSSTPYTFGGG<br>TKLEIK (SEQ ID NO: 360) |
| 13 | QVQLVQSGAEVKKPGASVKVSCKASGFTFSSYIMSWV<br>RQAPGQRLEWMGTIRSGGDNTKYSQKFQGRVTITRD<br>NSANTAYMELSSLRSEDTAVYYCAIYYGNYGGLAYWG<br>QGTLVTVSS (SEQ ID NO: 361) | EIVMTQSPATLSVSPGERATLSCRASGNIHNYLA<br>WYQQKPGQAPRLLVYNKTRATGIPARFSGSGS<br>GTEYTLTISSLQSEDFAVYYCQHFWSSTPYTFGGG<br>TKLEIK (SEQ ID NO: 362) |

In an alternative embodiment, the binding module comprises the phosphatidylserine-binding domain of a phosphatidylserine-binding protein. Such domains are known in the art and can be easily identified by the skilled persons (see, for example, WO 2006/079120 A2, the contents of which are herein incorporated in their entirety by reference). In some embodiments, the binding module comprises domain V of  $\beta$ 2-glycoprotein I (see WO 2006/079120 A2). In some embodiments, the binding module comprises KASCKVPVKKATVVYQGERVKIQEKFKNGMLHGDKVSFFCKNKEKKCSYTEDAQCIDGTIE VPKCFKEHSSLAFWKTDASDVKPC (SEQ ID NO: 178).

#### *Bispecific multivalent molecules*

In some embodiments, the proteinaceous molecule is bispecific and multivalent. In some embodiments, the scaffold module comprises two antigen-binding sites that bind to Factor IXa or Factor X, or the scaffold module comprises an antigen-binding site that binds to Factor IXa and an antigen-binding site that binds to Factor X.

Figures 1 and 4 disclose examples of bispecific multivalent molecules encompassed by the present invention. The bispecific multivalent molecules of the present invention can be subcategorized into two categories depending on the scaffold module used: 1) scaffold modules which comprise a first antigen-binding site that binds to Factor IXa and a second antigen-binding site that binds to Factor X (referred to as "IXa/X scaffold") and 2) scaffold modules which comprise two antigen-binding sites wherein both antigen-binding sites bind to Factor IXa or Factor X (referred to as "monospecific scaffold"). In some embodiments, the IXa/X scaffold is an antibody. In some embodiments, the monospecific scaffold is an antibody.

In order to make a trispecific multivalent proteinaceous molecule a single binding module can be attached to an IXa/X scaffold through any of the linkers and positions previously disclosed or the binding module may be inserted into a loop region. In this embodiment, the binding module comprises an antigen-binding site that binds to any of the other targets, i.e. not Factor IXa or Factor X, disclosed herein.

An IXa/X scaffold can also be made bispecific multivalent. In some embodiments, a single binding module can be attached to an IXa/X scaffold through any of the linkers and positions previously disclosed or the binding module may be inserted into a loop region. In this embodiment, the binding module comprises an antigen-binding site that binds to Factor IXa or Factor X.

The monospecific scaffold can only be made bispecific multivalent if only one binding module is attached/inserted. In some embodiments, a single binding module can be attached to a monospecific scaffold through any of the linkers and positions previously disclosed or the binding module may be inserted into a loop region. In this embodiment, the binding module comprises an antigen-binding site that binds to Factor IXa or Factor X.

However, in order to make a trispecific multivalent proteinaceous molecule comprising a monospecific scaffold, it is necessary for the proteinaceous molecule to comprise two binding modules. In this embodiment, the first binding module is attached to the monospecific scaffold through a linker, or the first binding module is inserted into a loop region. It, thus, follows that the second binding module may be attached to the scaffold module in a similar or different way as the first binding module. However, the antigen-binding site of the first binding module should bind to Factor IXa or Factor X and the antigen-binding site of the second binding module should bind to another target (i.e. not Factor IXa or Factor X) to make the proteinaceous molecule trispecific.

It is immediately apparent that various different macromolecular topologies are possible using the design considerations disclosed herein and that these different macromolecular topologies are within the scope of the present invention. We focus on several possible macromolecular topologies below to outline the utility and versatility of the present approach.

1) "1 by 3" or "3 by 1" topology

Examples of proteinaceous molecules which have a “3 by 1” or “1 by 3” topology are depicted in Figure 1. These proteinaceous molecules are bispecific multivalent and comprise a larger number of antigen-binding sites directed to one of the targets than the other.

- 5 In one aspect, the present invention provides a proteinaceous molecule comprising:
- (i) a scaffold module, wherein the scaffold module comprises a first antigen-binding site that binds to Factor IXa and a second antigen-binding site that binds to Factor X; and
  - (ii) a first and second binding module that comprise a third and fourth antigen-binding site, respectively,
- 10 wherein the third and fourth antigen-binding sites bind to Factor IXa or Factor X.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

- (a) an antibody or a bivalent fragment thereof that comprises:
    - (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;
    - (ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and
    - (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a; and
  - 20 (b) at least two binding modules that are scFvs or scFabs comprising:
    - (i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2a, and
    - (ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3.
- 25 In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (a)(iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) and (a)(iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or

LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

- 5 In some embodiments, the present invention provides a proteinaceous molecule comprising:
- (a) an antibody or a bivalent fragment thereof that comprises:
- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;
  - (ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the
  - 10 Factor X binding light chains disclosed in Table 1; and
  - (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2b; and
- (b) at least two binding modules that are scFvs or scFabs comprising:
- (i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains
  - 15 disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2b, and
  - (ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3.

In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (a)(iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) and (a)(iii) are the LCDR1, LCDR2 and LCDR3 of W206 and V245, LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W206, V198, V202, W128, W88, W127, V212, or W162 disclosed in

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35 Tables 1 and 2b.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding

light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the VL of (a)(ii) is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V245, VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W206 and V245, VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W206, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of W88 disclosed in Table 3; and

(iii) one light chain comprising the VL of V198 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of V198 disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of W88 disclosed in Table 3; and

(iii) one light chain comprising the VL of V198 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of V198 disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

- (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

- 5 (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;  
(ii) one light chain comprising the VL of W27 disclosed in Table 3; and  
(iii) one light chain comprising the VL of V202 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

- 10 (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of V202 disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and  
(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;  
20 (ii) one light chain comprising the VL of W128 disclosed in Table 3; and  
(iii) one light chain comprising the VL of V149 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

- (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of V128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and  
25 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

30 (a) an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;  
(ii) one light chain comprising the VL of W128 disclosed in Table 3; and  
(iii) one light chain comprising the VL of V198 disclosed in Table 4a; and

35 (b) at least two binding modules that are scFvs comprising:

- (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,

wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

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(ii) one light chain comprising the VL of W88 disclosed in Table 3; and

(iii) one light chain comprising the VL of V198 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

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(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W88 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

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(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of W128 disclosed in Table 3; and

(iii) one light chain comprising the VL of V141 disclosed in Table 4a; and

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(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

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(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

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(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of W127 disclosed in Table 3; and

(iii) one light chain comprising the VL of V202 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

- (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W127 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and
- (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of W162 disclosed in Table 3; and
- (iii) one light chain comprising the VL of V204 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

- (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and
- (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of W206 disclosed in Table 3; and
- (iii) one light chain comprising the VL of V245 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

- (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W206 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and
- (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183.

In some embodiments of any of the above, the binding modules are attached to the N- or C-terminus of the heavy or light chain through a linker. In some embodiments, the binding modules are attached to the C-terminus of the heavy or light chain. In some embodiments, the first binding module is attached to the C-terminus of the first heavy chain through a linker,

and the second binding module is attached to C-terminus of the second heavy chain through the linker.

In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the two LC sequences of any one of Lex#3, Bax#137, Bax#148, Bax#146, Lex#2, Lex#12, Bax#138 or Bax#145 disclosed in Table 8.

In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the two LC sequences of any one of Lex#3, Lex#131, Bax#137, Bax#148, Bax#146, Lex#2, Lex#12, Bax#138 or Bax#145 disclosed in Table 8.

In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence, one copy of the LC with lambda constant domain sequence, and one copy of the LC with kappa constant domain sequence of any one of Lex#3, Bax#137, Bax#148, Bax#146, Lex#2, Lex#12, Bax#138 or Bax#145 disclosed in Table 8.

In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence, one copy of the LC with lambda constant domain sequence, and one copy of the LC with kappa constant domain sequence of any one of Lex#3, Lex#131, Bax#137, Bax#148, Bax#146, Lex#2, Lex#12, Bax#138 or Bax#145 disclosed in Table 8.

**Table 8: Sequences of “3 by 1” and “1 by 3” constructs**

| ID    | LC with lambda constant domain                                                                                                                                                                                                                                                                | LC with kappa constant domain                                                                                                                                                                                                                                                             | Heavy chain sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lex#3 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLVIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYYCQVRDSVDDLYVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 193) | EIVLTQSPGTLISLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIIEA<br>SKRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGQG<br>TKVEIKRTVAAPSVFIFPP<br>SDEQLKSGTASVCLLN<br>NFYPRQAKVQWVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEK<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 194) | EVQLLESQGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWVSAISGSGGSTYYA<br>DSVKGRTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP<br>SSSLGTQTYICNVNHKPSNTKVDKRVPEKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYKCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LLESQGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWVSAISGSGGSTYYADSVK<br>GRFTISRDNKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGSG<br>GGGGSGGGSSYVLTQPPSVSVAPGKTARITC<br>GGDNIEAETVHWYQQKPGQAPVLVIYSDSIRP<br>SGIPERFSGSNSGNTATLTISRVEAGDEADYY |

|         |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                             | CQVRDSVDDLYVFGCGTKLTVL<br>(SEQ ID NO: 195)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Bax#137 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLIYR<br>DSDRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSVDDKA<br>VFGGGTKLTVLGQPKA<br>APSVTLFPPSSEELQA<br>NKATLVCLISDFYPGAV<br>TVAWKADSSPVKAGVE<br>TTTPSKQSNKYAASS<br>YLSLTPEQWKSHRSYS<br>CQVTHEGSTVEKTVAP<br>TECS<br>(SEQ ID NO: 196) | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSINYYVQ<br>WYQQRPSSPTTVIYNH<br>NKRPSGVPDRFSGSIDS<br>SSNSASLTISGLKTEDEA<br>DYCQSWTWSGEKVFG<br>GGTKLTVLRTVAAPSVFI<br>FPPSDEQLKSGTASVVC<br>LLNFPYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 197)  | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGSPVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFSCSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LLESGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVK<br>GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGSG<br>GGGGSGGGSSYVLTQPPSVSVAPGKTARITC<br>GGDNIEAETVHWYQQKPGQAPVLIYRDSR<br>PSGIPERFSGSNSGNTATLTISRVEAGDEADY<br>YCQVRDSVDDKAVFGCGTKLTVL<br>(SEQ ID NO: 198)   |
| Bax#148 | NFMLTQPHSVSESPGK<br>TVTISCTRSSGSINYY<br>VQWYQQRPSSPTTVI<br>YNHNKRPSGVPDRFS<br>GSIDSSNSASLTISGL<br>KTEDEADYYCQSWTW<br>EGLKVFGGGTKLTVLG<br>QPKAAPSVTLFPPSSE<br>ELQANKATLVCLISDFY<br>PGAVTVAWKADSSPVK<br>AGVETTPSKQSNKY<br>AASSYLSLTPEQWKSH<br>RSYSCQVTHEGSTVEK<br>TVAPTECS<br>(SEQ ID NO: 199) | EIVLTQSPGTLSPGER<br>ATLSCRASQEVDDNELA<br>WYQQKPGQAPRLIYGA<br>SSRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQQYNPDGLGYDGYTF<br>GGGKVEIKRTVAAPSVF<br>IFPPSDEQLKSGTASVVC<br>LLNFPYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 200) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGSPVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFSCSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LLESGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVK<br>GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGSG<br>GGGGSGGGSNFMLTQPHSVSESPGKTVTISC<br>TRSSGSINYYVQWYQQRPSSPTTVIYNHN<br>KRPSGVPDRFSGSIDSNSASLTISGLKTEDE<br>ADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 201) |
| Bax#146 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYCQVRDSVDDLYVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV                                                                                                            | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSINYYVQ<br>WYQQRPSSPTTVIYNH<br>NKRPSGVPDRFSGSIDS<br>SSNSASLTISGLKTEDEA<br>DYCQSWTWEGLKVF<br>GGTKLTVLRTVAAPSVFI<br>FPPSDEQLKSGTASVVC<br>LLNFPYPREAKVQWKVD                                                                                                     | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGSPVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|        |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|        | AWKADSSPVKAGVETT<br>TPSKQSNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 202)                                                                                                                                                                                       | NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 203)                                                                                                                                                                                            | HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGGSGGGGGSGGGGGSGGGGSEVQ<br>LLESAGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVK<br>GRFTISRDNKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGGSG<br>GGGGSGGGSNFMLTQPHSVSESPGKTVTISC<br>TRSSGSINYYVQWYQRPQSSPTTVIYNHN<br>KRPSGVPDRFSGSIDSSNSASLTISGLKTEDE<br>ADYYCQSWTWEGLKVFGCCTKLTVL<br>(SEQ ID NO: 204)                                                                                                                                                                                                                                                                                                                         |
| Lex#2  | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAETVH<br>WYQQKPGQAPVLIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYYCQVRDSVDDLYVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 205)  | EIVLTQSPGTLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIYE<br>SKRATGIPDRFSGSGS<br>TDFTLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGGQ<br>TKVEIKRTVAAPSVFIFP<br>SDEQLKSGTASVCLLN<br>NFYPREAKVQWKVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEK<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 206)      | EVQLLESAGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGGSGGGGGSGGGGGSGGGGSEVQ<br>LLESAGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVK<br>GRFTISRDNKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGGSG<br>GGGGSGGGSEIVLTQSPGTLSPGERATLSC<br>RASQSVTTGYLAWYQQKPGQAPRLIYEASK<br>RATGIPDRFSGSGGTDFLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGCCTKVEIK<br>(SEQ ID NO: 207) |
| Lex#12 | NFMLTQPHSVSESPGK<br>TVTISCTRSSGSINYY<br>VQWYQRPQSSPTTVI<br>YNHNKRPSGVPDRFS<br>GSIDSSNSASLTISGL<br>KTEDEADYYCQSWTW<br>EGLKVFGGKLTVLG<br>QPKAAPSVTLFPPSSE<br>ELQANKATLVCLISDFY<br>PGAVTVAWKADSSPVK<br>AGVETTTPSKQSNKY<br>AASSYLSLTPEQWKSH<br>RSYSCQVTHEGSTVEK<br>TVAPTECS<br>(SEQ ID NO: 208) | EIVLTQSPGTLSPGER<br>ATLSCRASQKVDDDELA<br>WYQQKPGQAPRLIYRA<br>SNRATGIPDRFSGSGS<br>TDFTLTISRLEPEDFAVY<br>YCQQYNPDGLGYEDYTF<br>GGGKVEIKRTVAAPSVF<br>IFPPSDEQLKSGTASVVC<br>LLNFYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 209) | EVQLLESAGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGGSGGGGGSGGGGGSGGGGSEVQ<br>LLESAGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVK<br>GRFTISRDNKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGGSG<br>GGGGSGGGSNFMLTQPHSVSESPGKTVTISC                                                                                                                   |

|         |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|         |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                             | TRSSGSINNYVQWYQQRPGSSPTTVIYNHN<br>KRPSGVPDRFSGSIDSSNSASLTISGLKTEDE<br>ADYYCQSWTWEGDKVFGCGTKLTVL<br>(SEQ ID NO: 210)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Bax#138 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAETVH<br>WYQQKPGQAPVLIYR<br>DSDRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSVDDKA<br>VFGGGTKLTVLGQPKA<br>APSVTLFPPSSEELQA<br>NKATLVCLISDFYPGAV<br>TVAWKADSSPVKAGVE<br>TTTPSKQSNKYAASS<br>YLSLTPEQWKSHRSYS<br>CQVTHEGSTVEKTVAP<br>TECS<br>(SEQ ID NO: 211) | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSINNYVQ<br>WYQQRPGSSPTTVIYNH<br>NKRPSGVPDRFSGSID<br>SSNSASLTISGLKTEDEA<br>DYYCQSWTWSGEKVFG<br>GGTKLTVLRTVAAPSVFI<br>FPPSDEQLKSGTASVVC<br>LLNNFYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 212) | EVQLLES GGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFSCSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LLES GGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKLEWWSAISGSGGSTYYADSVK<br>GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGSG<br>GGGGSGGGSNFMLTQPHSVSESPGKTVTISC<br>TRSSGSINNYVQWYQQRPGSSPTTVIYNHN<br>KRPSGVPDRFSGSIDSSNSASLTISGLKTEDE<br>ADYYCQSWTWSGEKVFGCGTKLTVL<br>(SEQ ID NO: 213) |
| Bax#145 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAETVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSNDDLIV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 214) | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSINNYVQ<br>WYQQRPGSSPTTVIYNH<br>NKRPSGVPDRFSGSID<br>SSNSASLTISGLKTEDEA<br>DYYCQSWTWEGDLVFG<br>GGTKVEIKRTVAAPSVFI<br>FPPSDEQLKSGTASVVC<br>LLNNFYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 215) | EVQLLES GGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFSCSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LLES GGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKLEWWSAISGSGGSTYYADSVK<br>GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA<br>KSYGAFDYWGQGLTVTVSSGGGGSGGGGSG<br>GGGGSGGGSNFMLTQPHSVSESPGKTVTISC<br>TRSSGSINNYVQWYQQRPGSSPTTVIYNHN<br>KRPSGVPDRFSGSIDSSNSASLTISGLKTEDE<br>ADYYCQSWTWEGDLVFGCGTKLTVL<br>(SEQ ID NO: 216) |
| Lex#131 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS<br>DSVRMSGIPERFSGSN<br>SWNTATLTISRVEAGD<br>EADYYCQVRDSIDDLIV<br>FGGGTKLTVLGQPKAA                                                                                                                                                   | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSISNYYVQ<br>WYQQRPGSSPTTVIYNH<br>NKRPSGVPDRFSGSID<br>SSNSASLTISGLKTEDEA<br>DYYCQSWTWSGEKVFG<br>GGTKLTVLRTVAAPSVFI                                                                                                                                            | EVQLLES GGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|  |                                                                                                                                                |                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO:378) | FPPSDEQLKSGTASVVC<br>LLNNFYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYSLSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO:379) | KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYCKKVSNAKALPAIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGGGEVQLLES GGGLVQPGGSLRL<br>SCAASGFTFSSYAMSWVRQAPGKCLEWWSAI<br>SGSGGSTYYADSVKGRFTISRDN SKNTLYLQM<br>NSLRAEDTAVYYCAKSYGAFDYWGQGLTVTV<br>SSGGGGSGGGGSGGGGSGGGGSGNFMILTQP<br>HSVSESPGKTVTISCTRSSGSISNYYVQWYQQ<br>RPGSSPTTVIYNHNKRPSGVPDRFSGSIDSSS<br>NSASLTISGLKTEADYYCQSWTWSGEKVF<br>GCGTKLTVL<br>(SEQ ID NO:380) |
|--|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 2) "2 by 2" model

Examples of proteinaceous molecules which have a "2 by 2" topology are depicted in Figure 1. These proteinaceous molecules are bispecific multivalent and comprise an equal number of antigen-binding sites that bind to Factor IXa or Factor X. This sort of topology uses a monospecific scaffold.

In one aspect, the present invention provides a proteinaceous molecule comprising:

- (i) a scaffold module, wherein the scaffold module comprises a first and second antigen-binding site that bind to Factor IXa or Factor X; and
- (ii) a first and second binding module that comprise a third and fourth antigen-binding site, respectively,

wherein the third and fourth antigen-binding sites bind to Factor IXa or Factor X and the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa and two antigen-binding sites that bind to Factor X.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

- (a) an antibody or bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and
- (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a; and

- (b) at least two binding modules that are scFvs or scFabs comprising:

- (i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2a, and

(ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

(ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b; and

(b) at least two binding modules that are scFvs or scFabs comprising:

(i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2b, and

(ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of V155, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V320, LCDR1, LCDR2 and LCDR3 of

V305, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W198, W206, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:  
(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

(ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of V212 disclosed in Table 2b; and

(b) at least two binding modules that are scFvs or scFabs comprising:

(i) the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and

(ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183, wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of (a)(ii) is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V245, VL of V155, VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W206, W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of V212 disclosed in Table 4b; and

5 (b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

10 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

20 (ii) two light chains each comprising the VL of V305 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

25 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

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(ii) two light chains each comprising the VL of V141 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

5 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183, wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

10 In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

15 (ii) two light chains each comprising the VL of V245 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

20 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

25 In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

30 (ii) two light chains each comprising the VL of V245 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

35 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

10 (ii) two light chains each comprising the VL of V245 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W206 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

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(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

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(ii) two light chains each comprising the VL of V155 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W127 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

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(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

5 (ii) two light chains each comprising the VL of V155 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

10 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

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(ii) two light chains each comprising the VL of V320 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W128 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

25

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

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(ii) two light chains each comprising the VL of V320 disclosed in Table 4b; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of V212 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W127 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to Factor IXa and at least two antigen binding sites that bind to Factor X. In some embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of W128 disclosed in Table 3; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of V212 disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,  
wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to  
Factor IXa and at least two antigen binding sites that bind to Factor X. In some  
embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2  
5 and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ  
10 ID NO: 4; and

(ii) two light chains each comprising the VL of V202 disclosed in Table 4a; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,  
wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of  
15 W127 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID  
NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to  
Factor IXa and at least two antigen binding sites that bind to Factor X. In some  
20 embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2  
and LCDR3 of each of the two binding modules are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ  
25 ID NO: 4; and

(ii) two light chains each comprising the VL of W127 disclosed in Table 3; and

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,  
30 wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of  
V212 disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID  
NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183,

wherein the proteinaceous molecule comprises at least two antigen-binding sites that bind to  
35 Factor IXa and at least two antigen binding sites that bind to Factor X. In some  
embodiments, the VL of each of the two light chains are identical, and the LCDR1, LCDR2  
and LCDR3 of each of the two binding modules are identical.

In some embodiments of any of the above, the binding modules are attached to the N- or –C terminus of the heavy or light chain through a linker. In some embodiments, the binding modules are attached to the C-terminus of the heavy or light chain. In some embodiments, the first binding module is attached to the C-terminus of the first heavy chain through a linker, and the second binding module is attached to C-terminus of the second heavy chain through the linker.

In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the light chain sequence of any one of Lex#84, Lex#85, Lex#86, Lex#87, Lex#88, Lex#96, Lex#97, Lex#60, Lex#63, Lex#71, Lex#72, Lex#73, Lex#74, Lex#75, Bax#144, Lex#59, Lex#53, Lex#99, Lex#102, Lex#103, or Lex#105 disclosed in Table 9.

In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the light chain sequence of any one of Lex#95, Lex#121, Lex#129, Lex#143, Lex#153, Lex#157, Lex#161, Lex#167, Lex#168, Lex#169, Lex#84, Lex#85, Lex#86, Lex#87, Lex#88, Lex#96, Lex#97, Lex#60, Lex#63, Lex#71, Lex#72, Lex#73, Lex#74, Lex#75, Bax#144, Lex#59, Lex#53, Lex#99, Lex#102, Lex#103, or Lex#105 disclosed in Table 9. In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the light chain sequence of Lex#153 disclosed in Table 9.

In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence and two copies of the light chain sequence of any one of Lex#84, Lex#85, Lex#86, Lex#87, Lex#88, Lex#96, Lex#97, Lex#60, Lex#63, Lex#71, Lex#72, Lex#73, Lex#74, Lex#75, Bax#144, Lex#59, Lex#53, Lex#99, Lex#102, Lex#103, or Lex#105 disclosed in Table 9.

In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence and two copies of the light chain sequence of any one of Lex#95, Lex#121, Lex#129, Lex#143, Lex#153, Lex#157, Lex#161, Lex#167, Lex#168, Lex#169, Lex#84, Lex#85, Lex#86, Lex#87, Lex#88, Lex#96, Lex#97, Lex#60, Lex#63, Lex#71, Lex#72, Lex#73, Lex#74, Lex#75, Bax#144, Lex#59, Lex#53, Lex#99, Lex#102, Lex#103, or Lex#105 disclosed in Table 9. In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence and two copies of the light chain sequence of Lex#153 disclosed in Table 9.

**Table 9: Sequences of “2 by 2” constructs**

| ID     | Light chain sequence                                                                                                                                                                                                                                                                                 | Heavy chain sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lex#84 | EIVLTQSPGTLISLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 217) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGGGGGEVQ<br>LLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSAIS<br>GSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYGA<br>FDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSES<br>PGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVF GCGTKLTVL<br>(SEQ ID NO: 218)  |
| Lex#85 | EIVLTQSPGTLISLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 219) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGGGGGGE<br>VQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVF GCGTKLTVL<br>(SEQ ID NO: 220) |
| Lex#86 | EIVLTQSPGTLISLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 221) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGGGGGSE<br>VQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVF GCGTKLTVL<br>(SEQ ID NO: 222) |
| Lex#87 | EIVLTQSPGTLISLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS                                    | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGGGGGSG<br>GGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCL<br>EWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYY<br>CAKSYGAFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGNFMILTQ<br>PHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPS                                                                           |

|        |                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|        | PVTKSFNRGEC<br>(SEQ ID NO: 223)                                                                                                                                                                                                                                                                | GVPDRFSGSIDSSNSASLTISGLKTEADYYCQSWTWEGLKVF GCGTK<br>LTVL<br>(SEQ ID NO: 224)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Lex#88 | EIVLTQSPGTLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVCLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 225) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVKPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGGGGSGG<br>GGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ<br>APGKCLEWWSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAE<br>DTAVYYCAKSYGAFDYWGQGT LVTVSSGGGGSGGGSGGGSGGGSGGGGS<br>NFM LTQPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYN<br>HNKRPSGVPDRFSGSIDSSNSASLTISGLKTEADYYCQSWTWEGLKV<br>FGCGTKLTVL<br>(SEQ ID NO: 226)                             |
| Lex#96 | EIVLTQSPGTLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVCLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 227) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVKPKSCGGGGSGGGSGGGSGGGSGGGSGDKHTCPPC<br>PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV<br>DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALP<br>APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE<br>WESNGQPENNYK TTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMH<br>EALHNHYTQKSLSLSPGGGGSGGGSGGGSGGGSGGGGSEVQLLESGGGL<br>VQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWWSAISGSGGSTYY<br>ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGT<br>LVTVSSGGGGSGGGSGGGSGGGSGGGSGNFM LTQPHSVSESPGKTVTISCT<br>RSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRFSGSIDSSNS<br>ASLTISGLKTEADYYCQSWTWEGLKVFGCGTKLTVL<br>(SEQ ID NO: 228) |
| Lex#97 | EIVLTQSPGTLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLTISRLEPE<br>DFAVYYCQQYNPDPL<br>GYEDYTFGGGTKVEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVCLNNFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 229) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVKPKSCGSAGSAGSGEFDKHTCPPCPAPEAAGGPS<br>VFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK<br>PREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY<br>K TTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSL<br>SLSPGGGGSGGGSGGGSGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCA<br>ASGFTFSSYAMSWVRQAPGKCLEWWSAISGSGGSTYYADSVKGRFTISRDN<br>SKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGT LVTVSSGGGGSGG<br>GGSGGGSGGGSGNFM LTQPHSVSESPGKTVTISCTRSSGSINNYVQ<br>WYQQRPGSSPTTVIYNHNKRPSGVPDRFSGSIDSSNSASLTISGLKTEDE<br>ADYYCQSWTWEGLKVFGCGTKLTVL<br>(SEQ ID NO: 230)             |
| Lex#60 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN                                                                                                                                  | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVKPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPVLDSDGS                                                                                                                                                                                                                                                                                                                                                                                               |

|        |                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|        | KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 231)                                                                                                                                                                    | FFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGGGGGGSG<br>GGGSGGGGGGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTLYLQMN<br>SLRAEDTAVYYCAKSYGAFDYWGQGLTVTVSSGGGGSGGGGGSGGGGGSG<br>GGGSNFMILTQPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPT<br>TVIYNHNKRPSGVPDRFSGSIDSSNSASLTISGLKTEDEADYYCQSWTWS<br>GEKVF GCGTKLTVL<br>(SEQ ID NO: 232)                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Lex#63 | NFMILTQPHSVSESPGK<br>TVTISCTRSSGSINNY<br>VQWYQQRPGSSPTTVI<br>YNHNKRPSGVPDRFS<br>GSIDSSNSASLTISGL<br>KTEDEADYYCQSWTW<br>EGLKVFGGGTKLTVLG<br>QPKAAPSVTLFPPSSE<br>ELQANKATLVCLISDFY<br>PGAVTVAWKADSSPVK<br>AGVETTPSKQSNKY<br>AASSYLSLTPEQWKSH<br>RSYSCQVTHEGSTVEK<br>TVAPTECS<br>(SEQ ID NO: 233) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGGGGGGSG<br>GGGSGGGGGGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTLYLQMN<br>SLRAEDTAVYYCAKSYGAFDYWGQGLTVTVSSGGGGSGGGGGSGGGGGSG<br>GGGSSYVLTQPPSVSVAPGKTARITCGGDNIEAESVHWYQKPGQAPVLV<br>IYNDNNRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVLLNDADEG<br>VFGCGTKLTVL<br>(SEQ ID NO: 234) |
| Lex#71 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 235)    | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGGGGGEVQ<br>LLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSAIS<br>GSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSYGA<br>FDYWGQGLTVTVSSGGGGSGGGGGSGGGGGSGGGGSNFMILTQPHSVSE<br>PGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSNSASLTISGLKTEDEADYYCQSWTWSGEKVF GCGTKLTVL<br>(SEQ ID NO: 236)                   |
| Lex#72 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 237)    | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSYG<br>AFDYWGQGLTVTVSSGGGGSGGGGGSGGGGGSGGGGSNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSNSASLTISGLKTEDEADYYCQSWTWSGEKVF GCGTKLTVL<br>(SEQ ID NO: 238)                |
| Lex#73 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE                                                                                                                                                                                               | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|         | ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 239)                                                                                                      | SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGGGGGSE<br>VQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWWSA<br>ISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFM LTQPHSVSE<br>SPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKVF GCGTKLTVL<br>(SEQ ID NO: 240)                                                                                                                                                                                                                                                                                                |
| Lex#74  | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 241) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGGGGGSG<br>GGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCL<br>EWWSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYY<br>CAKSYGAFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSGNFM LTQ<br>PHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPS<br>GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKVF GCGTK<br>LTVL<br>(SEQ ID NO: 242)          |
| Lex#75  | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 243) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGGGGGSG<br>GGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ<br>APGKCLEWWSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAE<br>DTAVYYCAKSYGAFDYWGQGT LVT VSSGGGGSGGGGSGGGGSGGGGSG<br>NFM LTQPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYN<br>HNKRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKV<br>FGCGTKLTVL<br>(SEQ ID NO: 244)      |
| Bax#144 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLIYR<br>DSDRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSVDDKA<br>VFGGGTKLTVLGQPKA<br>APSVTLFPPSSEELQA<br>NKATLVCLISDFYPGAV<br>TVAWKADSSPVKAGVE<br>TTTPSKQSNKYAASS<br>YLSLTPEQWKSHRSYS<br>CQVTHEGSTVEKTVAP<br>TECS<br>(SEQ ID NO: 245) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGGGGGSG<br>GGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAM<br>SWVRQAPGKCLEWWSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMN<br>SLRAEDTAVYYCAKSYGAFDYWGQGT LVT VSSGGGGSGGGGSGGGGSG<br>GGGSGNFM LTQPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPT<br>TVIYNHNKRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWS<br>GEKVFGCGTKLTVL<br>(SEQ ID NO: 246) |
| Lex#59  | NFM LTQPHSVSESPGK                                                                                                                                                                                                                                                                            | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|        | <p>TVTISCTRSSGSINNY<br/>VQWYQQRPGSSPTTVI<br/>YNHNKRPSGVPDRFS<br/>GSIDSSSNSASLTISGL<br/>KTEDEADYYCQSWTW<br/>SGEKVFGGGLKTLVLG<br/>QPKAAPSVTLFPPSSE<br/>ELQANKATLVCLISDFY<br/>PGAVTVAWKADSSPVK<br/>AGVETTPSKQSNKY<br/>AASSYLSLTPEQWKSH<br/>RSYSCQVTHEGSTVEK<br/>TVAPTECS<br/>(SEQ ID NO: 247)</p>                                                                                                                                                                                                                                                                                                        | <p>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br/>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br/>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br/>NHKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br/>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br/>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br/>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br/>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGSGG<br/>GGGSGGGSGGGGSEVQLLESGLLVQPGGSLRLSCAASGFTFSSYAM<br/>SWVRQAPGKCLEWVS AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMN<br/>SLRAEDTAVYYCAKSYGAFDYWGQGLTVTVSSGGGGSGGGGSGGGGSGG<br/>GGSSYVLTQPPSVSVAPGKTARITCGGDNIEAESVHWYQKPGQAPVLV<br/>IYNDNNRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVLLNDADEG<br/>VFGCGTKLTVL<br/>(SEQ ID NO: 248)</p>                                                         |
| Lex#53 | <p>EIVLTQSPGTLSPGE<br/>RATLSRASQKVDDE<br/>LAWYQQKPGQAPRLLI<br/>YRASNRATGIPDRFSG<br/>SGSGTDFTLISRLEPE<br/>DFAVYYCQYNDPDL<br/>GYEDYTFGGTKVEIK<br/>RTVAAPSVFIFPPSDEQ<br/>LKSGTASVCLLNNFY<br/>PREAKVQWKVDNALQ<br/>SGNSQESVTEQDSKD<br/>STYLSSTLTLSKADYE<br/>KHKVYACEVTHQGLSS<br/>PVTKSFNRGEC<br/>(SEQ ID NO: 249)</p>                                                                                                                                                                                                                                                                                      | <p>EVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br/>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br/>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br/>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br/>NHKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br/>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br/>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br/>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br/>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGSGG<br/>GGGSGGGSGGGGSEVQLLESGLLVQPGGSLRLSCAASGFTFSSYAM<br/>SWVRQAPGKCLEWVS AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMN<br/>SLRAEDTAVYYCAKSYGAFDYWGQGLTVTVSSGGGGSGGGGSGGGGSGG<br/>GGSNFMLTQPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPT<br/>TVIYNHNKRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWE<br/>GLKVFSGCGTKLTVL<br/>(SEQ ID NO: 250)</p> |
| Lex#99 | <p>SYVLTQPPSVSVAPGK<br/>TARITCGGDNIEAESVH<br/>WYQQKPGQAPVLVIYN<br/>DNNRPSGIPERFSGSN<br/>SGNTATLTISRVEAGDE<br/>ADYYCQVLLNDADEGV<br/>FGGGLKTLVLGQPKAA<br/>PSVTLFPPSSEELQAN<br/>KATLVCLISDFYPGAVT<br/>VAWKADSSPVKAGVET<br/>TTPSKQSNKYAASSY<br/>LSLTPEQWKSHRSYSC<br/>QVTHEGSTVEKTVAPT<br/>ECSGGGSGGGGSGG<br/>GGGSGGGGSEVQLLE<br/>SGGGLVQPGGSLRLS<br/>CAASGFTFSSYAMSW<br/>VRQAPGKCLEWVS AIS<br/>GSGGSTYYADSVKGR<br/>FTISRDNKNTLYLQM<br/>NSLRAEDTAVYYCAKS<br/>YGAFDYWGQGLTVTV<br/>SSGGGGSGGGGSGG<br/>GGSGGGGSNFMLTQP<br/>HSVSESPGKTVTISCTR<br/>SSGSINNYVQWYQQ<br/>RPGSSPTTVIYNHNKR<br/>PSGVPDRFSGSIDSSS</p> | <p>EVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br/>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br/>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br/>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br/>NHKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br/>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br/>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br/>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br/>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG<br/>(SEQ ID NO: 252)</p>                                                                                                                                                                                                                                                                                                        |

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|         | NSASLTISGLKTEDEAD<br>YYCQSWTWSGEKVFG<br>CGTKLTVL<br>(SEQ ID NO: 251)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Lex#102 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECSGGGGSGGGGSG<br>GGGSGGGGSEVQLE<br>SGGGLVQPGGSLRLS<br>CAASGFTFSSYAMSW<br>VRQAPGKCLEWVSAIS<br>GSGGSTYYADSVKGR<br>FTISRDNKNTLYLQM<br>NSLRAEDTAVYYCAKS<br>YGAFDYWGQGLTVTV<br>SSGGGSGGGGSGG<br>GGSGGGGSNFMLTQP<br>HSVSESPGKTVTISCTR<br>SSGSINNYVQWYQQ<br>RPGSSPTTVIYNHNKR<br>PSGVPDRFSGSIDSSS<br>NSASLTISGLKTEDEAD<br>YYCQSWTWSGEKVFG<br>CGTKLTVL<br>(SEQ ID NO: 253) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCGGGSGGGGSGGGGSGGGGSDKTHTCPPC<br>PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV<br>DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALP<br>APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE<br>WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH<br>EALHNHYTQKSLSLSPG<br>(SEQ ID NO: 254) |
| Lex#103 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECSGGGGSGGGGSG<br>GGGSGGGGSEVQLE<br>SGGGLVQPGGSLRLS<br>CAASGFTFSSYAMSW<br>VRQAPGKCLEWVSAIS<br>GSGGSTYYADSVKGR<br>FTISRDNKNTLYLQM<br>NSLRAEDTAVYYCAKS<br>YGAFDYWGQGLTVTV<br>SSGGGSGGGGSGG                                                                                                                                                                           | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHKPSNTKVDKRVEPKSCGSAGSAGSGEFDKTHTCPPCPAPEAAGGPS<br>VFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK<br>PREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY<br>KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL<br>SLSPG<br>(SEQ ID NO: 256)         |

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|         | GGSGGGGSNFMILTQP<br>HSVSESPGKTVTISCTR<br>SSGSINNYVQWYQQ<br>RPGSSPTTVIYNHNKR<br>PSGVPDRFSGSIDSS<br>NSASLTISGLKTEDEAD<br>YYCQSWTWSGEKVFG<br>CGTKLTVL<br>(SEQ ID NO: 255)                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Lex#105 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAESVH<br>WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 257)      | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVS<br>ESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPD<br>RFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKVFGCGTKLTVLG<br>GGGSGGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTF<br>SSYAMSWVRQAPGKLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTL<br>YLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLLTVSSASTKGPSVFPLAP<br>SSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLY<br>SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPA<br>PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG<br>VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP<br>IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE<br>SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA<br>LHNHYTQKSLSLSPG<br>(SEQ ID NO: 258) |
| Lex#95  | EIVLTQSPGTLISLSPGE<br>RATLSCRASQKVDDDE<br>LAWYQQKPGQAPRLLI<br>YRASNRATGIPDRFSG<br>SGSGTDFTLISRLEPE<br>DFAVYYCQYNDPDL<br>GYEDYTFGQGTKEIK<br>RTVAAPSVFIFPPSDEQ<br>LKSGTASVCLLNIFY<br>PREAKVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 381) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGSGAGSA<br>AGSGEFEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK<br>CLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVY<br>YCAKSYGAFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGNFMILT<br>QPHSVSESPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKR<br>PSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFGCG<br>TKLTVL<br>(SEQ ID NO: 382)       |
| Lex#121 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS<br>DSVRMSGIPERFSGSN<br>SWNTATLTISRVEAGD<br>EADYYCQVRDSIDDLIV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TTPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 383)     | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV<br>NHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGE<br>VQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFGCGTKLTVL<br>(SEQ ID NO: 384)                   |
| Lex#129 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS                                                                                                                                                                                                                                         | EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|         | DSVRMSGIPERFSGSN<br>SWNTATLTISRVEAGD<br>EADYYCQVRDSIDDLIV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TPPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 385)                                                                 | EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKVFSGCGTKLTVL<br>(SEQ ID NO: 386)                                                                                                                                                                   |
| Lex#143 | EIVLTQSPGTLTSLSPGE<br>RATLSCRASQSVDDDE<br>LAWYQQKPGQAPRLLI<br>YGASSRATGIPDRFSG<br>SGSGTDFTLISRLEPE<br>DFAVYYCQQYNDPDL<br>GYEGYTFGGGKVEIK<br>RTVAAPSVFIFFPSDEQ<br>LKSGTASVCLNNFY<br>PRAKVVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 387) | EVQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWSGEKVFSGCGTKLTVL<br>(SEQ ID NO: 388) |
| Lex#153 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAESVH<br>WYQQKPGQAPVLVIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADEGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TPPSKQSNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 389)     | EVQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 390) |
| Lex#157 | EIVLTQSPGTLTSLSPGE<br>RATLSCRASQSVDDDE<br>LAWYQQKPGQAPRLLI<br>YGASSRATGIPDRFSG<br>SGSGTDFTLISRLEPE<br>DFAVYYCQQYNDPDL<br>GYEGYTFGGGKVEIK<br>RTVAAPSVFIFFPSDEQ<br>LKSGTASVCLNNFY<br>PRAKVVQWKVDNALQ<br>SGNSQESVTEQDSKD<br>STYLSSTLTLSKADYE<br>KHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 391) | EVQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMILTQPHSVSE<br>SPGKTVTISCTRSSGSISNYVQWYQQRPGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 392) |
| Lex#161 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAESVH                                                                                                                                                                                                                                                             | EVQLLESAGGLVQPGGSLRLSCLASGFTFSSYAMSWVRQAPGKCLEWVSA<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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|         | WYQQKPGQAPVLIYN<br>DNNRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVLLNDADQGV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TPPSKQSNNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 393)                                          | GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKCLEWWSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMFLTPHVSSE<br>SPGKTVTISCTRSSGSISNYYVQWYQRPGRGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 394)                                                                                                          |
| Lex#167 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS<br>DSVRMSGIPERFSGSN<br>SWNTATLTISRVEAGD<br>EADYYCQVRDSIDDLIV<br>FGGGTKLTVLGQPKAA<br>PSVTLFPPSSEELQAN<br>KATLVCLISDFYPGAVT<br>VAWKADSSPVKAGVET<br>TPPSKQSNNKYAASSY<br>LSLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 395) | EVQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKLEWWS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKCLEWWSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMFLTPHVSSE<br>SPGKTVTISCTRSSGSISNYYVQWYQRPGRGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 396) |
| Lex#168 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS<br>DSVRMSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSIDDLIV<br>GGGKTLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 397)  | EVQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKLEWWS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKCLEWWSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMFLTPHVSSE<br>SPGKTVTISCTRSSGSISNYYVQWYQRPGRGSSPTTVIYNHNKRPSGVPDRF<br>SGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 398) |
| Lex#169 | SYVLTQPPSVSVAPGK<br>TARITCRGDNIEAETVG<br>WYQQKPGQAPVLIYS<br>DSVRMSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSIDDLIV<br>GGGKTLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 399)  | EVQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKLEWWS<br>AISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP<br>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV<br>NHNKPSNTKVDKRVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP<br>SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGS<br>FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGGGGGGE<br>VQLLESAGGLVQPGGSLRLSAAAGFTFSSYAMSWVRQAPGKCLEWWSA<br>ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSYG<br>AFDYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGNFMFLTPHVSSE<br>SPGKTVTISCTRSSGSINYYVQWYQRPGRGSSPTTVIYNHNKRPSGVPDR<br>FSGSIDSSSNSASLTISGLKTEDEADYYCQSWTWEGLKVFSGCGTKLTVL<br>(SEQ ID NO: 400)  |

*Trispecific multivalent molecules*

In some embodiments, the proteinaceous molecule is trispecific and multivalent.

Figures 2 and 3 disclose examples of trispecific multivalent molecules encompassed by the present invention. The trispecific multivalent molecules of the present invention can be subcategorized into two categories depending on the scaffold module used: 1) scaffold modules which comprise a first antigen-binding site that binds to Factor IXa and a second antigen-binding site that binds to Factor X (referred to as "IXa/X scaffold") and 2) scaffold modules which comprise two antigen-binding sites wherein both antigen-binding sites bind to Factor IXa or Factor X (referred to as "monospecific scaffold").

As already discussed, it is immediately apparent that various different macromolecular topologies are possible using the design considerations disclosed herein and that these different macromolecular topologies are within the scope of the present invention. We focus on several possible macromolecular topologies below to outline the utility and versatility of the present approach.

*1) Trispecific "IXa/X scaffold" topology*

Examples of proteinaceous molecules which have a trispecific "IXa/X scaffold" topology are depicted in Figure 2. These proteinaceous molecules are trispecific multivalent and comprise at least three antigen-binding sites that bind to different targets.

In one aspect, the present invention provides a proteinaceous molecule comprising:

- (i) a scaffold module, wherein the scaffold module comprises a first antigen-binding site that binds to Factor IXa and a second antigen-binding site that binds to Factor X; and
- (ii) a first and second binding module that comprise a third and fourth antigen-binding site, respectively,

wherein the third and fourth antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

- (a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

(ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and

5 (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a; and

(b) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

10 wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the  
 15 LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (a)(iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198,  
 20 LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) and (a)(iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198,  
 25 LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2a.

30 In some embodiments, the present invention provides a proteinaceous molecule comprising:  
 (a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

35 (ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and

(iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2b; and

(b) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, and the LCDR1, LCDR2 and LCDR3 of (a)(iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V320, LCDR1, LCDR2 and LCDR3 of V305, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) and (a)(iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W206 and V245, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2b.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker,

wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and
- (iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker,

wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V320, VL of V305, VL of V43, VL of V90, VL of V141, VL of V149, VL of V245, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W206 and V245, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules that are scFvs or scFabs comprising a VL domain and a VH domain, wherein the VL domain comprises SEQ ID NO: 184 and the VH domain comprises SEQ ID NO: 187, the VL domain comprises SEQ ID NO: 185 and the VH domain comprises SEQ ID NO: 188, or the VL domain comprises SEQ ID NO: 186 and the VH domain comprises SEQ ID NO: 189.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules that are scFvs or scFabs comprising a VL domain and a VH domain, wherein the VL domain comprises SEQ ID NO: 184 and the VH domain comprises SEQ ID NO: 187, the VL domain comprises SEQ ID NO: 185 and the VH domain comprises SEQ ID NO: 188, or the VL domain comprises SEQ ID NO: 186 and the VH domain comprises SEQ ID NO: 189.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W206, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V320, VL of V305, VL of V245, VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some

embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W206 and V245, W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain comprises SEQ ID NO: 4;

10 (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules comprising SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID  
15 NO: 192.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88  
20 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

25 (a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain comprises SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

30 (iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules comprising SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W206, VL of W88, VL of  
35 W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V320, VL of V305, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some

embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W206 and V245, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain comprises SEQ ID NO: 4;

10 (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a; and

(b) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I.

15 In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4a, and the binding module comprises SEQ ID NO: 178.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

25 (a) an antibody or a bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains wherein the VH domain comprises SEQ ID NO: 4;

(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and

30 (iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b; and

(b) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I.

In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W206, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (a)(iii) is the VL of V43, VL of V320, VL of V305, VL of V90, VL of V141, VL of V245, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b. In some embodiments, the VL of (a)(ii) and (a)(iii) are the VL of W206 and V245, VL of W88 and

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V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W128 and V141, VL of W162 and V204, VL of W83 and V217, VL of W88 and V90, or VL of W83 and V43, respectively, disclosed in Tables 3 and 4b, and the binding module comprises SEQ ID NO: 178.

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In some embodiments of any of the above, the binding modules are attached to the N- or –C terminus of the heavy or light chain through a linker. In some embodiments, the binding modules are attached to the C-terminus of the heavy or light chain. In some embodiments, the first binding module is attached to the C-terminus of the first heavy chain through a linker, and the second binding module is attached to C-terminus of the second heavy chain through the linker.

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In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and the two light chain (LC) sequences of any one of Bax#142, Lex#38, Lex#39, Bax#87, Bax#89, Lex#36, Lex#40 or Lex#41 disclosed in Table 10.

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In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence, one copy of the LC with lambda constant domain sequence, and one copy of the LC with kappa constant domain sequence of any one of Bax#142, Lex#38, Lex#39, Bax#87, Bax#89, Lex#36, Lex#40 or Lex#41 disclosed in Table 10.

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**Table 10: Sequences of “trispecific  $\kappa\lambda$ -body” constructs**

| ID      | LC with lambda constant domain                                                                                                                                                                                                                                                                | LC with kappa constant domain                                                                                                                                                                                                                                                                | Heavy chain sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bax#142 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLVIYR<br>DSDRPSGIPERFSGSN<br>SGNTATLTISRVEAGDE<br>ADYYCQVRDSVDDKA<br>VFGGGTKLTVLGQPKA<br>APSVTLFPPSSEELQA<br>NKATLVCLISDFYPGAV<br>TVAWKADSPVKAGVE<br>TTTPSKQSNNKYAASS<br>YLSLTPEQWKSHRSYS<br>CQVTHEGSTVEKTVAP<br>TECS<br>(SEQ ID NO: 259) | NFMLTQPHSVSESPGKT<br>VTISCTRSSGSINYYVQ<br>WYQQRPGSSPTTVIYNH<br>NKRPSGVPDRFSGSIDS<br>SSNSASLTISGLKTEDEA<br>DYYCQSWTWSGEKVFG<br>GGTKLTVLRTVAAPSVFI<br>FPPSDEQLKSGTASVVC<br>LLNFPYPREAKVQWKVD<br>NALQSGNSQESVTEQDS<br>KDSTYLSSTLTLSKADY<br>EKHKVYACEVTHQGLSS<br>PVTKSFNRGEC<br>(SEQ ID NO: 260) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKGLEWVSAISGSGGSTYYA<br>DSVKGRFTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP<br>SSSLGTQTYICNVNHKPSNTKVDKRVPEKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYKCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGKGGGSGGGGSGGGGSGGGGSEV<br>QLQQSGPELEKPGASVKLSCKASGYSFTGYN<br>MNWVKQSHGKCLEWIGHIDPYGDTSYNQKF<br>RGKATLTVDKSSSTAYMQLKSLTSEDSAVYYC<br>VKGGYYGHWFYFDVWGAGTTVTVSSGGGGSG<br>GGGSGGGGSGGGGSDIQMTQSPSSLSASLG<br>ERVSLTCRASQDIGSSLNLWQQGPDGTIKRLI<br>YATSSLD SGV PKR FSGSRSGSDYSLTISSLES |

|        |                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|        |                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                              | EDFVDYYCLQYVSSPPTFGCGTKLELKRADAA<br>P<br>(SEQ ID NO: 261)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Lex#38 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYYCQVRDSVDDLYVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 262)      | EIVLTQSPGTLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIIEA<br>SKRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGGQ<br>TKVEIKRTVAAPSVFIFPP<br>SDEQLKSGTASVCLLN<br>NFYPREAKVQWKVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEKH<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 263)     | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LQQSGPELEKPGASVKLSCKASGYSTGYNM<br>NWVKQSHGKCLEWIGHIDPYGDTSYNQKFR<br>GKATLTVDKSSSTAYMQLKSLTSEDSAVYYCV<br>KGGYYGHWYFDVWGAGTTTVTVSSGGGGSG<br>GGGSGGGGSGGGGSDIQTQSPSSLSASLG<br>ERVSLTCRASQDIGSSLNLQQGPDGTIKRLI<br>YATSSLD SGVPKRFSGSRSGSDYSLTISSLES<br>EDFVDYYCLQYVSSPPTFGCGTKLELK<br>(SEQ ID NO: 264) |
| Lex#39 | QSVLTQPPSVSGAPG<br>QRVTISCTGSSSNILTN<br>KNVHWYQQLPGTAPK<br>LLIYAIRRPSGVPDRF<br>SGSKSGTSASLAITGLQ<br>AEDEADYYCQSYDTSG<br>HTLTAVFGGGTKLTVL<br>GQPKAAPSVTLFPPSS<br>EELQANKATLVCLISDF<br>YPGAVTVAWKADSSPV<br>KAGVETTPSKQSNNK<br>YAASSYLSLTPEQWKS<br>HRSYSCQVTHEGSTVE<br>KTVAPTECS<br>(SEQ ID NO: 265) | DIQLTQSPSFLSASVGDR<br>VTITCRASQNIIVNHLRWY<br>QQKPGKAPKLLIYDNSPL<br>QSGVPSRFSGSGSGTEF<br>TLTISSLQPEDFATYYCQ<br>QAPYGHALSTFGQGTKV<br>EIKRTVAAPSVFIFPPSDE<br>QLKSGTASVCLLN NFY<br>PREAKVQWKVDNALQS<br>GNSQESVTEQDSKDSTY<br>SLSSTLTLSKADYEKHV<br>YACEVTHQGLSSPVTKS<br>FNRGEC<br>(SEQ ID NO: 266) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSEVQ<br>LQQSGPELEKPGASVKLSCKASGYSTGYNM<br>NWVKQSHGKCLEWIGHIDPYGDTSYNQKFR<br>GKATLTVDKSSSTAYMQLKSLTSEDSAVYYCV<br>KGGYYGHWYFDVWGAGTTTVTVSSGGGGSG<br>GGGSGGGGSGGGGSDIQTQSPSSLSASLG<br>ERVSLTCRASQDIGSSLNLQQGPDGTIKRLI<br>YATSSLD SGVPKRFSGSRSGSDYSLTISSLES<br>EDFVDYYCLQYVSSPPTFGCGTKLELK<br>(SEQ ID NO: 267) |
| Bax#87 | SYVLTQPPSVSVAPGK<br>TAILTCGGDNIEAESVH<br>WYQQKPDQAPLLVYT<br>DSYRPSGIPERFSGSN<br>SGNTATLTITRVEVGDE<br>ADYYCQVRDSNDDRA<br>VFGGGTKLTVLGQPKA<br>APSVTLFPPSSEELQA                                                                                                                                      | EIVLTQSPGTLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIIEA<br>SKRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGGQ<br>TKVEIKRTVAAPSVFIFPP<br>SDEQLKSGTASVCLLN                                                                                                                          | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|        |                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|        | NKATLVCLISDFYPGAV<br>TVAWKADSSPVKAGVE<br>TTTPSKQSNKYAASS<br>YLSLTPEQWKSHRSYS<br>CQVTHEGSTVEKTVAP<br>TECS<br>(SEQ ID NO: 268)                                                                                                                                                                     | NFYPREAKVQWKVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEKH<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 269)                                                                                                                                                                       | SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGKGGGSGGGGSGGGGSGGGGSGGGGSEV<br>QLQQSGPELEKPGASVKLSCKASGYSTGYN<br>MNWVKQSHGKCLEWIGHIDPYYGDTSYNQKF<br>RGKATLTVDKSSSTAYMQLKSLTSEDSAVYYC<br>VKGGYYGHWFYFDVWGAGTTVTVSSGGGGSG<br>GGGSGGGGSGGGGSDIQTQSPSSLSASLG<br>ERVSLTCRASQDIGSSLNLWQQGPDGTIKRLI<br>YATSSLD SGVPKRFSGSRSGSDYSLTISSLES<br>EDFVDYYCLQYVSSPPTFGCGTKLELKRADAA<br>P<br>(SEQ ID NO: 270)                                                                                                                                                                                                                                                                                             |
| Bax#89 | QSVLTQPPSVSGAPGQ<br>RVTISCTGSSSNILTNK<br>NVHWYQQLPGTAPKLL<br>IYAIRRPSGVPDRFSG<br>SKSGTSASLAITGLQAE<br>DEADYYCQSYDTSGHT<br>LTAVFGGGTKLTVLGQ<br>PKAAPSVTLFPPSSEEL<br>QANKATLVCLISDFYPG<br>AVTVAWKADSSPVKAG<br>VETTPSKQSNKYAA<br>SSYLSLTPEQWKSHRS<br>YSCQVTHEGSTVEKTV<br>APTECS<br>(SEQ ID NO: 271) | DIQLTQSPSFLSASVGDR<br>VTITCRASQAIHAHLRWY<br>QQKPGKAPKLLIYDNSPL<br>QSGVPSRFSGSGSGTEF<br>TLTISSLQPEDFATYYCQ<br>QATFGHALSTFGQGTKV<br>EIKRTVAAPSVFIFPPSDE<br>QLKSGTASVCLLNIFY<br>PREAKVQWKVDNALQS<br>GNSQESVTEQDSKDS<br>SLSSTLTLSKADYEKH<br>YACEVTHQGLSSPVTKS<br>FNRGEC<br>(SEQ ID NO: 272) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWVSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGKGGGSGGGGSGGGGSGGGGSGGGGSEV<br>QLQQSGPELEKPGASVKLSCKASGYSTGYN<br>MNWVKQSHGKCLEWIGHIDPYYGDTSYNQKF<br>RGKATLTVDKSSSTAYMQLKSLTSEDSAVYYC<br>VKGGYYGHWFYFDVWGAGTTVTVSSGGGGSG<br>GGGSGGGGSGGGGSDIQTQSPSSLSASLG<br>ERVSLTCRASQDIGSSLNLWQQGPDGTIKRLI<br>YATSSLD SGVPKRFSGSRSGSDYSLTISSLES<br>EDFVDYYCLQYVSSPPTFGCGTKLELKRADAA<br>P<br>(SEQ ID NO: 273) |
| Lex#36 | SYVLTQPPSVSVAPGK<br>TARITCGGDNIEAETVH<br>WYQQKPGQAPVLIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYYCQVRDSVDDLTVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 274)      | EIVLTQSPGTLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIYEA<br>SKRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQVTRRSPWTFGQG<br>TKVEIKRTVAAPSVFIFPP<br>SDEQLKSGTASVCLLN<br>NFYPREAKVQWKVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEKH<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 275) | EVQLLESGGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWVSAISGSGGSTYYA<br>DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLTVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNL<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGSGGGGSGGGGSGGGGSGGGGQVQ<br>LQQSGGGLVKPGGSLKLSAASGFTFSSYIMS<br>WVRQTPEKCLEWVATIRSGGDNTYYPDSVKG                                                                                                                                                                                                                                               |

|        |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|        |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                              | RFTISRDNANKNKLYLQMSSLRSEDTALYYCAIY<br>YGNYGGLAYWGQGLVTVSAGGGGSGGGGS<br>GGGGSGGGSDILMTQSPASLSASVGETVTIT<br>CRASGNIHNYLAWYQQKQKSPQLLVYNAKT<br>LADGVPSRFSGSGSGTQYSLKINSLQPEDFGS<br>YYCQHFWSPTYTFGCGTKLEIK<br>(SEQ ID NO: 276)                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Lex#40 | SYVLTQPPSVSVAPGK<br>TARITCGDNIEAETVH<br>WYQQKPGQAPVLIYS<br>DSIRPSGIPERFSGSNS<br>GNTATLTISRVEAGDEA<br>DYYCQVRDSVDDLTVF<br>GGGKLTVLGQPKAAP<br>SVTLFPPSSEELQANK<br>ATLVCLISDFYPGAVTV<br>AWKADSSPVKAGVETT<br>TPSKQSNNKYAASSYL<br>SLTPEQWKSHRSYSC<br>QVTHEGSTVEKTVAPT<br>ECS<br>(SEQ ID NO: 277)     | EIVLTQSPGTLSPGER<br>ATLSCRASQSVTTGYLA<br>WYQQKPGQAPRLIIEA<br>SKRATGIPDRFSGSGSG<br>TDFTLTISRLEPEDFAVY<br>YCQQVTRRSPWTFGQG<br>TKVEIKRTVAAPSVFIFPP<br>SDEQLKSGTASVCLLN<br>NFYPREAKVQWKVDNAL<br>QSGNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEKH<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 278)     | EVQLLESQGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGSPVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSGKAS<br>CKVPVKATVYQGERVKIQEFKNGMLHGD<br>KVSFFCKNKEKKCSYTEDAQCIDGTIEVPKCFK<br>EHSSLAFWKTDASDVKPC<br>(SEQ ID NO: 279) |
| Lex#41 | QSVLTQPPSVSGAPG<br>QRTISCTGSSSNILTN<br>KNVHWYQQLPGTAPK<br>LLIYASRRPSGVPDRF<br>SGSKSGTSASLAITGLQ<br>AEDEADYYCQSYDTS<br>HTLTAVFGGGTKLTVL<br>GQPKAAPSVTLFPPSS<br>EELQANKATLVCLISDF<br>YPGAVTVAWKADSSPV<br>KAGVETTPSKQSNNK<br>YAASSYLSLTPEQWKS<br>HRSYSCQVTHEGSTVE<br>KTVAPTECS<br>(SEQ ID NO: 280) | DIQLTQSPSFLSASVGDR<br>VTITCRASQNIIVNHLRWY<br>QQKPGKAPKLLIYDNSPL<br>QSGVPSRFSGSGSGTEF<br>TLTISSLQPEDFATYYCQ<br>QAPYGHALSTFGQGTKV<br>EIKRTVAAPSVFIFPPSDE<br>QLKSGTASVCLLN<br>NFYPREAKVQWKVDNALQS<br>GNSQESVTEQDSKDS<br>TYSLSSTLTLSKADYEKH<br>KVYACEVTHQGLSSPVT<br>KSFNRGEC<br>(SEQ ID NO: 281) | EVQLLESQGGLVQPGGSLRLSCAASGFTFSS<br>YAMSWVRQAPGKLEWWSAISGSGGSTYYA<br>DSVKGRFTISRDNKNTLYLQMNSLRAEDTAV<br>YYCAKSYGAFDYWGQGLVTVSSASTKGPSV<br>FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS<br>WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP<br>SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHTCPPCPAPEAAGGSPVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN<br>GKEYCKVSNKALPAPIEKTISKAKGQPREPQ<br>VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV<br>EWESNGQPENNYKTPPVLDSDGSFFLYSKL<br>TVDKSRWQQGNVFCFSVMHEALHNHYTQKS<br>LSLSPGGGGGSGGGGSGGGGSGGGGSGKAS<br>CKVPVKATVYQGERVKIQEFKNGMLHGD<br>KVSFFCKNKEKKCSYTEDAQCIDGTIEVPKCFK<br>EHSSLAFWKTDASDVKPC<br>(SEQ ID NO: 282) |

## 2) "2 by 2 trispecific" topology

Examples of proteinaceous molecules which have a "2 by 2 trispecific" topology are depicted in Figure 3. These proteinaceous molecules are trispecific multivalent and comprise an equal number of antigen-binding sites that bind to Factor IXa, Factor X or another target. This sort of topology uses a monospecific scaffold.

In one aspect, the present invention provides a proteinaceous molecule comprising:

(i) a scaffold module, wherein the scaffold module comprises a first and second antigen-binding site that bind to Factor IXa or Factor X;

(ii) a first and second binding module that comprise a third and fourth antigen-binding site, respectively; and

5 (iii) a third and fourth binding module that comprise a fifth and sixth antigen-binding site, respectively;

wherein the third and fourth antigen-binding sites bind to Factor IXa or Factor X, the fifth and sixth antigen-binding site bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker, and the proteinaceous molecule comprises two antigen-binding  
10 sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin),  
15 Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, annexins (preferably annexin V) or  $\beta_2$ -glycoprotein I.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

20 (a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

(ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light  
25 chains disclosed in Table 2a;

(b) at least two binding modules that are scFvs or scFabs comprising:

(i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2a, and

(ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is  
30 SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3, and

(c) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor  
35 IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1,

lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I.

- 5 In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) bind to the same target.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

- (a) an antibody or bivalent fragment thereof that comprises:
- 20 (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and
- (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b;
- 25 (b) at least two binding modules that are scFvs or scFabs comprising:
- (i) the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1 or the Factor IXa binding light chains disclosed in Table 2b, and
- (ii) an HCDR1, HCDR2 and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3, and
- 30 (c) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;
- wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and
- 35 the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor

V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I.

In some embodiments, the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1, or the LCDR1, LCDR2 and LCDR3 of (a)(ii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the LCDR1, LCDR2 and LCDR3 of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) bind to the same target.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a;

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and

the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) bind to the same target.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b;

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules comprising an antigen-binding site each, wherein both of the antigen-binding sites bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker;

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -

glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) bind to the same target.

In some embodiments, the present invention provides a proteinaceous molecule comprising:  
(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a;

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules that are scFvs or scFabs comprising a VL domain and a VH domain, wherein the VL domain comprises SEQ ID NO: 184 and the VH domain comprises SEQ ID NO: 187, the VL domain comprises SEQ ID NO: 185 and the VH domain comprises SEQ ID NO: 188, or the VL domain comprises SEQ ID NO: 186 and the VH domain comprises SEQ ID NO: 189,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43,

VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and  
 5 LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

10 (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b;

15 (b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ  
 20 ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules that are scFvs or scFabs comprising a VL domain and a VH domain, wherein the VL domain comprises SEQ ID NO: 184 and the VH domain comprises SEQ ID NO: 187, the VL domain comprises SEQ ID NO: 185 and the VH domain comprises  
 25 SEQ ID NO: 188, or the VL domain comprises SEQ ID NO: 186 and the VH domain comprises SEQ ID NO: 189,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and  
 30 the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of  
 35 W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are

that of W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

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In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

10 (ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a;

(b) at least two binding modules that are scFvs comprising:

15 (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183, and

20 (c) at least two binding modules comprising SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and  
 25 the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of  
 30 W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some  
 35 embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

5 (ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b;

(b) at least two binding modules that are scFvs comprising:

10 (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183, and

15 (c) at least two binding modules comprising SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and  
 20 the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta_2$ -glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b. In some embodiments, the VL of each of the two light chains are identical, the LCDR1,  
 25 LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

35 (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a;

(b) at least two binding modules that are scFvs comprising:

5 (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

10 (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and

15 the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta$ 2-glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a. In some  
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embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

30 (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b;

35 (b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,

wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker; and

the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha_5\beta_3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin (preferably annexin V) or  $\beta$ 2-glycoprotein I. In some embodiments, the VL of (a)(ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, or the VL of (a)(ii) is the VL of V43, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b, and the LCDR1, LCDR2 and LCDR3 of (b)(i) are that of W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

(a) an antibody or bivalent fragment thereof that comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

(ii) two light chains each comprising the VL of V245 disclosed in Table 4b;

(b) at least two binding modules that are scFvs comprising:

(i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,

wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W198 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and

(ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and

(c) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I,

wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine. In some embodiments, the VL of each of the two light chains are

identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are identical and the two binding modules of (c) are identical.

In some embodiments, the present invention provides a proteinaceous molecule comprising:

- 5 (a) an antibody or bivalent fragment thereof that comprises:
- (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and
  - (ii) two light chains each comprising the VL of V212 disclosed in Table 4b;
- (b) at least two binding modules that are scFvs comprising:
- 10 (i) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of W127 disclosed in Table 1, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182, and
- (ii) a VH domain, wherein the VH domain is SEQ ID NO: 183; and
- 15 (c) at least two binding modules comprising domain V of  $\beta$ 2-glycoprotein I, wherein the proteinaceous molecule comprises two antigen-binding sites that bind to Factor IXa, two antigen-binding sites that bind to Factor X and two antigen-binding sites that bind to phosphatidylserine. In some embodiments, the VL of each of the two light chains are identical, the LCDR1, LCDR2 and LCDR3 of each of the two binding modules of (b) are
- 20 identical and the two binding modules of (c) are identical.

In some embodiments of any of the above, the binding modules are attached to the N- or –C terminus of the heavy or light chain through a linker. In some embodiments, the binding modules are attached to the C-terminus of the heavy or light chain. In some embodiments,

25 the binding modules are attached to the C-terminus of the heavy chain and the C-terminus of the light chain.

In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and light chain sequence of either Lex#68 or Lex#69 disclosed in Table 11.

30 In some embodiments, the proteinaceous molecule comprises both the heavy chain sequence and light chain sequence of any one of Lex#134, Lex#135, Lex#68 or Lex#69 disclosed in Table 11.

35 In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence and two copies of the light chain sequence of either Lex#68 or Lex#69 disclosed in Table 11.

In some embodiments, the proteinaceous molecule consists of two copies of the heavy chain sequence and two copies of the light chain sequence of any one of Lex#134, Lex#135, Lex#68 or Lex#69 disclosed in Table 11.

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**Table 11: Sequences of “trispecific 2 by 2” constructs**

| ID      | Light chain sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Heavy chain sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lex#68  | EIVLTQSPGTLISLSPGERATLSCRASQKVD<br>DDELAWYQQKPGQAPRLIYRASNRATGIP<br>DRFSGSGSGTDFTLTISRLEPEDFAVYYCQ<br>QYNDPDLGYEDYTFGGGTKVEIKRTVAAPS<br>VFIFPPSDEQLKSGTASVCLLNFPYREA<br>KVQWKVDNALQSGNSQESVTEQDSKDST<br>YLSSTLTLSKADYEKHKVYACEVTHQGLS<br>SPVTKSFNRGECGGGSGGGSGGGSGGGGS<br>GGGGSEVQLLESGLVQPGGSLRLSCAA<br>SGFTFSSYAMSWVRQAPGKCLEWWSAIG<br>SGGSTYYADSVKGRFTISRDNKNTLYLQM<br>NSLRAEDTAVYYCAKSYGAFDYWGQGLV<br>TVSSGGGSGGGSGGGSGGGSGGGSGNFM<br>LTQPHSVSESPGKTVTISCTRSSGSINNY<br>VQWYQQRPGSSPTTVIYNHNKRPSPGVPDR<br>FSGSIDSSNSASLTISGLKTEADYYCQS<br>WTWEGLKVFSGCTKLTVL<br>(SEQ ID NO: 283) | EVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMSW<br>VRQAPGKCLEWWSAIGSGGSTYYADSVKGRFTISR<br>NSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQ<br>TLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK<br>DYFPEPVTWNSGALTSKVHFFPVLQSSGLYSLSS<br>VWTPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHCTCPPEAEEAAGGSPVFLFPPKPKDTLMISRTPEV<br>TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVSVLTVHLQDNLNGKEYCKVSNKALPAPI<br>EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV<br>KGFYPDSIAVEWESNGQPENNYKTPPVLDSDGSFLL<br>YSKLTVDKSRWQQGNVSCFVSVMHEALHNHYTQKSLS<br>LSPGGGGSGGGSGGGSGGGSGGGSGKASCKVPVKK<br>ATVYQGERVKIQEFKNGMLHGDKVSFFCKNKEKKC<br>SYTEDAQCIDGTIEVPKCFKEHSSLAFWKTDASDVK<br>C<br>(SEQ ID NO: 284)                                                                                                                                                                               |
| Lex#69  | EIVLTQSPGTLISLSPGERATLSCRASQKVD<br>DDELAWYQQKPGQAPRLIYRASNRATGIP<br>DRFSGSGSGTDFTLTISRLEPEDFAVYYCQ<br>QYNDPDLGYEDYTFGGGTKVEIKRTVAAPS<br>VFIFPPSDEQLKSGTASVCLLNFPYREA<br>KVQWKVDNALQSGNSQESVTEQDSKDST<br>YLSSTLTLSKADYEKHKVYACEVTHQGLS<br>SPVTKSFNRGECGGGSGGGSGGGSGGGGS<br>GGGSKASCKVPVKKATVYQGERVKIQE<br>KFKNGMLHGDKVSFFCKNKEKKCSYTEDA<br>QCIDGTIEVPKCFKEHSSLAFWKTDASDVK<br>PC<br>(SEQ ID NO: 285)                                                                                                                                                                                  | EVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMSW<br>VRQAPGKCLEWWSAIGSGGSTYYADSVKGRFTISR<br>NSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQ<br>TLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK<br>DYFPEPVTWNSGALTSKVHFFPVLQSSGLYSLSS<br>VWTPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHCTCPPEAEEAAGGSPVFLFPPKPKDTLMISRTPEV<br>TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVSVLTVHLQDNLNGKEYCKVSNKALPAPI<br>EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV<br>KGFYPDSIAVEWESNGQPENNYKTPPVLDSDGSFLL<br>YSKLTVDKSRWQQGNVSCFVSVMHEALHNHYTQKSLS<br>LSPGGGGSGGGSGGGSGGGSGGGSEVQLLESGLV<br>VQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKCLE<br>WWSAIGSGGSTYYADSVKGRFTISRDNKNTLYLQM<br>NSLRAEDTAVYYCAKSYGAFDYWGQGLTVTVSSGGG<br>SGGGSGGGSGGGSGGGSGNFMLTQPHSVSESPGKTV<br>TISCTRSSGSINNYVQWYQQRPGSSPTTVIYNHNKR<br>PSGVPDRFSGSIDSSNSASLTISGLKTEADYYCQS<br>WTWEGLKVFSGCTKLTVL<br>(SEQ ID NO: 286) |
| LEX#134 | SYVLTQPPSVSVAPGKTARITCRGDNIEAE<br>TVGWYQQKPGQAPVLIYSDSVRMGIPE<br>RFSGSNSWNTATLTISRVEAGDEADYYCQ<br>VRDSIDDLIVFGGKTLVLGQPKAAPSVTL<br>FPPSSEELQANKATLVCLISDFYPGAVTVA<br>WKADSSPVKAGVETTPSKQSNNKYAASS<br>YLSLTPEQWKSHRSYSCQVTHEGSTVEKT<br>VAPTECSGGGSGGGSGGGSGGGSGGGGS<br>KASCKVPVKKATVYQGERVKIQEFKNG                                                                                                                                                                                                                                                                                   | EVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMSW<br>VRQAPGKCLEWWSAIGSGGSTYYADSVKGRFTISR<br>NSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQ<br>TLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK<br>DYFPEPVTWNSGALTSKVHFFPVLQSSGLYSLSS<br>VWTPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD<br>KTHCTCPPEAEEAAGGSPVFLFPPKPKDTLMISRTPEV<br>TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVSVLTVHLQDNLNGKEYCKVSNKALPAPI                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|         |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | MLHGDKVSFFCKNKEKKCSYTEDAQCIDG<br>TIEVPKCFKEHSSLAFWKTDASDVKPC<br>(SEQ ID NO: 401)                                                                                                                                                                                                                                                                                                               | EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV<br>KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL<br>YSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLS<br>LSPGGGGGGGEVQLLESGGGGLVQPGGSLRLSCAASGF<br>TFSSYAMSWVRQAPGKCLEWWSAISGSGGSTYYADS<br>VKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSGGGGSGGGGSGGGGSGGGG<br>GSNFMLTQPHSVSESPGKTVTISCTRSSGSISNYYVQ<br>WYQQRPGSSPTTVIYNHNKRPSGVPDRFSGSIDSSSN<br>SASLTISGLKTEDEADYYCQSWTWEGLKVFGCGTKLT<br>VL<br>(SEQ ID NO: 402)                                                                                                                                                                                                                                                                                                                                                                          |
| LEX#135 | SYVLTQPPSVSVAPGKTARITCGGDNIEAE<br>SVHWYQQKPGQAPVLVIYNDNNRPSGIPE<br>RFSGSNSGNTATLTISRVEAGDEADYYCQV<br>LLNDADEGVFGGGTKLTVLGQPKAAPSVTL<br>FPPSSEELQANKATLVCLISDFYPGAVTVA<br>WKADSSPVKAGVETTTTPSKQSNNKYAASS<br>YLSLTPEQWKSHRSYSCQVTHEGSTVEKT<br>VAPTECSGGGGSGGGGSGGGGSGGGGSGGGG<br>KASCKVPVKATVVYQGERVKIQEFKNG<br>MLHGDKVSFFCKNKEKKCSYTEDAQCIDG<br>TIEVPKCFKEHSSLAFWKTDASDVKPC<br>(SEQ ID NO: 403) | EVQLLESGGGGLVQPGGSLRLSCAASGFTFSSYAMSW<br>VRQAPGKGLEWWSAISGSGGSTYYADSVKGRFTISR<br>NSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQ<br>TLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK<br>DYFPEPVTWNSGALTSGLVHTFPAVLQSSGLYSLSS<br>VWTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD<br>KTHCTCPPEAPEAAGGSPVFLFPPKPKDTLMISRTPEV<br>TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVVSVLTVHLQDNLNGKEYCKVSNKALPAPI<br>EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV<br>KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL<br>YSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLS<br>LSPGGGGGGGEVQLLESGGGGLVQPGGSLRLSCAASGF<br>TFSSYAMSWVRQAPGKCLEWWSAISGSGGSTYYADS<br>VKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY<br>GAFDYWGQGLTVTVSSGGGGSGGGGSGGGGSGGGG<br>GSNFMLTQPHSVSESPGKTVTISCTRSSGSINYYVQ<br>WYQQRPGSSPTTVIYNHNKRPSGVPDRFSGSIDSSSN<br>SASLTISGLKTEDEADYYCQSWTWSGEKVFGCGTKLT<br>VL<br>(SEQ ID NO: 404) |

### Pharmaceutical composition

The present invention also provides a pharmaceutical composition comprising the antibodies of the present invention and a pharmaceutically acceptable carrier and/or diluent.

5

In a second aspect, the present invention provides a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of the present invention and a pharmaceutically acceptable carrier or diluent.

10 As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable diluent" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients  
15 at the dosages and concentrations employed and, without limiting the scope of the present invention, include: additional buffering agents; preservatives; co-solvents; antioxidants,

including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g., Zn-protein complexes); biodegradable polymers, such as polyesters; salt-forming counterions, such as sodium, polyhydric sugar alcohols; amino acids, such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, and threonine; organic sugars or sugar alcohols, such as lactitol, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinositol, myoinositol, galactose, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate; low molecular weight proteins, such as human serum albumin, bovine serum albumin, gelatin, or other immunoglobulins; and hydrophilic polymers, such as polyvinylpyrrolidone.

A pharmaceutical composition as described herein may also contain other substances. These substances include, but are not limited to, cryoprotectants, lyoprotectants, surfactants, bulking agents, anti-oxidants, and stabilizing agents. In some embodiments, the pharmaceutical composition may be lyophilized.

The term "cryoprotectant" as used herein, includes agents which provide stability to the antibody against freezing-induced stresses, by being preferentially excluded from the antibody's surface. Cryoprotectants may also offer protection during primary and secondary drying and long-term product storage. Non-limiting examples of cryoprotectants include sugars, such as sucrose, glucose, trehalose, mannitol, mannose, and lactose; polymers, such as dextran, hydroxyethyl starch and polyethylene glycol; surfactants, such as polysorbates (e.g., PS-20 or PS-80); and amino acids, such as glycine, arginine, leucine, and serine. A cryoprotectant exhibiting low toxicity in biological systems is generally used.

In one embodiment, a lyoprotectant is added to a pharmaceutical composition described herein. The term "lyoprotectant" as used herein, includes agents that provide stability to the antibody during the freeze-drying or dehydration process (primary and secondary freeze-drying cycles), by providing an amorphous glassy matrix and by binding with the antibody's surface through hydrogen bonding, replacing the water molecules that are removed during the drying process. This helps to minimize product degradation during the lyophilization cycle, and improve the long-term product stability. Non-limiting examples of lyoprotectants include sugars, such as sucrose or trehalose; an amino acid, such as monosodium glutamate, non-crystalline glycine or histidine; a methylamine, such as betaine; a lyotropic salt, such as magnesium sulfate; a polyol, such as trihydric or higher sugar alcohols, e.g., glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol;

polyethylene glycol; pluronics; and combinations thereof. The amount of lyoprotectant added to a pharmaceutical composition is generally an amount that does not lead to an unacceptable amount of degradation of the strain when the pharmaceutical composition is lyophilized.

5

In some embodiments, a bulking agent is included in the pharmaceutical composition. The term "bulking agent" as used herein, includes agents that provide the structure of the freeze-dried product without interacting directly with the pharmaceutical product. In addition to providing a pharmaceutically elegant cake, bulking agents may also impart useful qualities in regard to modifying the collapse temperature, providing freeze-thaw protection, and enhancing the strain stability over long-term storage. Non-limiting examples of bulking agents include mannitol, glycine, lactose, and sucrose. Bulking agents may be crystalline (such as glycine, mannitol, or sodium chloride) or amorphous (such as dextran, hydroxyethyl starch) and are generally used in formulations in an amount from 0.5% to 10%.

15

Other pharmaceutically acceptable carriers, excipients, or stabilizers, such as those described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980) may also be included in a pharmaceutical composition described herein, provided that they do not adversely affect the desired characteristics of the pharmaceutical composition. As used herein, "pharmaceutically acceptable carrier" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed and include: additional buffering agents; preservatives; co-solvents; antioxidants, including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g., Zn-protein complexes); biodegradable polymers, such as polyesters; salt-forming counterions, such as sodium, polyhydric sugar alcohols; amino acids, such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, and threonine; organic sugars or sugar alcohols, such as lactitol, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinositol, myoinositol, galactose, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate; low molecular weight proteins, such as human serum albumin, bovine serum albumin, gelatin, or other immunoglobulins; and hydrophilic polymers, such as polyvinylpyrrolidone.

35

In some embodiments, the pharmaceutical composition may be a solution which is suitable for intravenous, intramuscular, conjunctival, transdermal, intraperitoneal and/or subcutaneous administration.

- 5 The pharmaceutical composition may further comprise common excipients and carriers which are known in the state of the art. For solution for injection, the pharmaceutical composition may further comprise cryoprotectants, lyoprotectants, surfactants, bulking agents, anti-oxidants, stabilizing agents and pharmaceutically acceptable carriers

10 Methods for obtaining bispecific antibodies

In general, in order to overcome the limitations of monoclonal and monovalent antibody therapeutics that can only target a single antigen or to overcome the limitations of combinations of monovalent antibody therapeutics, intense efforts have aimed at multiple antigen targeting using bispecific antibody formats. Such antibodies carrying more than one  
15 specificity are of interest in biotechnology and have great potential as therapeutic agents enabling novel therapeutic approaches (Fischer and Leger, Pathobiology 2007; 74:3-14; Morrison SL Nature Biotechnol 2007; 25:1233-1234). Bispecific antibodies are advantageous as they allow for multiple targeting, they increase therapeutic potential, they address redundancy of biological systems, and they provide novel mechanisms of action through  
20 abilities such as retargeting and/or increased specificity. As validated single therapeutic targets become more and more exhausted, combinations allowed by bispecific antibodies provide a new and expansive universe of targets for therapeutic agents and applications.

Several strategies have been used to generate such bispecific molecules, and any of these  
25 known strategies may be used to generate IXa/X scaffolds. These known strategies include such strategies as chemical cross-linking of antibody fragments, forced heterodimerization, quadroma technology, fusion of antibody fragments via polypeptide linkers and use of single domain antibodies. The availability of recombinant DNA technologies has lead to the generation of a multitude of bispecific antibody formats (see e.g., Ridgway JB et al. (1996)  
30 Protein Eng 9 : 617-621). Linkers and mutations have frequently been introduced into different regions of the antibody to force heterodimer formation or to connect different binding moieties into a single molecule. These approaches are further described below and the formats discussed are illustrated in Figure 1 of WO 2012/023053 A2.

- 35 *Chemical cross-linking.* The use of chemical cross-linking reagents to covalently link two antibodies is a conceptually straightforward approach. Antibody fragments generated from their respective parent antibodies by enzymatic digestion or generated through recombinant

technologies are conjugated using bifunctional reagents (Glennie MJ et al., J Exp Med 1992; 175:217-225).

*Quadromas.* Quadromas and triomas can be generated by fusing either two hybridomas or one hybridoma with a B lymphocyte, respectively (Suresh MR et al., Methods Enzymol 1986; 121: 210-228). In this case the simultaneous expression of two heavy and two light chains leads to the random assembly of 10 antibody combinations and the desired bispecific antibody (bsAb) represent only a small fraction of the secreted antibodies. The bsAb has to be purified using a combination of chromatographic techniques.

*Recombinant bispecific antibodies.* The majority of bispecific antibody formats have been generated by genetic engineering techniques using antibody fragment such as scFv or Fab fragments as building blocks connected via polypeptide linkers. Formats based on linked antibody fragments include tandem scFv (BiTE), diabodies and tandem-diabodies (Kipriyanov SM. Methods Mol Biol 2003; 207:323-333; Korn T et al, Int J Cancer 2002; 100:690-697). These building blocks can further be linked to an antibody Fc region given rise to 'IgGlike' molecules. These formats include diabody-Fc, tandem diabody-Fc, tandem diabody-CH3, (scFv)4-Fc and DVD-Ig (Lu D et al, J Immunol Methods 2003; 279: 219-232 ; Lu D et al, J Biol Chem 2005; 280: 19665-19672 ; Lu D et al, J Biol Chem 2004; 279: 2856-2865; Wu C et al., Nat Biotechnol 2007 25:1290-7).

Strategies based on forcing the heterodimerization of two heavy chains have been explored. A first approach coined 'knob into hole' aims at forcing the pairing of two different IgG heavy chains by introducing mutations into the CH3 domains to modify the contact interface (Ridgway JB et al., Protein Eng 1996; 9 : 617-621). On one chain amino acids with large side chains were introduced, to create a 'knob'. Conversely, bulky amino acids were replaced by amino acids with short side chains to create a 'hole' into the other CH3 domain. By coexpressing these two heavy chains, more than 90% heterodimer formation was observed ('knobhole') versus homodimers formation ('hole -hole' or 'knob-knob'). A similar concept was developed using strand-exchange engineered domain (SEED) human CH3 domains based on human IgG and human IgA sequences (Davis JH et al., 2010, PEDS 23:195-202). These engineered domains lead to the formation of heterodimeric molecules that can carry two different specificities. Recently an improvement over the 'knob into hole' approach has been described to solve the light chain pairing issue (WO 2009/080253 A1). This method involves the exchange of some of the light chain and heavy chain domains in addition to the 'knob into hole' mutations.

*Single domain based antibodies.* The immune systems of camelids (lamas and camels) and cartilaginous fish (nurse sharks) use single V-domains fused to a Fc demonstrating that a single domain can confer high affinity binding to an antigen. Camelid, shark and even human V domains represent alternatives to antibodies but they also be used for bsAbs generation.

5 They can be reformatted into a classical IgG in which each arm has the potential to bind two targets either via its VH or VL domain. This single domain-IgG would have biochemical properties similar to an IgG and potentially solve problems encountered with other bsAbs formats in terms of production and heterogeneity.

10 A representation of bispecific antibody formats described above is shown in Figure 1 of WO 2012/023053 A2. Some of these format representations are derived from Fischer and Leger, Pathobiology 2007; 74:3-14; and Morrison SL Nature Biotechnol 2007; 25:1233-1234.

#### Improved methods for generating bispecific and bivalent antibodies

15 In some embodiments, the IXa/X scaffold is composed of two copies of the same heavy chain polypeptide, a first light chain variable domain fused to a constant Kappa domain and second light chain variable domain fused to a constant Lambda domain (see Delves et al., 2017. Roitt's Essential Immunology 13<sup>th</sup> edition. ISBN: 978-1-118-41577-1 for a description of Kappa and Lambda light chains). Each antigen-binding site displays a different specificity  
20 to which both the heavy and light chain contribute. The light chain variable domains can be of the Lambda or Kappa family and can be fused to a Lambda and Kappa constant domains, respectively. However it is also possible to obtain bispecific antibodies by fusing a Kappa light chain variable domain to a constant Lambda domain for a first specificity and fusing a  
25 Lambda light chain variable domain to a constant Kappa domain for the second specificity (see Figure 3 of WO 2012/023053 A2). The bispecific antibodies described herein, which are produced in accordance with these embodiments, are also referred to as IgG Kappa Lambda ("κλ" in Greek letters, or "KL" as the abbreviation in English letters) antibodies or "KL bodies".

An essential step of the method of producing KL-bodies is the identification of two antibody  
30 Fv regions (each composed by a variable light chain and variable heavy chain domain) having different antigen specificities that share the same heavy chain variable domain. Numerous methods have been described for the generation of monoclonal antibodies and fragments thereof. (See, e.g., Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by  
35 reference). Fully human antibodies are antibody molecules in which there are no sequences derived from species other than human. Such antibodies are termed "human antibodies", or "fully human antibodies" herein; such human antibodies or fully human antibodies may

contain artificially introduced changes in their amino acid sequence. Human monoclonal antibodies can be prepared by using the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4 : 72); and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al, 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized and may be produced by using human hybridomas (see Cote, et al, 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

Monoclonal antibodies are generated, e.g., by immunizing an animal with a target antigen or an immunogenic fragment, derivative or variant thereof. Alternatively, the animal is immunized with cells transfected with a vector containing a nucleic acid molecule encoding the target antigen, such that the target antigen is expressed and associated with the surface of the transfected cells. A variety of techniques are well-known in the art for producing xenogenic non-human animals. For example, see U.S. Pat. No. 6,075,181 and No. 6,150,584, which is hereby incorporated by reference in its entirety.

Alternatively, the antibodies are obtained by screening a library that contains antibody or antigen binding site sequences for binding to the target antigen. This library is prepared, e.g., in bacteriophage as protein or peptide fusions to a bacteriophage coat protein that is expressed on the surface of assembled phage particles and the encoding DNA sequences contained within the phage particles (i.e., "phage displayed library").

Hybridomas resulting from myeloma/B cell fusions are then screened for reactivity to the target antigen. Monoclonal antibodies are prepared, for example, using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

Although not strictly impossible, the serendipitous identification of different antibodies having the same heavy chain variable domain but directed against different antigens is highly unlikely. Indeed, in most cases the heavy chain contributes largely to the antigen binding surface and is also the most variable in sequence. In particular the CDR3 on the heavy chain

is the most diverse CDR in sequence, length and structure. Thus, two antibodies specific for different antigens will almost invariably carry different heavy chain variable domains.

This limitation can be overcome through the use of antibody libraries in which the heavy chain variable domain is the same for all the library members and thus the diversity is confined to the light chain variable domain. Such libraries are described, for example, in application PCT/US2010/035619, filed May 20, 2010 and published on November 25, 2010 as PCT Publication No. WO 2010/135558 and application PCT/US2010/057780, filed November 23, 2010 each of which is hereby incorporated by reference in its entirety.

However, as the light chain variable domain is expressed in conjunction with the heavy variable domain, both domains can contribute to antigen binding. To further facilitate the process, antibody libraries containing the same heavy chain variable domain and either a diversity of Lambda variable light chains or Kappa variable light chains can be used in parallel for in vitro selection of antibodies against different antigens. This approach enables the identification of two antibodies having a common heavy chain but one carrying a Lambda light chain variable domain and the other a Kappa light chain variable domain that can be used as building blocks for the generation of a bispecific antibody. The bispecific antibodies can be of different isotypes and their Fc portion can be modified in order to alter the binding properties to different Fc receptors and in this way modify the effector functions of the antibody as well as its pharmacokinetic properties. Numerous methods for the modification of the Fc portion have been described and are applicable to the scaffold modules described herein (see for example Strohl, WR Curr Opin Biotechnol 2009 (6):685-91; U.S. Pat. No. 6,528,624; PCT/US2009/0191 199 filed Jan 9, 2009).

Another step which may be performed is the optimization of co-expression of the common heavy chain and two different light chains into a single cell to allow for the assembly of a bispecific antibody. If all the polypeptides get expressed at the same level and get assembled equally well to form an antibody molecule then the ratio of monospecific (same light chains) and bispecific (two different light chains) should be 50%. However, it is likely that different light chains are expressed at different levels and/or do not assemble with the same efficiency. Therefore the methods disclosed herein also provide means to modulate the relative expression of the different polypeptides to compensate for their intrinsic expression characteristics or different propensities to assemble with the common heavy chain. This modulation can be achieved via promoter strength, the use of internal ribosome entry sites (IRES) featuring different efficiencies or other types of regulatory elements that can act at transcriptional or translational levels as well as acting on mRNA stability. Different promoters of different strength could include CMV (Immediate-early Cytomegalovirus virus promoter);

EFI- 1 $\alpha$  (Human elongation factor 1 $\alpha$ -subunit promoter); Ubc (Human ubiquitin C promoter); SV40 (Simian virus 40 promoter). Different IRES have also been described from mammalian and viral origin. (See e.g., Hellen CU and Sarnow P. Genes Dev 2001 15: 1593-612). These IRES can greatly differ in their length and ribosome recruiting efficiency. Furthermore, it is possible to further tune the activity by introducing multiple copies of an IRES (Stephen et al. 2000 Proc Natl Acad Sci USA 97: 1536-1541). The modulation of the expression can also be achieved by multiple sequential transfections of cells to increase the copy number of individual genes expressing one or the other light chain and thus modify their relative expressions. In some embodiments, the modulation of the expression can also be applied to the expression of proteinaceous molecules of the present invention.

Purified bispecific antibodies can be characterized as described in WO 2012/023053 A2.

There is no requirement of having access to two antibodies having light chain variable domains of the Kappa and Lambda type for instant invention; the methods described herein allow for the generation of KL bodies with one or more hybrid light chain(s) in which a Lambda variable domain can be fused to a Kappa constant domain and/or conversely a Kappa variable domain can be fused to a Lambda constant domain as depicted in Figure 3 of WO 2012/023053 A2.

#### Methods for expressing and purifying the proteinaceous molecules of the present invention

##### *Expression*

The polynucleotide may be in an expression plasmid. The expression plasmid may have any number of origins of replication known to those of ordinary skill in the art. The polynucleotide or expression plasmid may be introduced into the host cell by any number of ways known to those of ordinary skill in the art. For example, a flow electroporation system, such as the MaxCyte GT®, MaxCyte VLX®, or MaxCyte STX® transfection systems, can be used to introduce the polynucleotide or expression plasmid into the host cell.

The polynucleotide sequence may be contained on one plasmid, or on more than one plasmid. For example, in some instances the heavy chain and light chain sequences would be on the same plasmid. In another example the heavy chains are on one plasmid and the light chains are on a separate plasmid. In some embodiments the ratio of the plasmids is 1:1. In some embodiments the ratio of the plasmids is altered such as 1:1, 1:5, 1:10. In some embodiments the antibody variant plasmid contains a selection marker for selecting stable cell lines. In some embodiments different selection makers are on different plasmids. For

example, one selection marker could be on the heavy chain plasmid while an alternate selection marker is on the light chain plasmid.

In various embodiments, the host cell expresses the nucleic acid. The host cell may express antibody variants at a level sufficient for fed-batch cell culture scale or other large scale. Alternative methods to produce antibody variants at a large scale include roller bottle cultures, bioreactor batch cultures, perfusion and pseudoperfusion methods. In some embodiments, an antibody variant protein is produced by cells cultured in suspension. In some embodiments, an antibody variant protein is produced by adherent cells.

#### *Production*

An antibody variant may be produced by any available means. For example, an antibody variant may be recombinantly produced by utilizing a host cell system engineered to express an antibody variant-encoding nucleic acid. Alternatively, an antibody variant can be produced in vivo by mRNA therapeutics or AAV/lentiviral gene therapy.

In some embodiments, antibody variants are produced in mammalian cells. Non-limiting examples of mammalian cells that may be used in accordance with the present invention include BALB/c mouse myeloma line (NSO/1, ECACC No: 85110503); human retinoblasts (PER.C6, CruCell, Leiden, The Netherlands); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (HEK293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59, 1977); human fibrosarcoma cell line (e.g., HT1080); baby hamster kidney cells (BHK21, ATCC CCL 10); Chinese hamster ovary cells +/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216, 1980), including CHO EBNA (Daramola O. et al., Biotechnol. Prog., 2014, 30(1):132-41) and CHO GS (Fan L. et al., Biotechnol. Bioeng. 2012, 109(4):1007-15; mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251, 1980); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1 587); human cervical carcinoma cells (HeLa, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., Annals N.Y. Acad. Sci., 383:44-68, 1982); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

In some embodiments, antibody variants are produced from human cells. In some embodiments, recombinant antibody variants are produced from CHO cells or HEK cells or HT1080 cells.

In certain embodiments, a host cell is selected for generating a cell line based on certain preferable attributes or growth under particular conditions chosen for culturing cells. It will be appreciated by one skilled in the art, such attributes may be ascertained based on known characteristic and/or traits of an established line (i.e. a characterized commercially available cell line) or through empirical evaluation. In some embodiments, a cell line may be selected for its ability to grow on a feeder layer of cells. In some embodiments, a cell line may be selected for its ability to grow in suspension. In some embodiments, a cell line may be selected for its ability to grow as an adherent monolayer of cells. In some embodiments a cell line may be chosen for preferential post translational modifications (e.g., glycosylation). In some embodiments, such cells can be used with any tissue culture vessel or any vessel treated with a suitable adhesion substrate. In some embodiments, a suitable adhesion substrate is selected from the group consisting of collagen (e.g. collagen I, II, III, or IV), gelatin, fibronectin, laminin, vitronectin, fibrinogen, BD Matrigel™, basement membrane matrix, dermatan sulfate proteoglycan, Poly-D-Lysine and/or combinations thereof. In some embodiments, an adherent host cell may be selected and modified under specific growth conditions to grow in suspension. Such methods of modifying an adherent cell to grown in suspension are known in the art. For example, a cell may be conditioned to grow in suspension culture, by gradually removing animal serum from the growth media over time. Typically, cells that are engineered to express a recombinant antibody variant may comprise a transgene that encodes a recombinant antibody variant described herein. Cells can be engineered to express the antibody variant in a transient or a stable expression system. It should be appreciated that the nucleic acids encoding recombinant antibody variants may contain regulatory sequences, gene control sequences, promoters, non-coding sequences and/or other appropriate sequences for expressing the recombinant antibody variant. Typically, the coding region is operably linked with one or more of these nucleic acid components.

In some embodiments antibody variants are expressed using a batch culture method. In some embodiments batch culture duration may be for 7-14 days. In some embodiments the batch culture may be for 14-21 days. In some embodiments antibody variants are expressed using a perfusion culture method (collection of culture medium over time each day). In some embodiments, antibody variants are expressed using a pseudoperfusion culture method (daily collection of culture medium at a single time point with replacement with fresh medium). In some embodiments specific feeding regimens/media may be used to promote optimal antibody variant production (improved glycan, reduce aggregate, improved kappa/lambda body ratio). In some embodiments the cell density may be

controlled/maintained to promote optimal antibody variant production (reduced aggregate, improved heavy/light chain, improved kappa/lambda body ratio).

#### *Purification*

- 5 Total IgGs from all multivalent and trispecific antibodies were first purified by one affinity chromatography step using a Protein A resin (eg. Mab Select Sure resin from GE Healthcare). Elution was performed with 100mM Glycine pH3.0 and neutralized with 1M Tris-HCl pH 9.
- 10 For KL-body based multivalent antibodies two additional affinity chromatography steps were required to isolate the KL-body and eliminate the two monospecific mAbs. Total IgGs were purified using a LambdaFabSelect resin (eg. from GE Healthcare) to get rid of IgG<sub>κκ</sub> (i.e. IgG comprising two light chains of Kappa type) followed by a Kappa resin (eg. Kappa XL from Thermo or KappaSelect from GE Healthcare) to eliminate the IgG<sub>λλ</sub> (i.e. IgG comprising two
- 15 light chains of Lambda type). Elution was with 100mM Glycine pH 3.0 with a 10min pause after the first three column volumes for the LambdaFabSelect resin and 100mM Glycine pH3.5 for the Kappa specific Resin and then neutralized with 1M Tris-HCl pH 9. The final purified antibody was dialyzed into Storage Buffer 20mM HEPES, 150mM NaCl pH 6.5.
- For symmetrical multivalent and trispecific antibodies (eg. 2by2s, 2by2s with beta2-GP1 or
- 20 other trispecific moieties) one additional purification step was applied following the Protein A resin. The second purification step could either be a SEC column (eg. Hi Prep 16/60 S-300 Hr SEC Column (17-1167-01)) or a Ceramic Hydroxyapatite (type I) Column (HA). For one skilled in the art, additional traditional chromatography could also be used to achieve the desired purity and homogeneity of the antibody (eg. Ion exchange, multimodal or
- 25 hydrophobic resins).

For the SEC column the Protein A eluted and neutralized antibodies were concentrated with a 100kd VivaSpin (P/N 28-9323-63) and 2.5mL of the concentrated antibody at ~15mg/mL was loaded (Running Buffer was 20mM HEPES, 150mM NaCl pH 6.5). Final purified

30 antibody was pooled based on SDS-PAGE and SEC-HPLC analysis demonstrating purity and homogeneity of the purified antibody. Final pool dialyzed into Storage Buffer 20mM HEPES, 150mM NaCl pH 6.5. For one skilled in the art, other methods of buffer exchange could be used, such as desalting columns, or ultrafiltration to achieve final buffer storage conditions.

35 For the HA method, ProteinA purified antibody was dialyzed overnight at 4°C in dPBS. The antibody was loaded at 30mg per mL onto the column (loading and wash buffer was 10mM

Na<sub>2</sub>HPO<sub>4</sub> pH6.5). A surface neutralization step using 25mM Tris 25mM NaCl, 5mM Na<sub>2</sub>HPO<sub>4</sub> pH 7.7 was performed for 5 column volumes (CV) and the antibody was then eluted with elution1 (10CV Step at 100% Elution Buffer 2M NaCl 10mM Na<sub>2</sub>HPO<sub>4</sub> 100mM MES pH 6.5) followed by elution2 (10CV gradient at 100% Elution Buffer 500mM Na<sub>2</sub>HPO<sub>4</sub> pH 6.5). Final purified antibody was pooled based on SDS-PAGE and SEC-HPLC analysis demonstrating purity and homogeneity of the purified antibody. Final pool dialyzed into Storage Buffer 20mM HEPES, 150mM NaCl pH 6.5. For one skilled in the art, other methods of buffer exchange could be used, such as desalting columns, or ultrafiltration to achieve final buffer storage conditions.

In one aspect, the present invention comprises the items listed below. These items may be combined with any of the above aspects or embodiments.

1. A proteinaceous molecule having procoagulant activity comprising:

(i) a scaffold module comprising a first antigen-binding site and a second antigen-binding site; and

(ii) at least a first binding module comprising a third antigen-binding site;

wherein at least one of the antigen-binding sites binds to Factor IXa and at least one of the antigen-binding sites binds to Factor X.

Item 1 refers to a proteinaceous molecule which has three antigen-binding sites. The target of one of the antigen-binding sites is not particularly limited as long as the binding to the target allows for procoagulant activity.

2. The proteinaceous molecule according to item 1, wherein the first binding module is attached to the scaffold module through a linker and, optionally, any further binding module(s) is or are attached to the scaffold module through a linker.

Item 2 defines that the first binding module and any one or more other binding modules are attached to the scaffold module through a linker. Possible linkers which could be used in this embodiment and any subsequent embodiment have been disclosed above.

3. The proteinaceous molecule according to item 1, wherein the first binding module is inserted within a loop region of the scaffold module and, optionally, any further binding module(s) is or are inserted within a loop region of the scaffold module.

Item 3 defines that the first binding module and any one or more other binding modules are inserted into a loop region of the scaffold module. Possible loop regions have been disclosed above. These loop regions may be especially suitable for an insertion of a peptide aptamer.

- 5     4.     The proteinaceous molecule according to any one of items 1-3, wherein the first antigen-binding site binds to Factor IXa, and the second antigen-binding site binds to Factor X.

10     Item 4 defines that the scaffold module is a "IXa/X" scaffold as discussed previously. These scaffold modules per se are bispecific.

- 15     5.     The proteinaceous molecule according to any one of items 1-4, wherein the third antigen-binding site of the first binding module binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

In item 5, the possible targets of the third antigen-binding site of the first binding module are defined. The binding module may make the proteinaceous molecule trivalent bispecific, or trivalent trispecific.

- 20     6.     The proteinaceous molecule according to item 5, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin  
25     is annexin V.

Item 6 refers to proteinaceous molecules which are trivalent trispecific. In this embodiment, the binding module provides the third valency and specificity. This proteinaceous molecule will be similar to that of Figure 2 except that proteinaceous molecules only comprising one  
30     binding module are also encompassed.

- 35     7.     The proteinaceous molecule according to items 5, wherein the third antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

Item 7 refers to proteinaceous molecules which are trivalent bispecific. In this embodiment, the binding module provides the third valency. This proteinaceous molecule will be similar to

the “3 by 1” or “1 by 3” molecules in Figure 1 except that proteinaceous molecules only comprising one binding module are also encompassed.

8. The proteinaceous molecule according to item 7, wherein the first binding module is a scFv or scFab.

The first binding module of the **trivalent bispecific** embodiments comprising a IXa/X scaffold are further defined in item 8.

9. The proteinaceous molecule according to item 8, wherein the first binding module comprises:
- (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;
  - (ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

In item 9, the first binding module is defined to comprise CDRs of binding arms that have been demonstrated to bind to Factor IXa or Factor X.

10. The proteinaceous molecule according to item 9, wherein the first binding module is a scFv and comprises:
- (i) a VH domain, wherein the VH domain is SEQ ID NO: 183;
  - (ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

- In item 10, the first binding module is defined to comprise variable domain sequences that have been demonstrated to bind to Factor IXa or Factor X.

11. The proteinaceous molecule according to any one of items 9-10, wherein the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

In item 11, the CDRs are limited to specific binding arms that have been used in the proteinaceous molecules of the Examples. Arms with a "W" denotation bind to Factor X and arms with a "V" denotation bind to Factor IXa.

- 5 12. The proteinaceous molecule according to item 6, wherein the first binding module is an scFv or scFab.

The first binding module of the **trivalent trispecific** embodiments comprising a IXa/X scaffold are further defined in item 12.

10

13. The proteinaceous molecule according to item 12, wherein the first binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

- 15 the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

In item 13, the first binding module is further defined through sequence information. SEQ ID NO: 184 and SEQ ID NO: 187 are comprised in bavituximab which is known to bind domain II of  $\beta$ 2-glycoprotein I. SEQ ID NO: 185 and SEQ ID NO: 188 are comprised in PS72 which is  
20 known to bind phosphatidylserine (Bujak et al., 2015. Invest New Drugs. 33(4):791-800). SEQ ID NO: 186 and SEQ ID NO: 189 are comprised in anti-LIBS which is known to bind GPIIb/IIIa (Stoll et al., 2007. Arterioscler Thromb Vasc Biol. 27(5):1206-12).

- 25 14. The proteinaceous molecule according to item 13, wherein the first binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

In item 14, the first binding module is defined by a specific sequence, wherein SEQ ID NO: 190 is bavituximab, SEQ ID NO: 191 is PS72, and SEQ ID NO: 192 is anti-LIBS.

- 30 15. The proteinaceous molecule according to item 6, wherein the first binding module comprises domain V of  $\beta$ 2-glycoprotein I.

In item 15, the first binding module is domain V of  $\beta$ 2-glycoprotein I which is known to bind phosphatidylserine.

35

16. The proteinaceous molecule according to any one of items 1-15, wherein the scaffold module is an antibody or a bivalent fragment thereof.

17. The proteinaceous molecule according to item 16, wherein the scaffold module is an antibody.

5 18. The proteinaceous molecule according to any one of items 1-17, wherein the scaffold module comprises two heavy chains and two light chains.

19. The proteinaceous molecule according to item 18, wherein one light chain comprises a light chain variable domain fused to a Kappa constant domain and the other light chain  
10 comprises a variable light chain domain fused to a Lambda constant domain.

In items 16-19, the "IXa/X" scaffold is defined by a number of structural features. In particular, item 19 restricts the "IXa/X" scaffold to a  $\kappa\lambda$ -body.

15 20. The proteinaceous molecule according to any one of items 18-19, wherein the scaffold module comprises:

(i) two heavy chains comprising identical CDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

(ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X  
20 binding light chains disclosed in Table 1; and

(iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a.

In item 20, the scaffold module is defined to comprise CDR sequences of binding arms that  
25 have been demonstrated to bind to Factor IXa or Factor X.

21. The proteinaceous molecule according to item 20, wherein the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or  
30 LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.

In item 21, specific Factor X-binding arm sequences are recited. These arm sequences were used in the proteinaceous molecules specified in the Examples.

35 22. The proteinaceous molecule according to any one of items 20-21, wherein the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and

LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a.

- 5 In item 22, specific Factor IXa-binding arm sequences are recited. These arm sequences were used in the proteinaceous molecules specified in the Examples.

23. The proteinaceous molecule according to any one of items 20-22, wherein the LCDR1, LCDR2 and LCDR 3 of (ii) and (iii) are the

- 10 LCDR1, LCDR2 and LCDR3 of W88 and V198,  
LCDR1, LCDR2 and LCDR3 of W127 and V202,  
LCDR1, LCDR2 and LCDR3 of V149 and W128,  
LCDR1, LCDR2 and LCDR3 of W128 and V198,  
LCDR1, LCDR2 and LCDR3 of W128 and V141,  
15 LCDR1, LCDR2 and LCDR3 of W162 and V204,  
LCDR1, LCDR2 and LCDR3 of W83 and V217,  
LCDR1, LCDR2 and LCDR3 of W88 and V90, or  
LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2a.

- 20 In item 22, specific Factor IXa-binding arm sequences ("V" sequences) are recited in combination with specific Factor X-binding arm sequences ("W" sequences). These arm sequence combinations were used in the proteinaceous molecules specified in the Examples.

- 25 24. The proteinaceous molecule according to any one of items 18-19, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;  
(ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed  
30 in Table 3; and  
(iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a.

- In item 24, the scaffold module is defined to comprise variable domain sequences of binding  
35 arms that have been demonstrated to bind to Factor IXa or Factor X.

25. The proteinaceous molecule according to item 24, wherein the VL of (ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a.

5

In item 25, specific Factor IXa-binding arm sequences ("V" sequences) and specific Factor X-binding arm sequences ("W" sequences) are recited. These arm sequences were used in the proteinaceous molecules specified in the Examples.

10 26. The proteinaceous molecule according to any one of items 24-25, wherein the VL of (ii) and (iii) are the VL of W88 and V198,  
VL of W127 and V202,  
VL of V149 and W128,  
VL of W128 and V198,  
15 VL of W128 and V141,  
VL of W162 and V204,  
VL of W83 and V217,  
VL of W88 and V90, or  
VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.

20

In item 26, specific Factor IXa-binding arm sequences ("V" sequences) are recited in combination with specific Factor X-binding arm sequences ("W" sequences). These arm sequence combinations were used in the proteinaceous molecules specified in the Examples.

25

27. The proteinaceous molecule according to any one of items 1-3, wherein each of the first antigen-binding site and the second antigen-binding site binds to Factor IXa, or each of the first antigen-binding site and the second antigen-binding site binds to Factor X.

30 In item 27, the proteinaceous molecules comprise a monospecific scaffold wherein both antigen-binding sites of the scaffold module bind to Factor IXa or Factor X. Embodiments with monospecific scaffolds comprising only one binding module comprising only one antigen-binding site can only be **bispecific trivalent** because the proteinaceous molecule must comprise at least one antigen-binding site that binds to Factor IXa and one antigen-  
35 binding site that binds to Factor X.

28. The proteinaceous molecule according to item 27, wherein the third antigen-binding site binds to Factor IXa or Factor X.

In item 28, the antigen-binding site of the first binding module binds to Factor IXa or Factor X.

5 This proteinaceous molecule will be similar in structure as the "2 by 2" topology depicted in Figure 1 except that this embodiment includes proteinaceous molecules comprising only a single binding module. This sort of topology could be achieved by, for example, fusing a Factor X-binding scFv to the C-terminus of a Factor IXa-binding light chain comprising a Kappa constant domain and using a second light chain that binds to Factor IXa that  
10 comprises a Lambda constant domain.

29. The proteinaceous molecule according to item 28, wherein the first binding module is a scFv or scFab.

15 Items 29-32 then define the first binding module that binds to Factor IXa or Factor X in a similar manner as in items 8-11.

30. The proteinaceous molecule according to item 29, wherein the first binding module comprises:

- 20 (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;  
(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

25 31. The proteinaceous molecule according to item 30, wherein the first binding module comprises:

- (i) a VH domain, wherein the VH domain is SEQ ID NO: 183;  
(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,  
wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of  
30 the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and  
wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

35 32. The proteinaceous molecule according to any one of items 30-31, wherein the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

33. The proteinaceous molecule according to any one of items 27-32, wherein the scaffold module is an antibody or a bivalent fragment thereof.

5 In items 33-41, the monospecific scaffold is further defined by incorporating more and more structural and sequence information. The Factor IXa- and Factor X-binding arms recited previously are also recited in these items.

34. The proteinaceous molecule according item 33, wherein the scaffold module is an  
10 antibody.

35. The proteinaceous molecule according to any one of items 27-34, wherein the scaffold module comprises two heavy chains and two light chains.

15 36. The proteinaceous molecule according to item 35, wherein the scaffold module comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

20 (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

37. The proteinaceous molecule according to item 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1,  
25 LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.

38. The proteinaceous molecule according to item 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1,  
30 LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a.

35 For the avoidance of any doubt, an embodiment of any one of items 36-38 is one where the two light chains comprise identical LCDR1, LCDR2 and LCDR3 sequences.

39. The proteinaceous molecule according to item 36, wherein the scaffold module comprises:

(i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and

5 (ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a.

40. The proteinaceous molecule according to item 39, wherein the VL of each of the two light chains is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed  
10 in Table 3.

41. The proteinaceous molecule according to item 39, wherein the VL of each of the two light chains is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a.

15 For the avoidance of any doubt, an embodiment of any one of items 39-41 is one where the two light chains comprise identical VL sequences.

42. The proteinaceous molecule according to any one of items 1-41, wherein the  
20 proteinaceous molecule further comprises at least a second binding module comprising a fourth antigen-binding site.

Item 42 describes an embodiment wherein the proteinaceous molecule comprises a first and a second binding module. Proteinaceous molecules encompassed by this embodiment  
25 include the tetravalent proteinaceous molecules depicted in Figures 1 and 2. As depicted in Figures 1 and 2, the second binding module contributes to the tetravalency of the proteinaceous molecule and may also contribute by making the proteinaceous molecule tri- or tetra-specific.

30 Item 42 describes an embodiment wherein the first and second binding modules are the same and items 43-53 allows for the second binding module to be different from the first binding module (allows for tetraspecificity).

43. The proteinaceous molecule according to item 42, wherein the second binding  
35 module is identical to the first binding module.

44. The proteinaceous molecule according to item 42, wherein the fourth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

- 5 45. The proteinaceous molecule according to item 44, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin  
10 is annexin V.

Item 45 also encompasses trispecific multivalent comprising a monospecific scaffold as depicted in, for example, Figure 3. This can be achieved by taking advantage of, for example, a light chain comprising a Kappa constant domain and a light chain comprising a  
15 Lambda constant domain. For example, both light chains may comprise LCDRs that bind to Factor IXa but one light chain may be fused to a scFv that is specific for Factor X and the other light may be fused to a scFv that is specific for phosphatidylserine.

- 20 46. The proteinaceous molecule according to item 44, wherein the fourth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

47. The proteinaceous molecule according to item 46, wherein the second binding module is a scFv or scFab.

- 25 48. The proteinaceous molecule according to item 47, wherein the second binding module comprises:

- (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;  
30 (ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

49. The proteinaceous molecule according to item 48, wherein the second binding module is a scFv and comprises:

- 35 (i) a VH domain, wherein the VH domain is SEQ ID NO: 183;  
(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,

wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

50. The proteinaceous molecule according to item 45, wherein the second binding module is an scFv or scFab.

51. The proteinaceous molecule according to item 50, wherein the second binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

52. The proteinaceous molecule according to item 51, wherein the second binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

53. The proteinaceous molecule according to item 45, wherein the second binding module comprises domain V of  $\beta$ 2-glycoprotein I.

54. The proteinaceous molecule according to any one of items 42-53, wherein the proteinaceous molecule further comprises at least a third binding module comprising a fifth antigen-binding site.

Item 54 describes an embodiment wherein the proteinaceous molecule comprises a first, second and third binding module. Proteinaceous molecules encompassed by this embodiment include pentavalent proteinaceous molecules. The third binding module contributes to the pentavalency of the proteinaceous molecule and may also contribute by making the proteinaceous molecule tri-, tetra- or penta-specific.

Item 55 allows for embodiments wherein the three binding modules are the same or only two of the three binding modules are the same. Items 56-65 allows for the third binding module to be different from the first and second binding module.

55. The proteinaceous molecule according to item 54, wherein the third binding module is identical to the first binding module.

56. The proteinaceous molecule according to item 54, wherein the fifth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

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57. The proteinaceous molecule according to item 56, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

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58. The proteinaceous molecule according to item 56, wherein the fifth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

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59. The proteinaceous molecule according to item 58, wherein the third binding module is a scFv or scFab.

60. The proteinaceous molecule according to item 59, wherein the the third binding module comprises:

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(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

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61. The proteinaceous molecule according to item 60, wherein the third binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

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wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

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62. The proteinaceous molecule according to item 57, wherein the third binding module is an scFv or scFab.

63. The proteinaceous molecule according to item 62, wherein the third binding module comprises a VL domain and a VH domain, wherein:  
the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,  
the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or  
the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

64. The proteinaceous molecule according to item 63, wherein the third binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

65. The proteinaceous molecule according to item 57, wherein the third binding module comprises domain V of  $\beta$ 2-glycoprotein I.

66. The proteinaceous molecule according to any one of items 54-65, wherein the proteinaceous molecule comprises at least a fourth binding module comprising a sixth antigen-binding site.

Item 66 describes an embodiment wherein the proteinaceous molecule comprises a first, second, third and fourth binding module. Proteinaceous molecules encompassed by this embodiment include hexavalent proteinaceous molecules. The fourth binding module contributes to the hexavalency of the proteinaceous molecule and may also contribute by making the proteinaceous molecule tri-, tetra- or penta-specific. An example of a hexavalent trispecific proteinaceous molecule is depicted in Figure 3.

Item 67 allows for embodiments wherein the four binding modules are the same and item 68 allows for embodiments wherein, for example, the first and the third binding module are identical and the first and the second binding module are identical as in Figure 3. Items 69-78 allows for the fourth binding module to be different from the first, second and third binding module.

67. The proteinaceous molecule according to item 66, wherein the fourth binding module is identical to the first binding module.

68. The proteinaceous molecule according to item 66, wherein the fourth binding module is identical to the third binding module.

69. The proteinaceous molecule according to item 66, wherein the sixth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

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70. The proteinaceous molecule according to item 69, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

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71. The proteinaceous molecule according to item 69, wherein the sixth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

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72. The proteinaceous molecule according to item 71, wherein the fourth binding module is a scFv or scFab.

73. The proteinaceous molecule according to item 72, wherein the fourth binding module comprises:

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(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

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74. The proteinaceous molecule according to item 73, wherein the fourth binding module is an scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

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wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

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75. The proteinaceous molecule according to item 70, wherein the fourth binding module is an scFv or scFab.

76. The proteinaceous molecule according to item 75, wherein the fourth binding module comprises a VL domain and a VH domain, wherein:  
the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,  
the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or  
the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

77. The proteinaceous molecule according to item 76, wherein the fourth binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

78. The proteinaceous molecule according to item 70, wherein the fourth binding module comprises domain V of  $\beta$ 2-glycoprotein I.

79. The proteinaceous molecule according to any one of items 66-78, wherein the proteinaceous molecule comprises at least a fifth binding module comprising a seventh antigen-binding site.

80. The proteinaceous molecule according to item 79, wherein the proteinaceous molecule comprises at least a sixth binding module comprising an eighth antigen-binding site.

81. The proteinaceous molecule according to anyone of items 79-80, wherein the seventh and/or eighth antigen-binding site bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

Items 79-81 allow for further binding modules. However, the number of binding modules which may be attached to the scaffold module is not particularly limited and various different kinds of topologies may be derived from the disclosure herein. Further exemplary topologies are provided in Figure 4 and are also encompassed by the present invention.

82. A pharmaceutical composition comprising the proteinaceous molecule according to any one of items 1-81 and a pharmaceutically acceptable carrier and/or diluent.

83. The proteinaceous molecule according to any one of items 1-81, or the pharmaceutical composition according to item 82 for use as a medicament.

84. The proteinaceous molecule according to any one of items 1-81, or the pharmaceutical composition according to item 82 for use in a method of treating and/or preventing a bleeding disorder, wherein a patient or animal is administered a therapeutically effective amount of the proteinaceous molecule or the pharmaceutical composition.

85. The proteinaceous molecule or pharmaceutical composition for use according to item 84, wherein the bleeding disorder is hemophilia A or acquired hemophilia.

In a further aspect, the present invention comprises the items listed below. These items may be combined with any of the above aspects or embodiments.

1. A proteinaceous molecule having a procoagulant activity comprising:

(i) a scaffold module comprising a first antigen-binding site and a second antigen-binding site; and

(ii) at least a first binding module comprising a third antigen-binding site;

wherein at least one of the antigen-binding sites binds to Factor IXa and at least one of the antigen-binding sites binds to Factor X.

2. The proteinaceous molecule according to item 1, wherein the first binding module is attached to the scaffold module through a linker and, optionally, any further binding module(s) is or are attached to the scaffold module through a linker.

3. The proteinaceous molecule according to item 1, wherein the first binding module is inserted within a loop region of the scaffold module and, optionally, any further binding module(s) is or are inserted within a loop region of the scaffold module.

4. The proteinaceous molecule according to any one of items 1-3, wherein the first antigen-binding site binds to Factor IXa, and the second antigen-binding site binds to Factor X.

5. The proteinaceous molecule according to any one of items 1-4, wherein the third antigen-binding site of the first binding module binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

6. The proteinaceous molecule according to item 5, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol

binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

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7. The proteinaceous molecule according to item 5, wherein the third antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

10 8. The proteinaceous molecule according to item 7, wherein the first binding module is a scFv or scFab.

9. The proteinaceous molecule according to item 8, wherein the first binding module comprises:

15 (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

20 10 The proteinaceous molecule according to item 9, wherein the first binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,

25 wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

30 11. The proteinaceous molecule according to any one of items 9-10, wherein the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

35 12. The proteinaceous molecule according to item 5 or 6, wherein the first binding module is an scFv or scFab.

13. The proteinaceous molecule according to item 12, wherein the first binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

5 the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

14. The proteinaceous molecule according to item 13, wherein the first binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

10 15. The proteinaceous molecule according to item 5 or 6, wherein the first binding module comprises domain V of  $\beta$ 2-glycoprotein I.

16. The proteinaceous molecule according to any one of items 1-15, wherein the scaffold module is an antibody or a bivalent fragment thereof.

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17. The proteinaceous molecule according to item 16, wherein the scaffold module is an antibody.

18. The proteinaceous molecule according to any one of items 1-17, wherein the scaffold module comprises two heavy chains and two light chains.

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19. The proteinaceous molecule according to item 18, wherein one light chain of the scaffold module comprises a light chain variable domain fused to a Kappa constant domain and the other light chain of the scaffold module comprises a variable light chain domain fused to a Lambda constant domain.

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20. The proteinaceous molecule according to any one of items 18-19, wherein the scaffold module comprises:

(i) two heavy chains comprising identical CDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;

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(ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and

(iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2a.

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21. The proteinaceous molecule according to item 20, wherein the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of

W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.

22. The proteinaceous molecule according to any one of items 20-21, wherein the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a.

23. The proteinaceous molecule according to any one of items 20-22, wherein the LCDR1, LCDR2 and LCDR 3 of (ii) and (iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2a.

24. The proteinaceous molecule according to any one of items 18-19, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and
- (iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4a.

25. The proteinaceous molecule according to item 24, wherein the VL of (ii) is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a.

26. The proteinaceous molecule according to any one of items 24-25, wherein the VL of (ii) and (iii) are the VL of W88 and V198,  
VL of W127 and V202,  
VL of V149 and W128,  
5 VL of W128 and V198,  
VL of W128 and V141,  
VL of W162 and V204,  
VL of W83 and V217,  
VL of W88 and V90, or  
10 VL of W83 and V43, respectively, disclosed in Tables 3 and 4a.
27. The proteinaceous molecule according to any one of items 1-3, wherein each of the first antigen-binding site and the second antigen-binding site binds to Factor IXa, or each of the first antigen-binding site and the second antigen-binding site binds to Factor X.  
15
28. The proteinaceous molecule according to item 27, wherein the third antigen-binding site binds to Factor IXa or Factor X.
29. The proteinaceous molecule according to item 28, wherein the first binding module is  
20 a scFv or scFab.
30. The proteinaceous molecule according to item 29, wherein the first binding module comprises:  
(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID  
25 NO: 2 and HCDR3 is SEQ ID NO: 3;  
(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.
31. The proteinaceous molecule according to item 30, wherein the first binding module  
30 comprises:  
(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;  
(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions,  
wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of  
the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains  
35 disclosed in Table 2a, and  
wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and  
FW4 is SEQ ID NO: 182.

32. The proteinaceous molecule according to any one of items 30-31, wherein the LCDR1, LCDR2 and LCDR3 are that of V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2a.

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33. The proteinaceous molecule according to any one of items 27-32, wherein the scaffold module is an antibody or a bivalent fragment thereof.

10

34. The proteinaceous molecule according to item 33, wherein the scaffold module is an antibody.

35. The proteinaceous molecule according to any one of items 27-34, wherein the scaffold module comprises two heavy chains and two light chains.

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36. The proteinaceous molecule according to item 35, wherein the scaffold module comprises:

(i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and

20 (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

37. The proteinaceous molecule according to item 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.

38. The proteinaceous molecule according to item 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2a.

39. The proteinaceous molecule according to item 36, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and
- (ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4a.

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40. The proteinaceous molecule according to item 39, wherein the VL of each of the two light chains is the VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3.

10 41. The proteinaceous molecule according to item 39, wherein the VL of each of the two light chains is the VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4a.

15 42. The proteinaceous molecule according to any one of items 1-41, wherein the proteinaceous molecule further comprises at least a second binding module comprising a fourth antigen-binding site.

43. The proteinaceous molecule according to item 42, wherein the second binding module is identical to the first binding module.

20

44. The proteinaceous molecule according to item 42, wherein the fourth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

25 45. The proteinaceous molecule according to item 44, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin

30 is annexin V.

46. The proteinaceous molecule according to item 44, wherein the fourth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

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47. The proteinaceous molecule according to item 46, wherein the second binding module is a scFv or scFab.

48. The proteinaceous molecule according to item 47, wherein the second binding module comprises:

(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

49. The proteinaceous molecule according to item 48, wherein the second binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

50. The proteinaceous molecule according to item 44 or 45, wherein the second binding module is an scFv or scFab.

51. The proteinaceous molecule according to item 50, wherein the second binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

52. The proteinaceous molecule according to item 51, wherein the second binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

53. The proteinaceous molecule according to item 44 or 45, wherein the second binding module comprises domain V of  $\beta$ 2-glycoprotein I.

54. The proteinaceous molecule according to any one of items 42-53, wherein the proteinaceous molecule further comprises at least a third binding module comprising a fifth antigen-binding site.

55. The proteinaceous molecule according to item 54, wherein the third binding module is identical to the first binding module.

56. The proteinaceous molecule according to item 54, wherein the fifth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

57. The proteinaceous molecule according to item 56, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

58. The proteinaceous molecule according to item 56, wherein the fifth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

59. The proteinaceous molecule according to item 58, wherein the third binding module is a scFv or scFab.

60. The proteinaceous molecule according to item 59, wherein the the third binding module comprises:

(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

61. The proteinaceous molecule according to item 60, wherein the third binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

62. The proteinaceous molecule according to item 56 or 57, wherein the third binding module is an scFv or scFab.

63. The proteinaceous molecule according to item 62, wherein the third binding module comprises a VL domain and a VH domain, wherein:  
the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,  
the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or  
the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

64. The proteinaceous molecule according to item 63, wherein the third binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

65. The proteinaceous molecule according to item 56 or 57, wherein the third binding module comprises domain V of  $\beta$ 2-glycoprotein I.

66. The proteinaceous molecule according to any one of items 54-65, wherein the proteinaceous molecule comprises at least a fourth binding module comprising a sixth antigen-binding site.

67. The proteinaceous molecule according to item 66, wherein the fourth binding module is identical to the first binding module.

68. The proteinaceous molecule according to item 66, wherein the fourth binding module is identical to the third binding module.

69. The proteinaceous molecule according to item 66, wherein the sixth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

70. The proteinaceous molecule according to item 69, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha$ 5 $\beta$ 3 integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta$ 2-glycoprotein I, preferably wherein the annexin is annexin V.

71. The proteinaceous molecule according to item 69, wherein the sixth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

5 72. The proteinaceous molecule according to item 71, wherein the fourth binding module is a scFv or scFab.

73. The proteinaceous molecule according to item 72, wherein the fourth binding module comprises:

10 (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a.

15 74. The proteinaceous molecule according to item 73, wherein the fourth binding module is an scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of  
20 the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2a, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

25 75. The proteinaceous molecule according to item 69 or 70, wherein the fourth binding module is an scFv or scFab.

76. The proteinaceous molecule according to item 75, wherein the fourth binding module comprises a VL domain and a VH domain, wherein:

30 the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

77. The proteinaceous molecule according to item 76, wherein the fourth binding module  
35 is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

78. The proteinaceous molecule according to item 69 or 70, wherein the fourth binding module comprises domain V of  $\beta$ 2-glycoprotein I.

79. The proteinaceous molecule according to any one of items 66-78, wherein the proteinaceous molecule comprises at least a fifth binding module comprising a seventh antigen-binding site.

80. The proteinaceous molecule according to item 79, wherein the proteinaceous molecule comprises at least a sixth binding module comprising an eighth antigen-binding site.

81. The proteinaceous molecule according to anyone of items 79-80, wherein the seventh and/or eighth antigen-binding site bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

82. A pharmaceutical composition comprising the proteinaceous molecule according to any one of items 1-81 and a pharmaceutically acceptable carrier and/or diluent.

83. The proteinaceous molecule according to any one of items 1-81, or the pharmaceutical composition according to item 82 for use as a medicament.

84. The proteinaceous molecule according to any one of items 1-81, or the pharmaceutical composition according to item 82 for use in a method of treating and/or preventing a bleeding disorder, wherein a patient or animal is administered a therapeutically effective amount of the proteinaceous molecule or the pharmaceutical composition.

85. The proteinaceous molecule or pharmaceutical composition for use according to item 84, wherein the bleeding disorder is hemophilia A or acquired hemophilia.

#### Medical methods

The present invention also provides the proteinaceous molecule or pharmaceutical composition of the present invention for use as a medicament. Further, the present invention provides the proteinaceous molecule or pharmaceutical composition of the present invention for use in a method of treating and/or preventing a bleeding disorder, wherein a patient or animal is administered a therapeutically effective amount of the proteinaceous molecule.

A method of treating and/or preventing a bleeding disorder wherein the patient or animal is administered a therapeutically effective amount of the proteinaceous molecule or pharmaceutical composition of the present invention is also provided. Further, the present invention provides the use of the proteinaceous molecule or pharmaceutical composition of the present invention for the manufacture of a medicament for the treatment and/or prevention of a bleeding disorder.

In various aspects, the coagulation or bleeding disorder is caused by the absence of a coagulation factor. One of skill in the art would appreciate the types of coagulation or bleeding disorders associated with the absence of a coagulation factor. In some aspects, the coagulation or bleeding disorder may be hemophilia or von Willebrand disease. In another aspect, the coagulation or bleeding disorder is hemophilia A or acquired hemophilia. In a particular aspect, the coagulation or bleeding disorder is hemophilia A. In another aspect, the coagulation or bleeding disorder is acquired hemophilia where the subject no longer produces FVIII.

In various aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with mild hemophilia A, moderate hemophilia A, or severe hemophilia A. In another aspect, the proteinaceous molecules or pharmaceutical compositions disclosed herein may be administered to a subject with factor plasma levels of 6% to 30%, 2% to 5%, or 1% or less.

In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with hemophilia A or suspected of having hemophilia A when there is an external wound on the subject. In another aspect, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with hemophilia A or suspected of having hemophilia A with an existing external wound on the subject. In another aspect, proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with an external wound until the wound has healed. In some aspects, the wound may include, but not limited to, an abrasion, a laceration, a puncture, or an avulsion.

In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with hemophilia, A or suspected of having hemophilia A, prior to, during, or after surgery, a serious injury, or dental work.

In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with hemophilia A, or suspected of having hemophilia A, and has experienced spontaneous bleeding. In another aspect, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject with hemophilia A, or suspected of having hemophilia A, and has experienced bleeding once, twice, or more times in a week.

In various aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject of any age group suffering from, or suspected of having hemophilia A. In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a child of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 years of age suffering from, or suspected of having hemophilia A. In another aspect, the proteinaceous molecules or pharmaceutical compositions of the present invention thereof may be administered to an infant suffering from or suspected of having hemophilia A.

In yet another aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention may be administered to a subject who is an infant of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months of age suffering from, or suspected of having hemophilia A.

In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention are administered to a subject at an early age before the first episode of bleeding.

In other aspects, administering the proteinaceous molecules or pharmaceutical compositions of the present invention before the first episode of bleeding protects against further bleeding and development of joint damage in the future.

In some embodiments, administering a proteinaceous molecules or pharmaceutical compositions of the present invention to subjects may have the following effects, but is not limited to, hemostasis, reduced pain, and improved mobility.

Also provided is method of promoting FX activation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the proteinaceous molecule or pharmaceutical composition of the present invention.

Also provided is a method of reducing the frequency or degree of a bleeding episode in a subject in need thereof, comprising administering to the subject an effective amount of the proteinaceous molecule or pharmaceutical composition of the present invention.

- 5 In some aspects, the subject has developed, has a tendency to develop, and is at risk to develop an inhibitor against Factor VIII ("FVIII"). In some aspects, the inhibitor against FVIII is a neutralizing antibody against FVIII. In some aspect, the subject is undergoing treatment with FVIII or is a candidate for treatment with FVIII, e.g., FVIII replacement therapy.
- 10 In some aspects, the bleeding episode is the result of hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, bleeding in the iliopsoas sheath, or any
- 15 combinations thereof.

The present invention also provides a method of treating a blood coagulation disorder in a subject in need thereof, comprising administering to the subject an effective amount of the proteinaceous molecule or pharmaceutical composition of the present invention.

- 20 In some aspects, the blood coagulation disorder is hemophilia A or hemophilia B. In some aspects, the subject is a human subject.

- In some aspects, the subject is undergoing or has undergone FVIII replacement therapy. In
- 25 some aspects, the proteinaceous molecule or pharmaceutical composition of the present invention is administered in combination with a hemophilia therapy. In some aspects, the hemophilia therapy is a FVIII replacement therapy. In some aspects, the proteinaceous molecule or pharmaceutical composition of the present invention is administered before, during or after administration of the hemophilia therapy. In some aspects, the proteinaceous
- 30 molecule or pharmaceutical composition of the present invention is administered intravenously or subcutaneously.

- In some aspects, administration of the proteinaceous molecules or pharmaceutical compositions of the present invention reduces the frequency of break-through bleeding
- 35 episodes, spontaneous bleeding episodes, or acute bleeding. In some aspects, administration of proteinaceous molecules or pharmaceutical compositions of the present invention reduces the annualized bleed rate by 5%, 10%, 20%, 30%, or 50%.

The proteinaceous molecules or pharmaceutical compositions of the present invention may be administered by any route appropriate to the condition to be treated. The proteinaceous molecules or pharmaceutical compositions of the present invention will typically be administered parenterally, i.e., infusion, subcutaneous, intramuscular, intravenous, or intradermal. In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention are administered subcutaneously.

In certain aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention are administered intermittently or discontinuously. In various aspects, dose levels of the proteinaceous molecules of the present invention, for example, administered via injection, such as subcutaneous injection, range from about 0.0001 mg/kg to about 100 mg/kg bodyweight.

In some aspects, the proteinaceous molecules or pharmaceutical compositions of the present invention are administered until disease progression or unacceptable toxicity.

### **Examples**

#### **EXAMPLE 1: Phage display selection using human scFv libraries containing fixed variable heavy chain**

General procedures for construction and handling of human scFv libraries displayed on M13 bacteriophage are described in Vaughan et al., (Nat. Biotech. 1996, 14:309-314), hereby incorporated by reference in its entirety. The libraries used for selection and screening encode scFv that all share the same VH domain and are solely diversified in the VL domain. Methods for the generation of fixed VH libraries and their use for the identification and assembly of bispecific antibodies are described in US 2012/0184716 and WO 2012/023053, each of which is hereby incorporated by reference in its entirety. The procedures to identify scFv binding to human Factor IXa (hFIXa) or human Factor X (hFX) are described below.

*Protein selections.* Aliquots of scFv phage libraries ( $10^{12}$  Pfu) were blocked with PBS containing 3% (w/v) skimmed milk for one hour at room temperature on a rotary mixer. Blocked phage was deselected on streptavidin magnetic beads (Dynabeads™ M-280, Dynal) for one hour at room temperature on a rotary mixer. Deselected phage was incubated with in vitro biotinylated hFIXa or hFX (100 nM) captured on streptavidin magnetic beads for two hours at room temperature on a rotary mixer. Beads were captured using a magnetic stand followed by five washes with PBS/0.1% Tween 20 and two washes with PBS. Phage were eluted with 100 nM TEA for 30 minutes at room temperature on a rotary mixer. Eluted phage

and beads were neutralized with Tris-HCl 1M pH 7.4 and directly added to 10 ml of exponentially growing TG1 cells and incubated for one hour at 37 °C with slow shaking (90 rpm). An aliquot of the infected TG1 was serially diluted to titer the selection output. The remaining infected TG1 were spun at 3800 rpm for 10 minutes and resuspended in 2 ml 2xTY and spread on 2xTYAG (2xTY medium containing 100 µg/ml ampicillin and 2% glucose) agar Bioassay plates. After overnight incubation at 30 °C, 10 ml of 2xTY was added to the plates and the cells were scraped from the surface and transferred to a 50 ml polypropylene tube. 50% glycerol solution was added to the cell suspension to obtain a final concentration of 17% glycerol. Aliquots of the selection rounds were kept at -80°C.

*Phage rescue.* 50 µl of cell suspension obtained from previous selection rounds were added to 50 ml of 2xTYAG and grown at 37 °C with agitation (240 rpm) until an OD<sub>600</sub> of 0.3 to 0.5 is reached. The culture was then super-infected with 1.2x10<sup>11</sup> M13KO7 helper phage and incubated for one hour at 37°C (90 rpm). The medium was changed by centrifuging the cells at 3800 rpm for 10 minutes, removing the medium and resuspending the pellet in 50 ml of 2xTYAK (100 µg/ml ampicillin; 50 µg/ml kanamycin). The culture is then grown overnight at 30°C (240 rpm). The next day, 10 µl of the phage containing supernatant was used for the next round of selection.

## EXAMPLE 2: Screening for scFv binding to hFIXa or hFX

*scFv periplasmic preparation for binding assays.* Individual TG1 clones were inoculated into a 96-well deep well plate containing 0.9 ml per well of 2xTYAG medium (0.1% glucose) and grown at 37 °C for 5-6 hours (240 rpm). 100 µl per well of 0.2 mM IPTG in 2xTY medium were then added to give a final concentration of 0.02 mM IPTG. The plate was incubated overnight at 30 °C with shaking at 240 rpm. The deep well plate was centrifuged at 3200 rpm for 10 minutes at 4°C and the supernatant carefully removed. The pellets were resuspended in 150 µl TES buffer (50 mM Tris-HCl (pH 8), 1 mM EDTA (pH 8), 20% sucrose, complemented with Complete protease inhibitor, Roche). A hypotonic shock was produced by adding 150 µl of diluted TES buffer (1:5 TES:water dilution) and incubation on ice for 30 minutes. The plate was centrifuged at 4000 rpm for 10 minutes at 4 °C to pellet cells and debris. The supernatants were carefully transferred into a 96-well microtiter plate and kept on ice for immediate testing in functional assays or binding assays.

*Binding:* Screening of scFv for binding to hFIXa or hFX was tested in a homogenous assay using CellInsight technology. The following reagents were mixed in each well of a 384-well clear bottom plate (Corning): 30 µl of a streptavidin polystyrene bead suspension (Polysciences; 3000 beads/well) coated with biotinylated hFIXa or hFX or a control protein

(hFII); 60 µl of blocked scFv periplasmic preparation; 10 µl of detection buffer (PBS containing mouse anti-c-myc antibody at 5 µg/ml; anti-mouse Fc AlexaFluor® 647 diluted 1:200). After mixing at 600 rpm for 5 minutes, the 384-well plate was incubated at room temperature and read after 2 hours on a CellInsight™ CX5 High-Content Screening platform (Thermo Fisher Scientific). Clones expressing scFv giving a specific signal for either hFIXa or hFX and not hFII were selected for further analysis or sequencing.

*Phage clone sequencing.* Single TG1 clones are inoculated into a 96-well deep well plate containing 1 ml LBAG medium (LB medium with 100 µg/ml ampicillin and 2% glucose) per well and grown overnight at 37 °C, 240 rpm. DNA was extracted using the Zyppy-96 Plasmid Miniprep kit (Zymo Research). 5 µl of the eluted DNA was sequenced using the fdtseqlong primer, 5'-GTCGTCTTTCCAGACGTTAGTAAATG-3' (SEQ ID NO: 363).

### **EXAMPLE 3: Fixed VH candidates reformatting into (monospecific) IgG and transient expression in mammalian cells**

After screening, scFv candidates against hFIXa or hFX were reformatted into IgG and expressed by transient transfection into PEAK cells. The VH and VL sequences of selected scFv were amplified with specific oligonucleotides and cloned into an expression vector containing the heavy and light chain constant domains and the constructions were verified by sequencing. The expression vectors were transfected into mammalian cells using the Lipofectamine 2000 Transfection Reagent (Thermo Fisher Scientific, Waltham, MA). Transient transfections were performed using a mix containing 30 µg of DNA and 42 µL of Lipofectamine 2000 transfection reagent (Invitrogen) in 2 mL of DMEM for 107 cells per T175 flask in 50 mL of complete DMEM.

IgG expression was measured using the Octet RED96 with protein A-coated biosensors (Pall ForteBio). According to antibody concentration, supernatants were harvested 7 to 10 days after transfection and clarified by centrifugation 10 min at 2000 rpm. Total IgGs were purified by one affinity chromatography step using the FcXL resin (Thermo Fischer Scientific).

### **EXAMPLE 4: Generation of bispecific antibodies containing a hybrid light chain**

One way to assemble KL bodies is to co-express a complete variable light chain of the kappa type (i.e. variable and constant kappa domains) with a complete variable light chain of the lambda type (i.e. variable and constant lambda domains) and a common heavy chain (i.e. variable and constant heavy domains). However, it is also possible to use two variable domain of the same type (i.e. two kappa variable domains or two lambda variable domains) and generate a hybrid light chain. In this case, the variable domain of a lambda light chain

can be fused to a constant domain of the kappa type or conversely the variable domain of kappa a light chain can be fused to a constant domain of the lambda type as described in US 2012/0184716 and WO 2012/023053. Such hybrid chains were generated for several anti-FIXa and anti-FX arms. Downstream purification of bsAb containing hybrid chain follows the same strategy and affinity purification resins, as one light chain contains a kappa constant domain and the other contains a lambda constant domain.

**EXAMPLE 5: Expression and purification of bispecific antibodies carrying a Lambda and a Kappa constant light chain domain.**

The simultaneous expression of one heavy chain and two lights chain in the same cell can lead to the assembly of three different antibody forms, two monospecific antibodies and one bsAb. Simultaneous expression can be achieved in different ways such as that the transfection of multiple vectors expressing some of the chains to be co-expressed or by using vectors that drive multiple gene expression.

*Expression using a single vector.* A vector pNovi  $\kappa$ H $\lambda$  (i.e. pNovi Kappa H Lambda) was previously generated to allow for the co-expression of one heavy chain, one Kappa light chain and one Lambda light chain as described in US 2012/0184716 and WO 2012/023053, each of which is hereby incorporated by reference in its entirety. The expression of the three genes is driven by human cytomegalovirus promoters (hCMV) and the vector also contains a glutamine synthetase gene (GS) that enables the selection and establishment of stable cell lines. The VH and VL gene of the anti-FIXa or the anti-FX were cloned in the above-mentioned vector pNovi  $\kappa$ H $\lambda$ , for transient expression in mammalian cells.

*Expression via co-transfection of two vectors.* In order to rapidly screen panels of bsAb candidates for biological activity without the need of additional cloning steps, co-transfections using vectors described in Example 3 were also performed in Peak cells. The expression vectors were transfected into mammalian cells using the Lipofectamine2000 Transfection Reagent (Thermo Fisher Scientific, Waltham, MA). Transient transfections were performed using a mix containing 20+20  $\mu$ g of DNA and 60  $\mu$ L of Lipofectamine 2000 transfection reagent in 2 mL of DMEM for  $10^7$  cells per T175 flask in 50 mL of complete DMEM.

IgG expression was measured using the Octet RED96 with protein A-coated biosensors (Pall ForteBio). According to antibody concentration, supernatants were harvested 7 to 10 days after transfection.

*Bispecific antibody purification.* After 7-10 and days of antibody production, the supernatant was harvested, clarified by centrifugation 10 min at 2000 rpm. Total IgGs were purified by one

affinity chromatography step using the FcXL resin (Thermo Fischer Scientific). Then, two additional affinity chromatography steps were required to isolate the KL body and eliminate the two monospecific mAbs: one purification on the KappaSelect resin (GE Healthcare) to eliminate the IgG $\lambda\lambda$  (i.e. IgG comprising two light chains of Lambda type) and one  
5 purification on the LambdaFabSelect resin (GE Healthcare) to get rid of IgG $\kappa\kappa$  (i.e. IgG comprising two light chains of Kappa type).

Elution was performed with glycine 50 mM at pH 3.0. Following purification, the KL body were formulated into 25mM histidine, 125mM NaCl at pH 6.0, by desalting on Amicon Ultra-4  
10 centrifugal filters with membrane Ultracel 50 kDa (Merck Millipore) previously equilibrated with formulation buffer.

The final product was quantified using the Nanodrop. Purified bispecific antibodies were analyzed by electrophoresis in denaturing and reducing conditions. The Agilent 2100  
15 Bioanalyzer was used with the Protein 80 kit as described by the manufacturer (Agilent Technologies, Santa Clara, CA, USA). 4  $\mu$ L of purified samples were mixed with sample buffer supplemented with dithiothreitol (DTT; Sigma Aldrich, St. Louis, MO). Samples were heated at 95°C for 5 min and then loaded on the chip.

#### 20 **EXAMPLE 6: Optimization of lead anti-FIXa and anti-FX arms**

Several anti-FIXa and anti-FX antibodies that – when combined into a bispecific antibody – provided an increase in FVIII mimetic activity were selected for optimization.

All these antibodies share the same variable heavy chain but have different variable light  
25 chains. Several phage libraries displaying scFv variants were generated by introducing diversity into the CDR1, CDR2 and CDR3 of the variable light chain domain while the heavy chain variable domain was kept unmodified. Libraries of at least  $5 \times 10^9$  transformants were generated for each candidate. These libraries were used for phage display selections as described in Example 1. The stringency of the selection conditions was maintained relatively  
30 low using target concentration in the 10-100nM range in order to enable enrichment for candidates with a wide range of affinities. After selection variants were screened for the capacity to bind to FIXa or FX. Candidate scFv giving a specific signal for binding to their respective target were then reformatted into different antibody constructs encompassed by the present invention, expressed as multivalent antibody variants, characterized and tested  
35 in functional assays as e.g. described in Example 7.

#### **EXAMPLE 7: Calibrated automated thrombography assay**

Thrombin generation (TG) was evaluated via calibrated automated thrombography (CAT), a method described by Hemker et al., 2003. *Pathophysiol Haemost Thromb.* 33(1):4-15. The assay is based on the measurement of fluorescence that is generated by the cleavage of the fluorogenic substrate Z-G-G-R-AMC by thrombin over time. For each plasma sample, a  
5 thrombin calibrator is included to correct for inner filter effects, different coloration of plasma, substrate depletion and instrumental differences.

To keep the plasma background constant, platelet poor pooled human plasma (PPP, George King Bio-Medical Inc., Overland Park, KS, USA) was used as matrix. Hemophilic conditions  
10 were simulated by mixing PPP with heat-inactivated anti-human FVIII goat plasma (4488 Bethesda units [BU]/mL) (see Knappe et al., 2013. *Thromb Haemost.* 109:450-457), resulting in an inhibitor concentration of 50 BU/mL.

Pre-warmed (37°C) FVIII inhibited plasma (80 µL) was added to each well of a 96-well  
15 micro-plate (Immulon 2HB, U-bottom; Thermo Electron). Thrombin generation was triggered by 10 µL of PPP-reagent LOW (Thrombinoscope BV, Maastricht, The Netherlands) containing recombinant human tissue factor (rTF), a phospholipid mixture (48 µM) (MP reagent, Thrombinoscope BV, Maastricht, The Netherlands) and 62 µg/mL corn trypsin inhibitor (Hematologic Technologies Inc., Essex Junction, VT, USA or Enzyme Research  
20 Laboratories, South Bend, IN, USA). A final TF concentration of 1 pM was selected to provide sensitivity to FVIII in the assay system. The final assay well volume was adjusted to 120 µL by adding 10 µL HNa-BSA buffer for the blank or sample. Thrombin generation was started by dispensing 20 µL of FluCa reagent (Thrombinoscope BV, Maastricht, The Netherlands) containing fluorogenic substrate and Hepes buffered CaCl<sub>2</sub> (100 mM) into each  
25 well. Fluorescence measurements were performed in a Fluoroskan Ascent® reader (Thermo Labsystems, Helsinki, Finland; filters 390 nm excitation and 460 nm emission) at 37°C for 90 minutes with 20 seconds measurement intervals. All samples were analyzed in duplicate. The parameters of the resulting TG curves were calculated using the Thrombinoscope™ software (Thrombinoscope BV, Maastricht, The Netherlands). With the thrombin calibrator  
30 (Thrombinoscope BV, Maastricht, The Netherlands) as a reference, the molar concentration of thrombin in the test wells was derived. The thrombin amounts at the peak of each TG curve (peak thrombin, nM; C<sub>max</sub>), lag time (time interval between starting measurement and start of thrombin generation), peak time (time interval between starting measurement and C<sub>max</sub>), and endogenous thrombin potential (area under curve of thrombin concentration  
35 versus time) were recorded. Further analysis was performed in Microsoft Excel 2010 and/or GraphPad Prism 7. Graphs were created in GraphPad Prism 7.

## Results

In FVIII inhibited plasma the addition of Hemlibra (100 nM) resulted in a modest increase in TG with a peak thrombin level of  $15.8 \pm 0.97$  nM (Fig. 5-10). The normal plasma pool and the FVIII inhibited normal plasma resulted in peak thrombin levels of  $77.2 \pm 7.16$  nM and  $11.0 \pm 0.96$  nM, respectively.

**Table 12: Peak thrombin concentration at different concentrations of antibody variant**

| Construct number | Name          | Peak Thrombin (nM) at 300 nM (* = 200 nM) antibody conc. | Peak Thrombin (nM) at 100 nM (* = 60 nM) antibody conc. | Peak thrombin (nM) at 25 nM (* = 30 nM) antibody conc. | Peak thrombin (nM) at 6.3 nM (* = 10 nM) antibody conc. |
|------------------|---------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------|
| 1                | BAX#89        | 30.4*                                                    | 25*                                                     | nd                                                     | 19.7                                                    |
| 2                | BAX#87        | 20.5*                                                    | 16.9*                                                   | nd                                                     | 13.8                                                    |
| 3                | BAX#144       | 4.3                                                      | 14.5                                                    | 22.1                                                   | 18.4                                                    |
| 4                | BAX#145       | 10.1                                                     | 45.8                                                    | 60.8                                                   | 24.9                                                    |
| 5                | BAX#138       | 26.6                                                     | 43.9                                                    | 46.3                                                   | 20.7                                                    |
| 6                | BAX#146       | 16.1                                                     | 60.4                                                    | 85.0                                                   | 36.0                                                    |
| 7                | BAX#148       | 53.3                                                     | 91.5                                                    | 62.2                                                   | 21.1                                                    |
| 8                | LEX#105       | 42.0                                                     | 77.6                                                    | 67.6                                                   | 40.4                                                    |
| 9                | LEX#69        | 46.5                                                     | 72.0                                                    | 83.8                                                   | 38.1                                                    |
| 10               | LEX#68        | 39.0                                                     | 55.7                                                    | 59.0                                                   | 27.9                                                    |
| 11               | LEX#41        | nd                                                       | 46.7                                                    | 16.3                                                   | 14.7                                                    |
| 12               | LEX#40        | nd                                                       | 36.8                                                    | 23.5                                                   | 22.1                                                    |
| 13               | LEX#36        | nd                                                       | 13.6                                                    | 13.5                                                   | 12.6                                                    |
| 14               | LEX#39        | nd                                                       | 13.1                                                    | 12.4                                                   | 11.0                                                    |
| 15               | LEX#38        | nd                                                       | 25.1                                                    | 21.2                                                   | 20.5                                                    |
| 16               | LEX#103       | 34.2                                                     | 62.9                                                    | 49.3                                                   | 26.6                                                    |
| 17               | LEX#102       | 35.4                                                     | 64.2                                                    | 48.5                                                   | 26.2                                                    |
| 18               | LEX#99 (N=3)  | 27.4                                                     | 47.8                                                    | 47.5*                                                  | 32.8*                                                   |
| 19               | LEX#53        | nd                                                       | 64.6                                                    | 48.5                                                   | 23.0                                                    |
| 20               | LEX#59        | 20.3                                                     | 27.9                                                    | 23.4                                                   | 15.2                                                    |
| 21               | LEX#75        | 44.7                                                     | 68.6                                                    | 49.6                                                   | 22.6                                                    |
| 22               | LEX#74        | 50.2                                                     | 75.3                                                    | 48.6                                                   | 21.0                                                    |
| 23               | LEX#73        | 57.1                                                     | 77.5                                                    | 49.9                                                   | 21.4                                                    |
| 24               | LEX#72 (N=3)  | 56.0                                                     | 81.0                                                    | 64.6*                                                  | 41.3*                                                   |
| 25               | LEX#71        | 59.2                                                     | 75.6                                                    | 47.3                                                   | 22.0                                                    |
| 26               | LEX#63        | 16.4                                                     | 23.8                                                    | 23.4                                                   | 18.2                                                    |
| 27               | LEX#60        | 32.4                                                     | 64.5                                                    | 56.1                                                   | 28.8                                                    |
| 28               | LEX#97        | 24.6                                                     | 59.7                                                    | 47.1                                                   | 25.1                                                    |
| 29               | LEX#96        | 24.5                                                     | 61.0                                                    | 45.9                                                   | 24.9                                                    |
| 30               | LEX#88        | 43.3                                                     | 85.8                                                    | 56.1                                                   | 23.7                                                    |
| 31               | LEX#87        | 52.1                                                     | 97.7                                                    | 64.2                                                   | 25.9                                                    |
| 32               | LEX#86        | 56.5                                                     | 100.5                                                   | 65.9                                                   | 26.8                                                    |
| 33               | LEX#85 (N=3)  | 37.3                                                     | 83.9                                                    | 81.5*                                                  | 57.9*                                                   |
| 34               | LEX#84        | 59.2                                                     | 97.2                                                    | 56.0                                                   | 23.2                                                    |
| 35               | LEX#12        | nd                                                       | 60.0                                                    | 54.7                                                   | 20.5                                                    |
| 36               | LEX#2         | nd                                                       | 37.6                                                    | 30.2                                                   | 20.8                                                    |
| 37               | LEX#95        | 44.7                                                     | 87.9                                                    | 56.3*                                                  | 24.6*                                                   |
| 38               | LEX#121 (N=3) | 56.2                                                     | 81.3                                                    | 63.7*                                                  | 42.3*                                                   |
| 39               | LEX#129 (N=3) | 47.6                                                     | 70.2                                                    | 63.6*                                                  | 40.9*                                                   |
| 40               | LEX#131 (N=3) | 49.2                                                     | 69.5                                                    | 67.9*                                                  | 57.6*                                                   |
| 41               | LEX#134       | 80.0                                                     | 94.0                                                    | 92.3*                                                  | 67.9*                                                   |
| 42               | LEX#135 (N=3) | 107.4                                                    | 120.6                                                   | 92.7*                                                  | 47.3*                                                   |

|    |                 |      |       |        |       |
|----|-----------------|------|-------|--------|-------|
| 43 | LEX#143 (N=3)   | 53.4 | 92.5  | 82.8*  | 55.6* |
| 44 | LEX#153 (N=3)   | 45.5 | 89.2  | 92.3*  | 63.3* |
| 45 | LEX#157 (N=3)   | 53.7 | 107.3 | 120.2* | 84.4* |
| 46 | LEX#161         | 48.4 | 83.5  | 76.0*  | 50.7* |
| 47 | LEX#167 (N=3)   | 40.9 | 72.7  | 64.5*  | 39.6* |
| 48 | LEX#168 (N=3)   | 36.2 | 85.5  | 97.6*  | 77.8* |
| 49 | LEX#169 (N=3)   | 18.7 | 64.5  | 76.1*  | 59.0* |
|    | Hemlibra (N=10) | 25.7 | 16    | 13.3*  | 12.7* |

No different results were obtained when SIA was used instead of Hemlibra.

#### EXAMPLE 8: Measurement of FIXa and FX binding by Octet

- 5 Kinetics of antibody binding was studied using bilayer interferometry (Octet) in an HTX instrument in high-throughput mode. Anti-Human Fab-CH1 2nd generation (FAB2G) sensors were re-hydrated off-line for 10min, in PBST buffer (1x PBS containing 0.05% tween-20) and conditioned during the assay with three- five seconds stripping and regeneration steps, using 500mM phosphoric acid, and 40mM HEPES pH 7.4, 150mM NaCl buffer respectively.
- 10 Antibodies were then immobilized at constant 3.3µg/ml in PBST for five minutes resulting in immobilization levels of about 2.5 nm. Sensors were subsequently equilibrated 60 sec in assay buffer (40mM HEPES pH 7.4, 150mM NaCl, 0.05% BSA and 0.05% tween-20) and binding to 100nM either human FIXa, human FX, or a mixture of human FIXa and FX, each also at 100nM, were then analyzed for 300sec association and 300sec dissociation, in assay
- 15 buffer. A total of three consecutive cycles of stripping, regeneration, antibody loading and factor binding were performed on same set of sensors to allow antibody binding measurement to all different factors. A Shire proprietary control antibody, of non-related binding specificity, was run in each experiment as reference. Analysis was performed using the instrument supplied analysis software (version 11.0). Octet traces were reference
- 20 subtracted, aligned at average of -5 and 0 sec before association and inter-step shift corrected by aligning to dissociation. Savitzky-Golay filtering was applied. Binding was analyzed by measuring response values at the end of association phase. All measurements were performed at room temperature (~21-23°C) with 1000 rpm agitation.

#### 25 Results

**Table 13: Response (nm) of binding between the antibodies and Factor IXa and/or Factor X at the end of the association phase**

| Construct number | Name    | FIXa (nm) | FX (nm) | FIXa + FX (nm) |
|------------------|---------|-----------|---------|----------------|
| 1                | BAX#89  | 0.37      | 0.26    | 0.52           |
| 2                | BAX#87  | 0.24      | 0.27    | 0.40           |
| 3                | BAX#142 | ND        | ND      | ND             |
| 4                | BAX#144 | 0.74      | 0.64    | 1.12           |
| 5                | BAX#145 | 0.42      | 0.72    | 1.00           |
| 6                | BAX#138 | 0.42      | 0.58    | 0.85           |

|    |          |      |      |      |
|----|----------|------|------|------|
| 7  | BAX#146  | 0.48 | 0.88 | 1.14 |
| 8  | BAX#148  | 0.58 | 0.58 | 1.03 |
| 9  | BAX#137  | 1.12 | 0.13 | 1.14 |
| 10 | LEX#105  | 0.22 | 0.46 | 0.51 |
| 11 | LEX#69   | 0.58 | 0.61 | 1.02 |
| 12 | LEX#68   | 0.53 | 0.48 | 0.83 |
| 13 | LEX#41   | 0.30 | 0.43 | 0.64 |
| 14 | LEX#40   | ND   | ND   | ND   |
| 15 | LEX#36   | ND   | ND   | ND   |
| 16 | LEX#39   | ND   | ND   | ND   |
| 17 | LEX#38   | ND   | ND   | ND   |
| 18 | LEX#103  | 0.20 | 0.38 | 0.49 |
| 19 | LEX#102  | 0.22 | 0.41 | 0.51 |
| 20 | LEX#99   | 0.23 | 0.40 | 0.51 |
| 21 | LEX#53   | 0.48 | 0.50 | 0.84 |
| 22 | LEX#59   | 0.27 | 0.15 | 0.33 |
| 23 | LEX#75   | 0.50 | 0.20 | 0.59 |
| 24 | LEX#74   | 0.55 | 0.22 | 0.63 |
| 25 | LEX#73   | 0.45 | 0.19 | 0.53 |
| 26 | LEX#72   | 0.39 | 0.18 | 0.49 |
| 27 | LEX#71   | 0.40 | 0.19 | 0.49 |
| 28 | LEX#63   | 0.28 | 0.25 | 0.45 |
| 29 | LEX#60   | 0.24 | 0.48 | 0.61 |
| 30 | LEX#97   | 0.44 | 0.44 | 0.78 |
| 31 | LEX#96   | 0.44 | 0.45 | 0.78 |
| 32 | LEX#88   | 0.43 | 0.41 | 0.74 |
| 33 | LEX#87   | 0.43 | 0.40 | 0.72 |
| 34 | LEX#86   | 0.43 | 0.41 | 0.74 |
| 35 | LEX#85   | 0.43 | 0.42 | 0.73 |
| 36 | LEX#84   | 0.46 | 0.42 | 0.75 |
| 37 | LEX#12   | 0.29 | 0.70 | 0.88 |
| 38 | LEX#2    | ND   | ND   | ND   |
| 39 | LEX#3    | ND   | ND   | ND   |
| 37 | LEX#95   | 0.44 | 0.42 | 0.76 |
| 38 | LEX#121  | 0.20 | 0.58 | 0.60 |
| 39 | LEX#129  | 0.16 | 0.53 | 0.55 |
| 40 | LEX#131  | 0.13 | 0.56 | 0.57 |
| 41 | LEX#134  | 0.23 | 0.62 | 0.65 |
| 42 | LEX#135  | 0.20 | 0.31 | 0.40 |
| 43 | LEX#143  | 0.44 | 0.39 | 0.65 |
| 44 | LEX#153  | 0.32 | 0.81 | 0.86 |
| 45 | LEX#157  | 0.44 | 0.42 | 0.68 |
| 46 | LEX#161  | 0.35 | 0.79 | 0.89 |
| 47 | LEX#167  | 0.24 | 0.83 | 0.86 |
| 48 | LEX#168  | 0.67 | 0.87 | 1.18 |
| 49 | LEX#169  | 0.59 | 0.79 | 1.06 |
|    | Hemlibra | ND   | ND   | ND   |
|    | Synagis  | ND   | ND   | ND   |

**EXAMPLE 9: ELISAs**Phospholipid ELISA*Materials*

- 5 Dulbecco's PBS and FBS were obtained from Gibco. Calcium chloride dehydrate and BSA were obtained from Sigma, as well as 1,2-Diacyl-sn-glycero-3-phospho-L-serine and 1,2-

Dipalmitoyl-sn-glycero-3-phosphocholine. ELISAs were carried out in ninety-six-well plates LumiNunc MaxiSorp from Nunc. Antibodies have been produced by Icosagen (Estonia), Absolute Antibody (UK) or in-house manufacturing (Lexington/Cambridge, MA, USA). For detection a commercial antibody from Sigma was used.

5

#### *Methods*

Phospholipids were dissolved in Methanol to a final concentration of 20µg/ml. 50µl of this solution were added to 96-well microtiter plates to reach a final coating concentration of 10µg/ml. After evaporation of the solvent, the plates were blocked over night at +4°C with  
10 either 5% BSA or 10% FBS, both diluted in Dulbecco's PBS containing 2mmol/L Ca<sup>2+</sup>.

Plates were washed four times with PBS (without Ca<sup>2+</sup>). Antibodies were diluted in PBS to an initial concentration of 2.5µg/ml. Serial 2-fold dilutions in the respective blocking buffer were prepared and 100µl per well added to the plates. The plates were then incubated at room temperature for 45min. After washing, horseradish peroxidase goat anti-human IgG  
15 (diluted 1:10.000) was used for detection (45min incubation at room temperature). The secondary reagent was detected by adding 100µl TMB. After incubation for 10min 100µl of 1.8M sulfuric acid were added to each well followed by reading plates at 450nm using a microplate reader.

#### 20 β2-glycoprotein I ELISA

##### *Materials*

Dulbecco's PBS and FBS were obtained from Gibco. Calcium chloride dihydrate and BSA were obtained from Sigma. rhApoH Apolipoprotein H (recombinant human β2GP1) was obtained from R&D Systems. Ninety-six-well plates were LumiNunc MaxiSorp from Nunc.  
25 Antibodies have been produced by Icosagen (Estonia), Absolute Antibody (UK) or in-house manufacturing (Lexington/Cambridge, MA, USA). For detection a commercial antibody from Sigma was used.

##### *Methods*

30 rhApoH was dissolved in Dulbecco's PBS to a concentration of 10µg/ml. 100µl of this solution were added to 96-well microtiter plates. After incubation over night at +4°C the plates were blocked for 2 hours at +4°C with 5% BSA diluted in Dulbecco's PBS containing 2mmol/L Ca<sup>2+</sup>.

35 Plates were washed four times with PBS (without Ca<sup>2+</sup>). Antibodies were diluted in PBS to an initial concentration of 2.5µg/ml. Serial 2-fold dilutions in blocking buffer were prepared and 100µl per well added to the plates. The plates were then incubated at room temperature

for 45min. After washing, horseradish peroxidase goat anti-human IgG (diluted 1:10.000) was used for detection (45min incubation at room temperature). The secondary reagent was detected by adding 100µl TMB. After incubation for 10min 100µl of 1.8M sulfuric acid were added to each well followed by reading plates at 450nm using a microplate reader.

5

### GPIIb/IIIa ELISA

#### *Materials*

Dulbecco's PBS and FBS were obtained from Gibco. Calcium chloride dihydrate and BSA were obtained from Sigma. Natural human Integrin alpha 2b+ beta 3 protein was obtained from abcam. Ninety-six-well plates were LumiNunc MaxiSorp from Nunc. Antibodies have been produced by Icosagen (Estonia), Absolute Antibody (UK) or in-house manufacturing (Lexington/Cambridge, MA, USA). For detection a commercial antibody from Sigma was used. For detection a commercial antibody from Sigma was used.

#### *Methods*

Natural human Integrin alpha 2b+ beta 3 protein was dissolved in Dulbecco's PBS to a concentration of 10µg/ml. 100µl of this solution were added to 96-well microtiter plates. After incubation over night at +4°C the plates were blocked for 2 hours at +4°C with 5% BSA diluted in Dulbecco's PBS containing 2mmol/L Ca<sup>2+</sup>.

20

Plates were washed four times with PBS (without Ca<sup>2+</sup>). Antibodies were diluted in PBS to an initial concentration of 2.5µg/ml. Serial 2-fold dilutions in blocking buffer were prepared and 100µl per well added to the plates. The plates were then incubated at room temperature for 45min. After washing, horseradish peroxidase goat anti-human IgG (diluted 1:10.000) was used for detection (45min incubation at room temperature). The secondary reagent was detected by adding 100µl TMB. After incubation for 10min 100µl of 1.8M sulfuric acid were added to each well followed by reading plates at 450nm using a microplate reader.

25

### **Example 10: Bispecific antibodies with light chain specificity for factor IXa and X improve thrombin generation in hemophilia A plasma**

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In the context of the present invention, the following has been performed and is disclosed herein:

**Background:** Bispecific antibodies (bsAbs) partially mimic the function of activated factor (F)VIII by bridging FIXa and FX. They facilitate FX activation and improve hemostatic potential under hemophilic conditions. The κλ body platform enables the development of

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bsAbs in which the light chains drive specific target binding. The native human IgG architecture of  $\kappa\lambda$  bodies is suitable for long-term therapy.

**Aim:** To identify bsAbs targeting FIXa and FX that significantly increase thrombin generation in hemophilia A patient plasma.

**Methods:** Antibodies against FIX(a) and FX(a) were selected using phage display. To produce  $\kappa\lambda$  bodies, one common heavy and two light chains were co-expressed. Functional screening of cell culture supernatants identified numerous hits which were further optimized. Promising bsAbs were purified and subjected to activity testing by a FXIa-triggered thrombin generation (TG) assay in hemophilia A plasma and Octet measurements to assess binding properties.

**Results:** Starting from 350 FIXa and FX binders and followed by extensive optimization, over 17,000 bsAbs were screened and 1200 unique bsAbs expressed, purified and characterized. The bsAbs varied in their specificity, binding capacity, target binding region, and/or their procoagulant effect in the TG assay. For example, TG increased gradually in a bsAb concentration range of 10-300 nM. Some bsAbs reached a maximum of >350 nM peak thrombin. In comparison, a normal plasma control showed peak thrombin of 525 nM. These results show that FIXa/FX binding bsAbs with different binding properties can lead to a similar functional outcome.

**Conclusion:** The  $\kappa\lambda$  body technology was used for the generation of a large panel of native human bsAbs against FIXa/FX. Optimization of  $\kappa\lambda$  bodies resulted in improved binding properties to FIXa/FX and thereby led to significantly increased TG in plasma of hemophilia A patients. Optimization efforts continue to potentially provide a differentiated antibody-based therapy for hemophilia A in the future.

## CLAIMS

1. A proteinaceous molecule having a procoagulant activity comprising:  
(i) a scaffold module comprising a first antigen-binding site and a second antigen-binding site; and  
(ii) at least a first binding module comprising a third antigen-binding site;  
wherein at least one of the antigen-binding sites binds to Factor IXa and at least one of the antigen-binding sites binds to Factor X.
2. The proteinaceous molecule according to claim 1, wherein the first binding module is attached to the scaffold module through a linker and, optionally, any further binding module(s) is or are attached to the scaffold module through a linker.
3. The proteinaceous molecule according to claim 1, wherein the first binding module is inserted within a loop region of the scaffold module and, optionally, any further binding module(s) is or are inserted within a loop region of the scaffold module.
4. The proteinaceous molecule according to any one of claims 1-3, wherein the first antigen-binding site binds to Factor IXa, and the second antigen-binding site binds to Factor X.
5. The proteinaceous molecule according to any one of claims 1-4, wherein the third antigen-binding site of the first binding module binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.
6. The proteinaceous molecule according to claim 5, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.
7. The proteinaceous molecule according to claims 5, wherein the third antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

8. The proteinaceous molecule according to claim 7, wherein the first binding module is a scFv or scFab.

9. The proteinaceous molecule according to claim 8, wherein the first binding module comprises:

(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

10. The proteinaceous molecule according to claim 9, wherein the first binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

11. The proteinaceous molecule according to any one of claims 9-10, wherein the LCDR1, LCDR2 and LCDR3 are that of W206, W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

12. The proteinaceous molecule according to claim 5 or 6, wherein the first binding module is an scFv or scFab.

13. The proteinaceous molecule according to claim 12, wherein the first binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

14. The proteinaceous molecule according to claim 13, wherein the first binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

15. The proteinaceous molecule according to claim 5 or 6, wherein the first binding module comprises domain V of  $\beta$ 2-glycoprotein I.
16. The proteinaceous molecule according to any one of claims 1-15, wherein the scaffold module is an antibody or a bivalent fragment thereof.
17. The proteinaceous molecule according to claim 16, wherein the scaffold module is an antibody.
18. The proteinaceous molecule according to any one of claims 1-17, wherein the scaffold module comprises two heavy chains and two light chains.
19. The proteinaceous molecule according to claim 18, wherein one light chain of the scaffold module comprises a light chain variable domain fused to a Kappa constant domain and the other light chain of the scaffold module comprises a variable light chain domain fused to a Lambda constant domain.
20. The proteinaceous molecule according to any one of claims 18-19, wherein the scaffold module comprises:
- (i) two heavy chains comprising identical CDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3;
  - (ii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1; and
  - (iii) one light chain comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor IXa binding light chains disclosed in Table 2b.
21. The proteinaceous molecule according to claim 20, wherein the LCDR1, LCDR2 and LCDR3 of (ii) is the LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.
22. The proteinaceous molecule according to any one of claims 20-21, wherein the LCDR1, LCDR2 and LCDR3 of (iii) is the LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b.

23. The proteinaceous molecule according to any one of claims 20-22, wherein the LCDR1, LCDR2 and LCDR 3 of (ii) and (iii) are the LCDR1, LCDR2 and LCDR3 of W88 and V198, LCDR1, LCDR2 and LCDR3 of W127 and V202, LCDR1, LCDR2 and LCDR3 of V149 and W128, LCDR1, LCDR2 and LCDR3 of W128 and V198, LCDR1, LCDR2 and LCDR3 of W128 and V141, LCDR1, LCDR2 and LCDR3 of W162 and V204, LCDR1, LCDR2 and LCDR3 of W83 and V217, LCDR1, LCDR2 and LCDR3 of W206 and V245, LCDR1, LCDR2 and LCDR3 of W88 and V90, or LCDR1, LCDR2 and LCDR3 of W83 and V43, respectively, as disclosed in Tables 1 and 2b.

24. The proteinaceous molecule according to any one of claims 18-19, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical VH domains wherein the VH domain is SEQ ID NO: 4;
- (ii) one light chain comprising the VL of any one of the Factor X binding light chains disclosed in Table 3; and
- (iii) one light chain comprising the VL of any one of the Factor IXa binding light chains disclosed in Table 4b.

25. The proteinaceous molecule according to claim 24, wherein the VL of (ii) is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3, and the VL of (iii) is the VL of V43, VL of V245, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b.

26. The proteinaceous molecule according to any one of claims 24-25, wherein the VL of (ii) and (iii) are the VL of W88 and V198, VL of W127 and V202, VL of V149 and W128, VL of W128 and V198, VL of W206 and V245, VL of W128 and V141, VL of W162 and V204,

VL of W83 and V217,  
VL of W88 and V90, or  
VL of W83 and V43, respectively, disclosed in Tables 3 and 4b.

27. The proteinaceous molecule according to any one of claims 1-3, wherein each of the first antigen-binding site and the second antigen-binding site binds to Factor IXa, or each of the first antigen-binding site and the second antigen-binding site binds to Factor X.

28. The proteinaceous molecule according to claim 27, wherein the third antigen-binding site binds to Factor IXa or Factor X.

29. The proteinaceous molecule according to claim 28, wherein the first binding module is a scFv or scFab.

30. The proteinaceous molecule according to claim 29, wherein the first binding module comprises:

- (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;
- (ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

31. The proteinaceous molecule according to claim 30, wherein the first binding module comprises:

- (i) a VH domain, wherein the VH domain is SEQ ID NO: 183;
- (ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

32. The proteinaceous molecule according to any one of claims 30-31, wherein the LCDR1, LCDR2 and LCDR3 are that of W206, W198, V198, V202, W128, W88, W127, V212, or W162 disclosed in Tables 1 and 2b.

33. The proteinaceous molecule according to any one of claims 27-32, wherein the scaffold module is an antibody or a bivalent fragment thereof.

34. The proteinaceous molecule according to claim 33, wherein the scaffold module is an antibody.

35. The proteinaceous molecule according to any one of claims 27-34, wherein the scaffold module comprises two heavy chains and two light chains.

36. The proteinaceous molecule according to claim 35, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical HCDRs, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO:3; and
- (ii) two light chains each comprising the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

37. The proteinaceous molecule according to claim 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of W206, LCDR1, LCDR2 and LCDR3 of W83, LCDR1, LCDR2 and LCDR3 of W88, LCDR1, LCDR2 and LCDR3 of W128, LCDR1, LCDR2 and LCDR3 of W127, or LCDR1, LCDR2 and LCDR3 of W162 disclosed in Table 1.

38. The proteinaceous molecule according to claim 36, wherein the LCDR1, LCDR2 and LCDR3 of each of the two light chains is the LCDR1, LCDR2 and LCDR3 of V320, LCDR1, LCDR2 and LCDR3 of V305, LCDR1, LCDR2 and LCDR3 of V155, LCDR1, LCDR2 and LCDR3 of V245, LCDR1, LCDR2 and LCDR3 of V43, LCDR1, LCDR2 and LCDR3 of V90, LCDR1, LCDR2 and LCDR3 of V141, LCDR1, LCDR2 and LCDR3 of V149, LCDR1, LCDR2 and LCDR3 of V198, LCDR1, LCDR2 and LCDR3 of V202, LCDR1, LCDR2 and LCDR3 of V204, LCDR1, LCDR2 and LCDR3 of V212, or LCDR1, LCDR2 and LCDR3 of V217 disclosed in Table 2b.

39. The proteinaceous molecule according to claim 36, wherein the scaffold module comprises:

- (i) two heavy chains comprising identical VH domains, wherein the VH domain is SEQ ID NO: 4; and
- (ii) two light chains each comprising the VL of any one of the Factor X binding light chains disclosed in Table 3, or the Factor IXa binding light chains disclosed in Table 4b.

40. The proteinaceous molecule according to claim 39, wherein the VL of each of the two light chains is the VL of W206, VL of W83, VL of W88, VL of W128, VL of W127, or VL of W162 disclosed in Table 3.

41. The proteinaceous molecule according to claim 39, wherein the VL of each of the two light chains is the VL of V320, VL of V305, VL of V155, VL of V245, VL of V43, VL of V90, VL of V141, VL of V149, VL of V198, VL of V202, VL of V204, VL of V212, or VL of V217 disclosed in Table 4b.

42. The proteinaceous molecule according to any one of claims 1-41, wherein the proteinaceous molecule further comprises at least a second binding module comprising a fourth antigen-binding site.

43. The proteinaceous molecule according to claim 42, wherein the second binding module is identical to the first binding module.

44. The proteinaceous molecule according to claim 42, wherein the fourth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

45. The proteinaceous molecule according to claim 44, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

46. The proteinaceous molecule according to claim 44, wherein the fourth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

47. The proteinaceous molecule according to claim 46, wherein the second binding module is a scFv or scFab.

48. The proteinaceous molecule according to claim 47, wherein the second binding module comprises:

- (i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;
- (ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

49. The proteinaceous molecule according to claim 48, wherein the second binding module is a scFv and comprises:

- (i) a VH domain, wherein the VH domain is SEQ ID NO: 183;
- (ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

50. The proteinaceous molecule according to claim 44 or 45, wherein the second binding module is an scFv or scFab.

51. The proteinaceous molecule according to claim 50, wherein the second binding module comprises a VL domain and a VH domain, wherein:

- the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,
- the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or
- the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

52. The proteinaceous molecule according to claim 51, wherein the second binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

53. The proteinaceous molecule according to claim 44 or 45, wherein the second binding module comprises domain V of  $\beta$ 2-glycoprotein I.

54. The proteinaceous molecule according to any one of claims 42-53, wherein the proteinaceous molecule further comprises at least a third binding module comprising a fifth antigen-binding site.

55. The proteinaceous molecule according to claim 54, wherein the third binding module is identical to the first binding module.

56. The proteinaceous molecule according to claim 54, wherein the fifth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

57. The proteinaceous molecule according to claim 56, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha 5\beta 3$  integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta 2$ -glycoprotein I, preferably wherein the annexin is annexin V.

58. The proteinaceous molecule according to claim 56, wherein the fifth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

59. The proteinaceous molecule according to claim 58, wherein the third binding module is a scFv or scFab.

60. The proteinaceous molecule according to claim 59, wherein the the third binding module comprises:

(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

61. The proteinaceous molecule according to claim 60, wherein the third binding module is a scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

62. The proteinaceous molecule according to claim 56 or 57, wherein the third binding module is an scFv or scFab.

63. The proteinaceous molecule according to claim 62, wherein the third binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

64. The proteinaceous molecule according to claim 63, wherein the third binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

65. The proteinaceous molecule according to claim 56 or 57, wherein the third binding module comprises domain V of  $\beta$ 2-glycoprotein I.

66. The proteinaceous molecule according to any one of claims 54-65, wherein the proteinaceous molecule comprises at least a fourth binding module comprising a sixth antigen-binding site.

67. The proteinaceous molecule according to claim 66, wherein the fourth binding module is identical to the first binding module.

68. The proteinaceous molecule according to claim 66, wherein the fourth binding module is identical to the third binding module.

69. The proteinaceous molecule according to claim 66, wherein the sixth antigen-binding site binds to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

70. The proteinaceous molecule according to claim 69, wherein the phosphatidylserine-binding protein is Protein Z, Tissue Factor, Factor VIII, LOX-1, lactadherin, an oxysterol binding protein, Protein C, Protein S, Factor II (prothrombin), Factor V, Factor VII, Mer,  $\alpha$ 5 $\beta$ 3 integrin, the CR3 complement receptor, the CR4 complement receptor, the phosphatidylserine receptor, an annexin, or  $\beta$ 2-glycoprotein I, preferably wherein the annexin is annexin V.

71. The proteinaceous molecule according to claim 69, wherein the sixth antigen-binding site binds to a phosphatidylserine-binding protein selected from the list consisting of Factor IXa and Factor X.

72. The proteinaceous molecule according to claim 71, wherein the fourth binding module is a scFv or scFab.

73. The proteinaceous molecule according to claim 72, wherein the fourth binding module comprises:

(i) an HCDR1, HCDR2, and HCDR3, wherein HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2 and HCDR3 is SEQ ID NO: 3;

(ii) an LCDR1, LCDR2, and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b.

74. The proteinaceous molecule according to claim 73, wherein the fourth binding module is an scFv and comprises:

(i) a VH domain, wherein the VH domain is SEQ ID NO: 183;

(ii) a VL domain consisting of LCDR1, LCDR2, LCDR3 and four framework regions, wherein the LCDR1, LCDR2 and LCDR3 are the LCDR1, LCDR2 and LCDR3 of any one of the Factor X binding light chains disclosed in Table 1, or the Factor IXa binding light chains disclosed in Table 2b, and

wherein FW1 is SEQ ID NO: 179, FW2 is SEQ ID NO: 180, FW3 is SEQ ID NO: 181 and FW4 is SEQ ID NO: 182.

75. The proteinaceous molecule according to claim 69 or 70, wherein the fourth binding module is an scFv or scFab.

76. The proteinaceous molecule according to claim 75, wherein the fourth binding module comprises a VL domain and a VH domain, wherein:

the VL domain is SEQ ID NO: 184 and the VH domain is SEQ ID NO: 187,

the VL domain is SEQ ID NO: 185 and the VH domain is SEQ ID NO: 188, or

the VL domain is SEQ ID NO: 186 and the VH domain is SEQ ID NO: 189.

77. The proteinaceous molecule according to claim 76, wherein the fourth binding module is SEQ ID NO: 190, SEQ ID NO: 191 or SEQ ID NO: 192.

78. The proteinaceous molecule according to claim 69 or 70, wherein the fourth binding module comprises domain V of  $\beta$ 2-glycoprotein I.

79. The proteinaceous molecule according to any one of claims 66-78, wherein the proteinaceous molecule comprises at least a fifth binding module comprising a seventh antigen-binding site.

80. The proteinaceous molecule according to claim 79, wherein the proteinaceous molecule comprises at least a sixth binding module comprising an eighth antigen-binding site.

81. The proteinaceous molecule according to anyone of claims 79-80, wherein the seventh and/or eighth antigen-binding site bind to phosphatidylserine, a phosphatidylserine-binding protein or a platelet surface marker.

82. A pharmaceutical composition comprising the proteinaceous molecule according to any one of claims 1-81 and a pharmaceutically acceptable carrier and/or diluent.

83. The proteinaceous molecule according to any one of claims 1-81, or the pharmaceutical composition according to claim 82 for use as a medicament.

84. The proteinaceous molecule according to any one of claims 1-81, or the pharmaceutical composition according to claim 82 for use in a method of treating and/or preventing a bleeding disorder, wherein a patient or animal is administered a therapeutically effective amount of the proteinaceous molecule or the pharmaceutical composition.

85. The proteinaceous molecule or pharmaceutical composition for use according to claim 84, wherein the bleeding disorder is hemophilia A or acquired hemophilia.

Figure 1

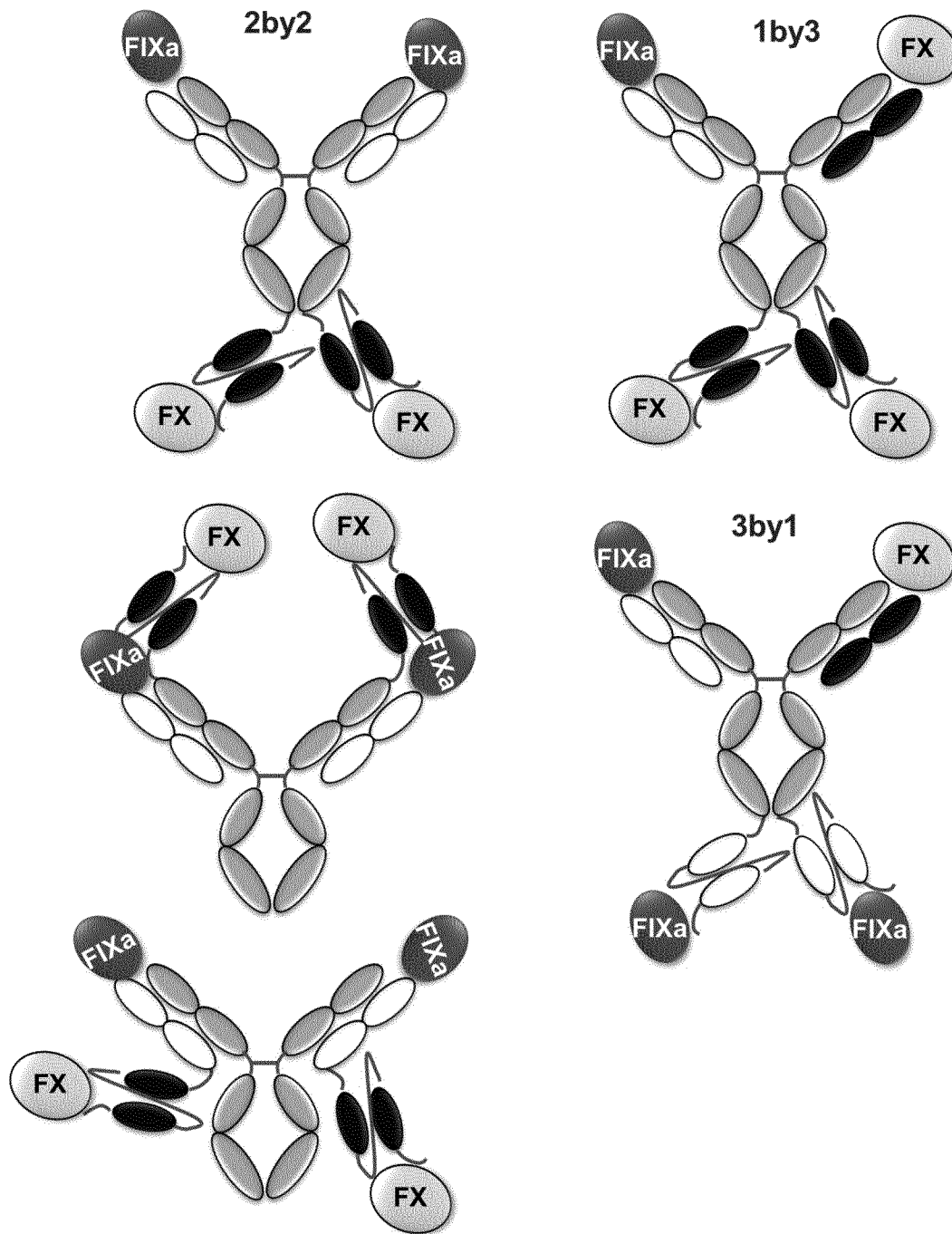


Figure 2

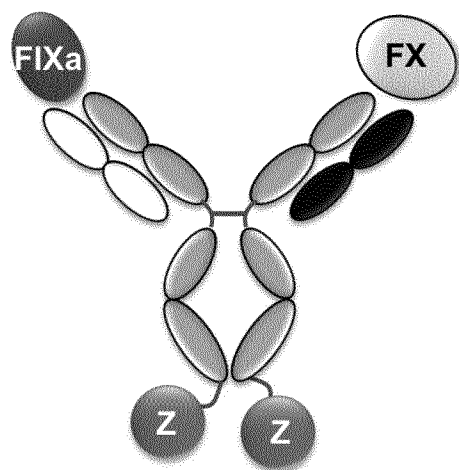


Figure 3

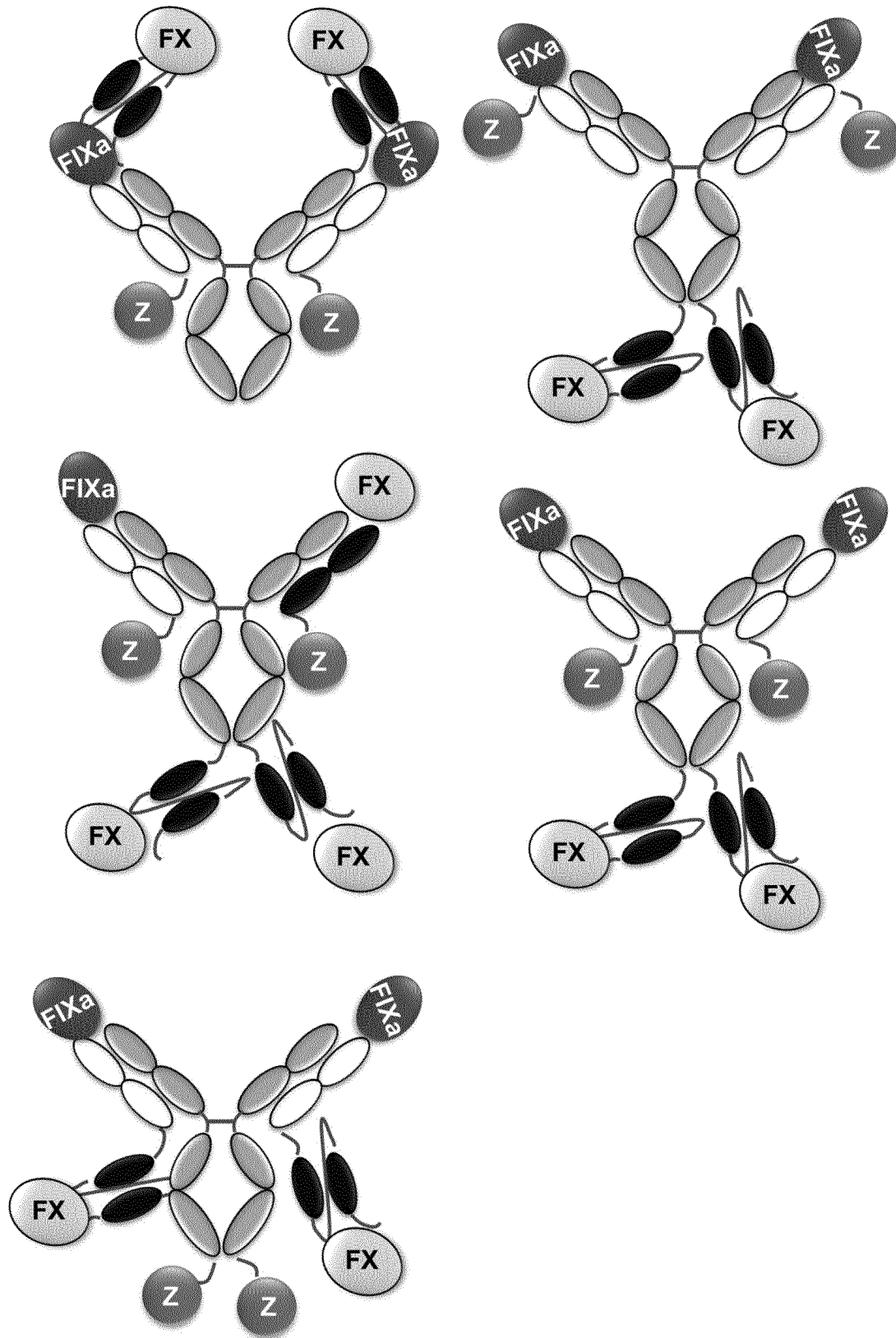


Figure 4

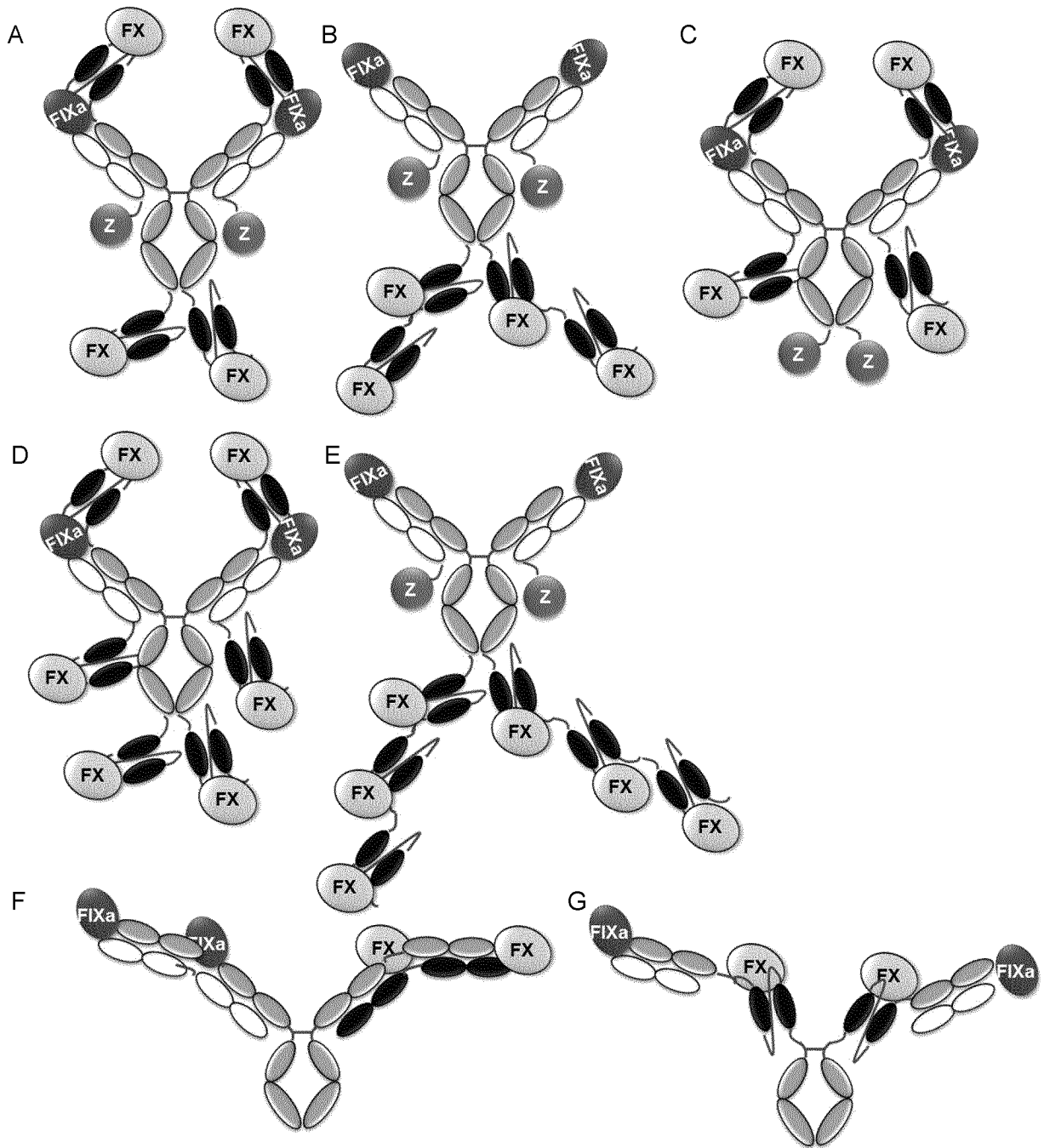


Figure 5

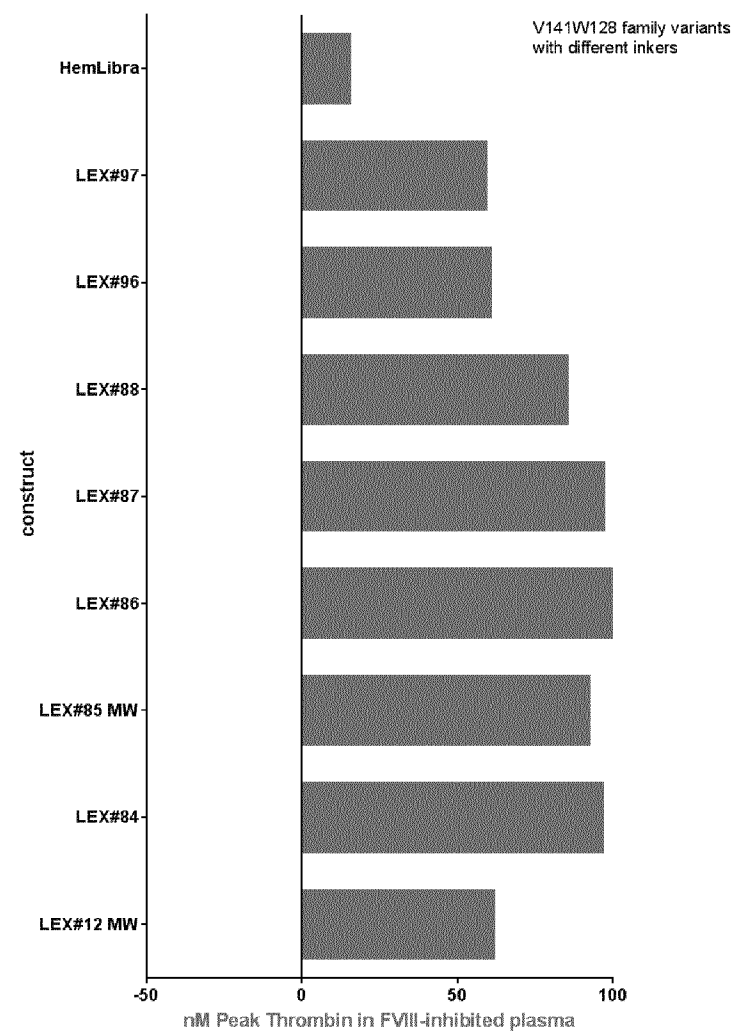


Figure 6

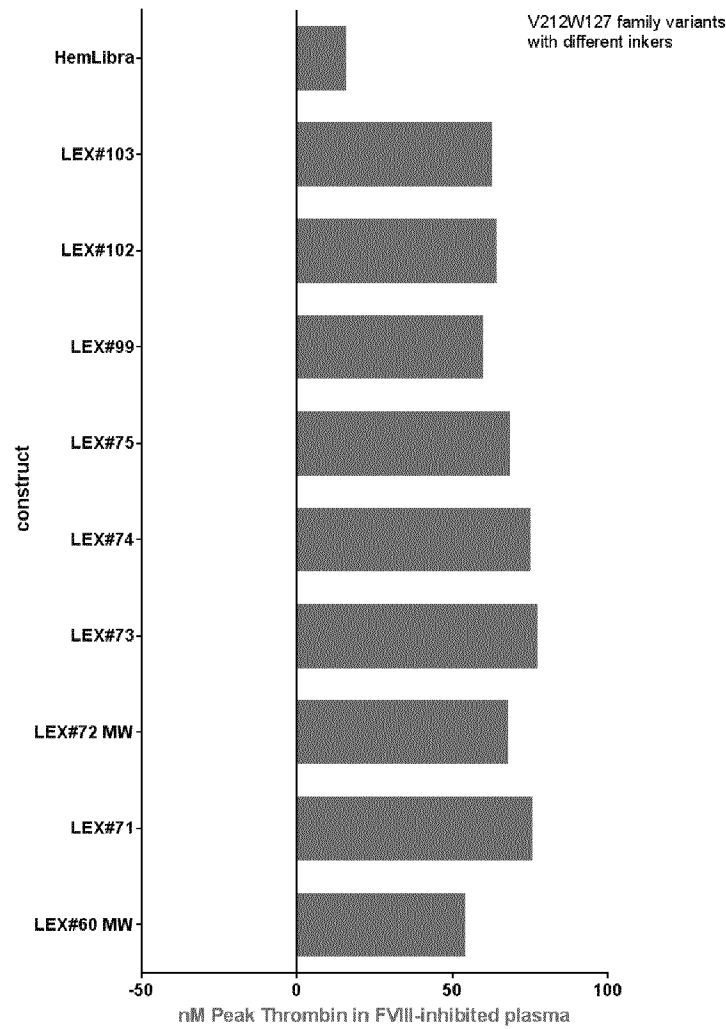


Figure 7

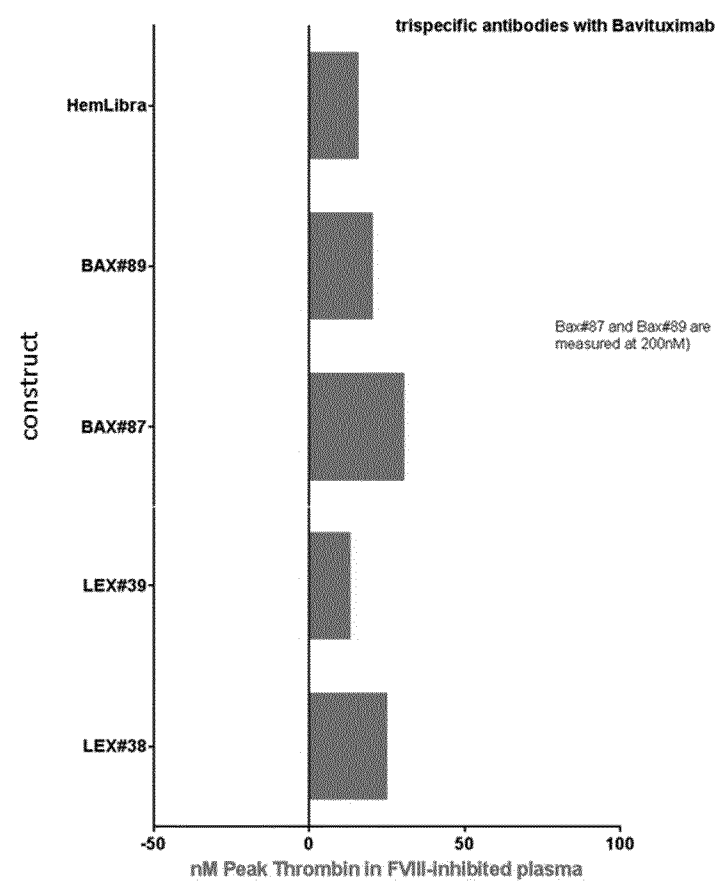


Figure 8

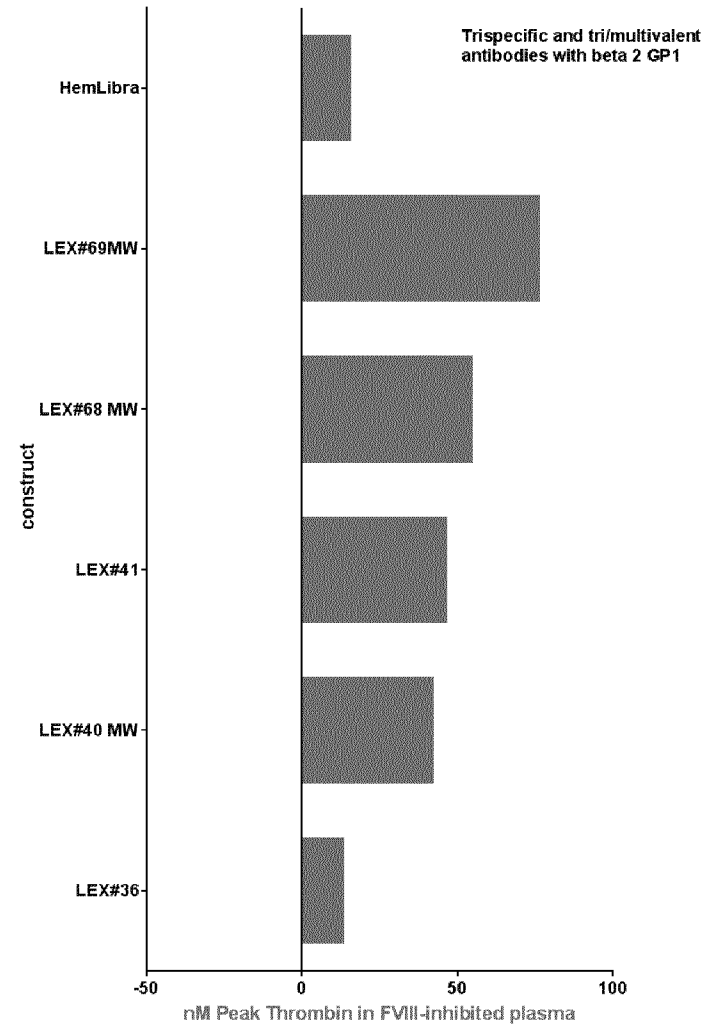


Figure 9

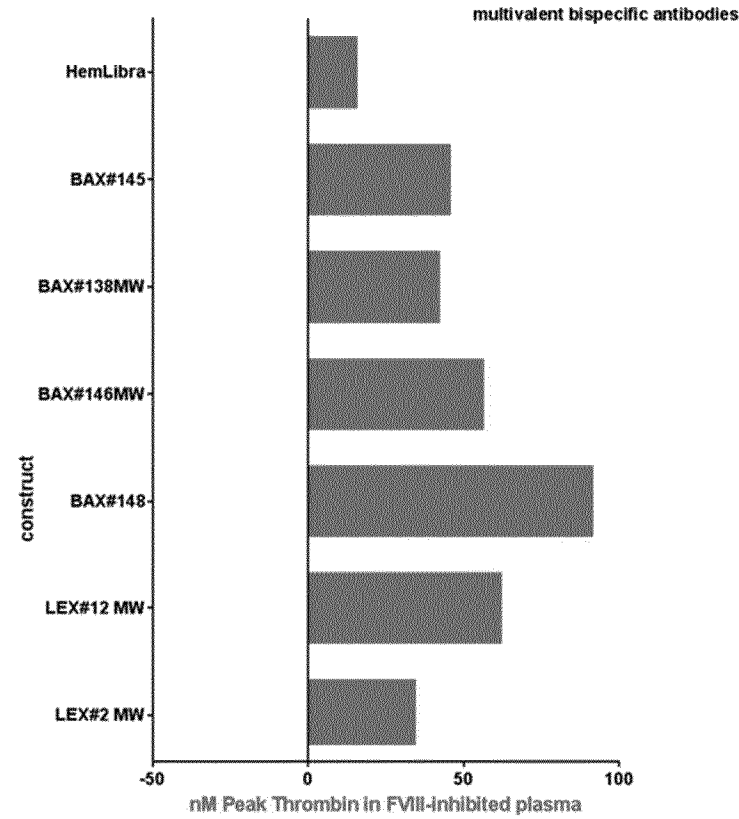


Figure 10

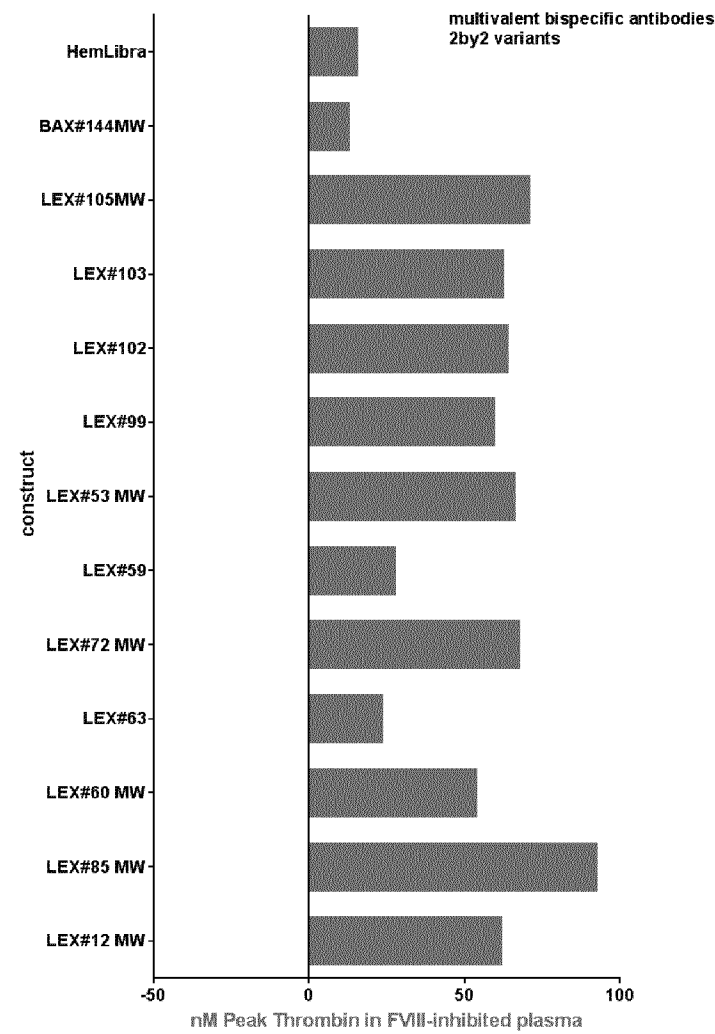


Figure 11

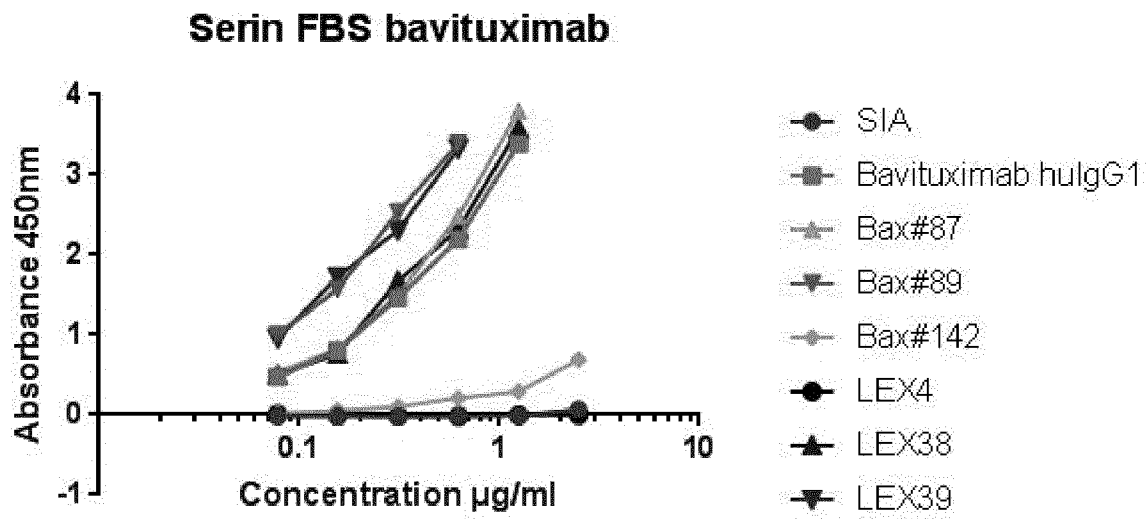


Figure 12

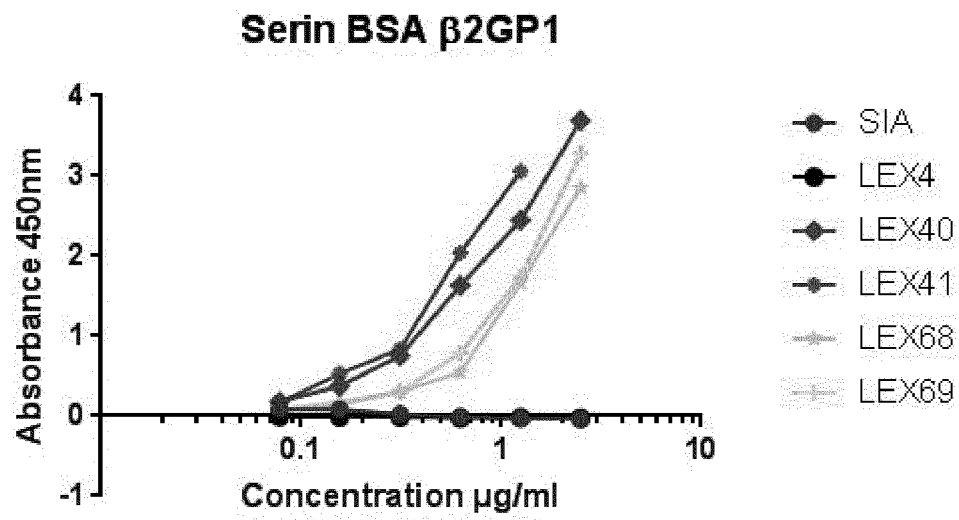
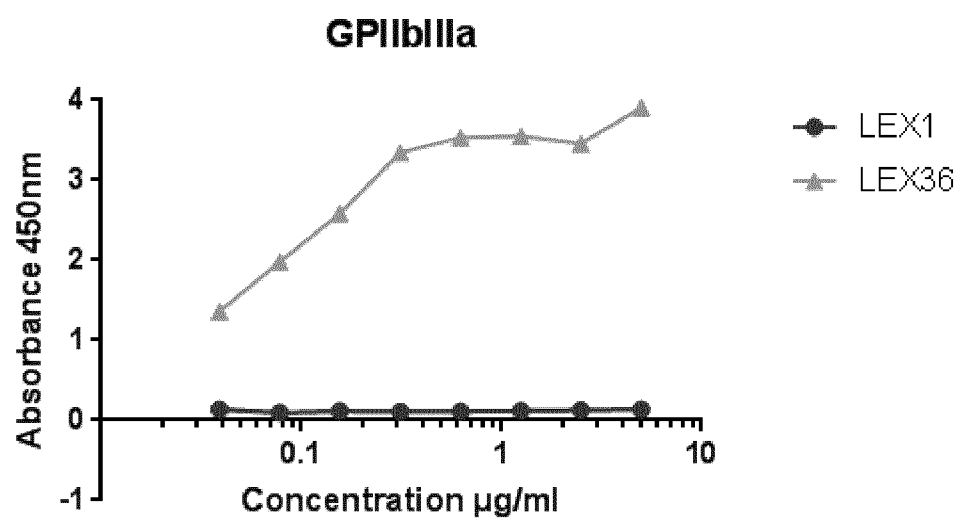


Figure 13



## INTERNATIONAL SEARCH REPORT

International application No  
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| A. CLASSIFICATION OF SUBJECT MATTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                          |                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| INV.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | C07K16/18<br>C07K16/46                                                                                   | C07K14/775<br>C07K16/36<br>A61P7/04<br>A61K39/395                    |
| ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                          |                                                                      |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                          |                                                                      |
| B. FIELDS SEARCHED                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                          |                                                                      |
| Minimum documentation searched (classification system followed by classification symbols)<br>C07K A61P                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                          |                                                                      |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                          |                                                                      |
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| C. DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                          |                                                                      |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Citation of document, with indication, where appropriate, of the relevant passages                       | Relevant to claim No.                                                |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -/-                                                                                                      |                                                                      |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                          |                                                                      |
| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>"&" document member of the same patent family |                                                                                                          |                                                                      |
| Date of the actual completion of the international search<br><br>18 February 2020                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                          | Date of mailing of the international search report<br><br>26/02/2020 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                          | Authorized officer<br><br>Saame, Tina                                |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2019/083998

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