Factor XI as target for antithrombotic therapy
van Montfoort, M.L.

Citation for published version (APA):
van Montfoort, M. L. (2014). Factor XI as target for antithrombotic therapy
In vitro and in vivo characterization of the first humanized inhibitory factor XI antibody

M.L. van Montfoort
P. Boross
V.L. Knaup
J.A. Marquart
K. Bakhtiari
F.J. Castellino
L. Boon
P. Simons
C.E. Hack
J.C.M. Meijers

Preliminary report
Abstract

Introduction: Inhibitory factor XI antibodies can safely prevent arterial and venous thrombosis in mice. Here we investigate the anti-thrombotic properties of three novel inhibitory anti-human factor XI antibodies, mAb 34.2, mAb 15F8.3 and mAb PRO-01.

Methods and Results: Monoclonal antibodies 34.2 and 15F8.3 were generated by conventional methods after injection of mice with human factor XI. mAb PRO-01 is a humanized form of mAb 34.2 and was produced using composite antibody technology. All three antibodies dose-dependently reduced factor XI activity levels in vitro, which was accompanied by a concomitant increase in aPTT. Using calibrated automated thrombography, all antibodies inhibited thrombin generation initiated via the intrinsic pathway. Furthermore, mAbs 34.2 and PRO-01 inhibited tissue factor-initiated thrombin generation at low concentrations of tissue factor, while mAb 15F8.3 did not inhibit tissue factor-initiated thrombin generation. In addition, all three antibodies prevented thrombosis in a ferric chloride induced inferior vena cava thrombosis model with a similar efficacy as enoxaparin. Antibodies 34.2 and 15F8.3 did not prolong the bleeding time in a tail bleeding assay. However, mAb PRO-01 prolonged the bleeding time to a similar extent as enoxaparin.

Conclusions: Two novel inhibitory factor XI antibodies (mAb 34.2 and 15F8.3) safely prevented thrombosis in mice. mAb PRO-01, which is a humanized form of mAb 34.2, also prevented thrombosis in the ferric chloride induced thrombosis model, but this was accompanied by a prolonged bleeding time.
Introduction

With the introduction of the novel direct oral anticoagulants (DOACs) a new era in the treatment and prevention of venous thromboembolism (VTE) has started. These new anticoagulants are as effective as vitamin K antagonists (VKA) and more convenient for patients(1). However, the number of major and clinically relevant bleedings in these patients is still a cause of concern and indicates that the ideal anticoagulant has not been developed yet(2). An approach that may help to enhance efficacy by reducing bleeding includes blocking contact-induced coagulation activation while preserving the tissue factor-induced coagulation pathways. Particularly coagulation factor XI (FXI) appears to be an attractive target for safe anticoagulation for the following reasons. First, patients with a FXI deficiency have a reduced incidence of deep vein thrombosis (DVT) when compared to the normal population(3). Second, FXI deficient mice are protected against several forms of artificially induced thrombosis(4-6). Third, increased plasma FXI levels have been associated with DVT, which indicates that FXI contributes to pathological thrombus formation(7). Finally, FXI deficiency in humans is associated with a mild bleeding tendency and in some individuals even may be unnoticed(8;9). Taken together, these results suggest that inhibition of FXI might be an effective therapeutic approach for anticoagulation without a risk for severe bleeding.

Previously, we reported the anti-thrombotic properties of two inhibitory anti-human FXI antibodies(10). These antibodies have a distinct working mechanism and they both prevented venous/arterial thrombosis in a murine thrombosis model. However, for a pharmaceutical, the antibodies have a medium-high affinity for FXI (2-5 nM), and are not suitable for administration to humans. Therefore, we developed two novel high-affinity antibodies against FXI (mAb 15F8.3 and mAb 34.2) of which we investigated the antithrombotic potential. Furthermore, one of the antibodies, Ab 34.2, was adapted in such a way that it can be administered to humans (mAb PRO-01).

Methods

Materials

Enoxaparin (Clexane) was from Sanofi-Aventis (Paris, France). Human coagulation FXI (Hemoleven) was purchased from LFB Biomedicaments (Les Ulis, France). FXI and factor XII (FXII) deficient plasmas were obtained from Siemens Healthcare Diagnostics (Marburg, Germany). Purified factor X (FX), FXII and high molecular weight kininogen (HK) were from Haematologic Technologies Inc. (Essex Junction, VT, USA). Factor VIII (FVIII) was from Wyeth Pharmaceuticals (Berkshire, United Kingdom) and factor IX
(FIX) was from Baxter (Deerfield, IL, USA). Chromogenic substrates S-2366 and S-2222 were from Chromogenix (Milano, Italy). Thrombin was a generous gift from Dr. W. Kisiel, University of Albuquerque, NM, USA. FXI was purified from human plasma as described before(11). Corn trypsin inhibitor (CTI) was from Sigma-Aldrich (St. Louis, MO, USA).

Antibodies
Monoclonal antibodies were generated by conventional methods after injection of Balb/c mice with a mixture of purified human FXI and FXIa. Antibody-producing clones were tested for coagulation inhibitory properties in an aPTT coagulation test. Two antibodies were identified, designated Ab 15F8.3 and Ab 34.2.

The humanized antibody (mAb PRO-01) was produced using composite antibody technology (Antitope Ltd, Cambridge, UK). In short, a human gene database was searched for the most compatible homologue variable gene sequence based on the murine antibody sequence. Then, it was investigated whether these sequences indeed interact with factor XI, after which several heavy and light chains with the particular sequence are expressed. All antibodies were produced as IgG4 with a hinge region mutation to stabilize the inter-chain disulphide bridges. Antibodies were also scanned for T-cell epitopes and ability to activate T-cells and complement.

Coagulation assays
Normal pooled plasma, derived from more than 200 healthy volunteers, was supplemented with antibodies and incubated for 30 minutes at room temperature before analysis. Activated partial thromboplastin time (aPTT) and FXI levels were measured on an automated coagulation analyzer (Behring Coagulation System, BCS) with reagents and protocols from the manufacturer (Siemens Healthcare Diagnostics).

The Calibrated Automated Thrombogram assays the generation of thrombin in clotting plasma. The assay was carried out as described (12) and the Thrombinoscope manual. Coagulation was triggered by recalcification either in the presence of 1 pM recombinant human tissue factor (Innovin, Siemens Healthcare Diagnostics), or aPTT reagent (8 times diluted; Pathromtin SL, Siemens Healthcare Diagnostics), 4 μM phospholipids, and 417 μM fluorogenic substrate Z-Gly-Gly-Arg-AMC (Bachem, Bubendorf, Switzerland). Fluorescence was monitored using a Fluoroskan Ascent fluorometer (ThermoLabsystems, Helsinki, Finland), and the ETP, peak, time-to-peak, lag time and velocity index were calculated using Thrombinoscope® software (Thrombinoscope, Maastricht, The Netherlands).
**Factor XI activation by thrombin or factor XIIa**

50 nM FXI was incubated with either Ab 15F8.3, Ab 34.2 or Ab PRO-01 (500 nM) in a buffer containing 25 mM HEPES, 137 mM NaCl, 3.5 mM KCl, 3 mM CaCl<sub>2</sub>, 0.1 mg/ml BSA, pH 7.4 (assay buffer) and incubated for 30 minutes at room temperature. Then, 10 nM of thrombin or 5 nM of FXIIa was added, thrombin was incubated overnight at room temperature and FXIIa was incubated for 2 hours at 37°C. Subsequently, 1 unit of hirudin was added to inhibit thrombin or 0.2 units of CTI to inhibit FXIIa and incubated for 20 minutes at room temperature. Chromogenic substrate S-2366 (f.c. 0.5 mM) was added and changes in OD 405 nm were monitored for 5 minutes. Activation of FXI by FXIIa was performed in absence or presence of 50 nM HK.

**Factor IX activation by factor XIa**

10 nM FXIa was incubated with Ab 15F8.3, Ab 34.2 or Ab PRO-01 (500 nM) in the previously described assay buffer and 5 nM FVIII for 30 minutes at 37°C. Then, 100 nM of FIX was added and incubated for 10 minutes at 37°C followed by addition of 100 nM FX, which was also incubated for 10 minutes 37°C. Finally, chromogenic substrate S-2222 was added and changes in OD 405 nm were monitored for 5 minutes.

**Solid-phase binding assay**

The interaction of the monoclonal antibodies with FXI was determined with a solid-phase binding assay. The individual apple domains of FXI as fusion protein with tPA(13) or FXI were coated on microtiter wells (100 μl, 50 nM in coating buffer: 50 mM Na<sub>2</sub>CO<sub>3</sub>, pH 9.6) and incubated overnight at 4°C. After washing the plate 3 times with Tris-buffered saline (TBS; pH 7.4), the plate was blocked with 200 μl blocking buffer (TBS/1.5% BSA) for 30 minutes at room temperature, followed by incubation with the antibodies (Ab 15F8.3, Ab 34.2 and Ab PRO-01, in TBS/1.5% BSA) for 1 hour at room temperature. Antibodies were diluted to 10 nM in blocking buffer, followed by a concentration series of 10 to 0.08 nM in a subset of experiments. Then, the plate was washed 3 times with TBS/Tween-20 (0.1%), followed by detection with peroxidase-labelled goat anti-mouse immunoglobulins (Dako, Glostrup, Denmark) for antibodies 15F8.3 and 34.2 or peroxidase-labelled rabbit anti-human immunoglobulins (Dako, Glostrup, Denmark) for antibody PRO-01. O-phenylenediamine dihydrochloride (OPD) tablets (Sigma-Aldrich, St. Louis, MO, USA) dissolved in phosphate-citrate buffer (50 mM citric acid, 114 mM NaH<sub>2</sub>PO<sub>4</sub>, pH 4.5) was used as substrate after which the reaction was stopped with 50 μl 1.0 M H<sub>2</sub>SO<sub>4</sub>. Absorption was read at 490 nm.
Animal experiments

Eight-week-old male FXI knock out-mice on C57BL/6 background were given plasma derived human FXI concentrate (Hemoleven) prior to the surgical procedure, which completely restores FXI levels. Dosage of Hemoleven was based on our previous experiments with this compound. Thereafter, the mice were intravenously injected with Ab 15F8.3, Ab 34.2, Ab PRO-01 or saline. Enoxaparin (LMWH) was injected subcutaneously 6 hours before the procedure. Dosages for the antibodies were based on the in vitro experiments presented here. Enoxaparin concentration was based on the dosage used in humans treated for DVT or PE (1 mg/kg).

Mice were housed in micro-isolator cages on a constant light-dark cycle and were given access to food and water ad libitum. All animal procedures were performed at the Academic Medical Center (Amsterdam, The Netherlands) and approved by the Animal Care and Use Committee of the institute.

Collection of mouse plasma samples

Blood samples were collected by cardiac puncture under anaesthesia. Blood was quickly withdrawn from the heart using a 1-mL plastic syringe with a 27-G needle and collected into a final ratio of 9 parts of whole blood to one part of 3.2% sodium citrate. Blood samples were immediately mixed by tapping and inverting the tube 5 times to ensure proper anticoagulation and then centrifuged for 15 minutes at 600 g at room temperature. Plasma was stored at -80°C until assayed.

FeCl₃-induced inferior vena cava thrombosis

The antithrombotic properties of Ab 15F8.3, Ab 34.2 and Ab PRO-01 were studied using a well established ferric chloride induced inferior vena cava (IVC) thrombosis model. In short, mice anesthetized with 2.5% inhalant isoflurane and an intraperitoneal injection of ketamin/xylazin (2:1), received a midline incision after which the IVC was exposed by blunt dissection. A filter paper soaked in a 10% FeCl₃ solution was placed below the renal veins on the IVC for 3 minutes after which the paper was removed and venous flow was measured for 30 minutes using a tissue perfusion monitor (type BLF22; Transonic Systems Inc. Ithaca, NY, USA). The flow before administration was set at 100% after which the decline in flow was calculated accordingly.

Tail vein bleeding assay

A mouse tail bleeding assay was used as described(6). Bleeding was assessed by determining the time until bleeding stopped with a maximum recording time of 30 minutes. Furthermore, the total amount of blood loss was analyzed as described(14).
Statistical analysis
Statistical comparisons were made using student t tests, 1way ANOVA or Mann-Whitney U tests. P values less than .05 were considered significant. Data were analyzed using SPSS software package for Windows, Version 20.0 (SPSS). Graphics were constructed using GraphPad Prism, Version 5 for Windows (GraphPad Software).

Results

Three antibodies against factor XI were generated and characterized. Two were mouse monoclonal antibodies (Ab 15F8.3 and Ab 34.2), while the third was a ‘humanized’ version of Ab 34.2. All three antibodies prolonged the aPTT in normal plasma with a maximum of 60 seconds (Fig. 1). Ab PRO-01 prolonged the aPTT clotting time at low concentrations (≥1.5 μg/ml), whereas the Ab 15F8.3 and Ab 34.2 prolonged the aPTT at somewhat higher concentrations ≥5 μg/ml.

Figure 1. Effect of Ab 15F8.3, Ab 34.2 and Ab PRO-01 on aPTT in human plasma. The antibodies were added to normal human plasma in various concentrations (0-100 μg/ml) after which the aPTT was determined.

FXI is a homodimer consisting of 4 tandem repeats called apple domains (apple1-4) and a catalytic domain. We tested the binding of the antibodies to the individual apple domains using solid-phase binding assays. Ab 15F8.3 binds to both factor XI and the apple domain 2 (Fig. 2a), while Ab 34.2 and Ab PRO-01 reacted with factor XI but did not interact with any of the apple domains (Fig. 2b and 2c). This suggests that Ab 34.2 and Ab PRO-01 bind to the catalytic domain of FXI. Furthermore, all three antibodies showed a high affinity for FXI (Fig. 3), with dissociation constants of 442 pM for Ab 15F8.3, 281 pM for Ab 34.2 and 234 pM for Ab PRO-01.
Figure 2. Binding properties of Ab 15F8.3, Ab 34.2 and Ab PRO-01 to factor XI. The binding site of both antibodies was assessed with solid-phase binding assays using individual human factor XI apple domains linked to tPA. Individual apple domains were coated on microtiter wells and incubated with either Ab 15F8.3 (2 μg/ml; a), Ab 34.2 (2 μg/ml; b) or Ab PRO-01 (2 μg/ml; c) after which binding to the apple domains was determined.
In vitro and in vivo characterization of the first humanized inhibitory factor XI antibody

c. Ab PRO-01

Figure 2. Binding properties of Ab 15F8.3, Ab 34.2 and Ab PRO-01 to factor XI. The binding site of both antibodies was assessed with solid-phase binding assays using individual human factor XI apple domains linked to tPA. Individual apple domains were coated on microtiter wells and incubated with either Ab 15F8.3 (2 µg/ml; a), Ab 34.2 (2 µg/ml; b) or Ab PRO-01 (2 µg/ml; c) after which binding to the apple domains was determined.

Figure 3. Solid-phase affinity assay. The affinity for FXI of both antibodies was evaluated using solid-phase affinity assays. FXI was coated on microtiter wells and incubated with Ab 15F8.3, Ab 34.2 or Ab PRO-01 with concentrations ranging from 0.08 to 10 nM after which binding to FXI was determined. A representative experiment is shown (n=3).

Effect of Ab 15F8.3, Ab 34.2 and Ab PRO-01 on thrombin generation in human plasma

Upon tissue factor (TF)-initiated thrombin generation, Ab 15F8.3 did not inhibit thrombin generation (Fig. 4a), while Ab 34.2 and Ab PRO-01 were able to inhibit thrombin generation at TF concentrations up to 1 pM (Fig. 4b/c). No inhibition of thrombin generation was observed with any antibody at concentrations of TF of 5 pM or higher (data not shown). All three antibodies inhibited thrombin generation initiated via the intrinsic pathway in normal plasma (Fig. 4d/e/f). This suggests that Ab 15F8.3 inhibits FXIIa-mediated activation of FXI, and that Ab 34.2 and Ab PRO-01 inhibit FXIa-mediated activation of FIX or activation of FXI by either FXIIa or thrombin.
To further elucidate the working mechanism, we tested the effects of the antibodies in a purified system. The antibodies did not affect FXI activation by thrombin (Fig. 5a). In contrast, Ab 15F8.3 was able to inhibit FXII mediated activation of FXI in the presence of HK, while Ab 34.2 and Ab PRO-01 had a moderate effect on FXI activation by FXIIa (Fig. 5b). Strikingly, in the absence of HK, Ab 15F8.3 was not able to inhibit FXI activation by FXIIa (Fig. 5b), indicating that this antibody prevents the binding of FXI(a) to HK.
This could be confirmed in direct binding assays with HK (data not shown). HK did not influence the inhibitory effect of Ab 34.2 or Ab PRO-01 on factor XIIa-mediated activation of FXI. Finally, both Ab 34.2 and Ab PRO-01 inhibited FIX activation by FXIa in a purified system (Fig. 5c).

Figure 5. Effect of Ab 15F8.3, Ab 34.2 and Ab PRO-01 on factor XI activity in a purified system. Factor XI (50 nM) was incubated with Ab 15F8.3, Ab 34.2 or Ab PRO-01 and 10 nM thrombin and subsequently factor Xa activity was measured using a chromogenic substrate S-2366 (a). A similar experiment was performed using factor XIIa (5 nM) as activator of factor XI in the absence or presence of HK (50 nM) (b). 10 nM FXIa was incubated with Ab 15F8.3, Ab 34.2 or Ab PRO-01 after which FVIII (5 nM) and FIX (100 nM) were added. FIX activity was measured indirectly using FX (100 nM) and chromogenic substrate S-2222 (c).

Ferric chloride induced IVC thrombosis
The antibodies were raised in mice against human factor XI(a), and in order to perform animal experiments in mice, it was necessary to use factor XI<sup>−/−</sup> mice reconstituted with human factor XI as described before(10). Intravenous administration of 5 U factor XI restored factor XI plasma levels to more than 100% (Fig. 6a). The subsequent administration of inhibiting factor XI antibodies or enoxaparin decreased measurable factor XI levels in mice, with a concomitant increase in aPTT (Fig 6a/b).
Figure 6. Reconstitution of factor XI in FXI-/− mice. FXI-/− mice were injected with human-derived factor XI concentrate, which restored factor XI levels (a) and aPTT clotting time (b). Subsequent administration of the inhibiting factor XI antibodies or enoxaparin increased aPTT and decreased factor XI activity. Each symbol represents one animal and the horizontal line indicates median.

All three antibodies prevented ferric chloride induced IVC thrombosis, while saline treated animals revealed a rapid decline in flow (Fig. 7a/b/c). The antibodies had a similar effectiveness as enoxaparin in this model (Fig. 7d).
**In vitro and in vivo characterization of the first humanized inhibitory factor XI antibody**

**Figure 7. Mouse inferior vena cava thrombosis model.** FXI<sup>−/−</sup> mice were given human derived factor XI concentrate followed by a single dose of either saline (control), enoxaparin (1 mg/kg), Ab 15F8.3 (4 mg/kg), Ab 34.2 (4 mg/kg) or Ab PRO-01 (2 mg/kg). Thrombosis was induced by applying a filter paper soaked in 10% ferric chloride for 3 minutes to the inferior vena cava, and venous blood flow was measured for 30 minutes. Each symbol represent the mean value of 6-8 animals, bars indicate SD, ***P<0.0001.
Bleeding
Infusion of Ab 15F8.3 and Ab 34.2 in mice was safe, as bleeding time and blood loss were not increased in the tail bleeding assay (Fig. 8a/b). Interestingly, bleeding time and blood loss were increased in animals treated with Ab PRO-01, the adapted antibody developed for human administration. As shown in fig. 8a, bleeding time was significantly longer than saline treated animals and comparable to enoxaparin. Blood loss was also increased, but this did not reach statistical significance (p=0.08).

![Figure 8. Effect of inhibiting factor XI antibodies and enoxaparin on bleeding in mice. FXI-/- mice were given human derived factor XI concentrate followed by a single dose of either saline (control), enoxaparin (1 mg/kg), Ab 15F8.3 (4 mg/kg), Ab 34.2 (4 mg/kg) or Ab PRO-01 (2 mg/kg). Subsequently, tail bleeding (a) and amount of blood loss (b), depicted as hemoglobin (Hb) content, were evaluated. Each symbol represents one animal, and the horizontal line indicates median. **P<0.01, ***P<0.0001, ns=non-significant.]

Discussion
We identified three novel inhibiting FXI antibodies, one of which inhibited the factor XIIa-mediated factor XI activation (Ab 15F8.3) and the other two interfered with the activation of factor IX by factor XIa (Ab 34.2 and Ab PRO-01). Furthermore, all three antibodies revealed a very high affinity for FXI, approximately 10 fold higher than the antibodies we previously described(10). This is also reflected in the thrombin generation experiments where even a low concentration of antibody was sufficient to inhibit thrombin generation. This indicates that these antibodies are probably more suitable as a pharmaceutical than antibodies 175 and 203 from our previous report. Interestingly, Ab 34.2 and Ab PRO-01 interacted with the catalytic domain of FXI, which suggests that these antibodies interact close to the active site of factor XI. However, future experiments are necessary to determine the exact binding site of Ab 34.2 and Ab PRO-01 to factor...
XI. In contrast, Ab 15F8.3 binds to the apple 2 domain of FXI, thereby preventing the activation of FXI by FXIIa and this reaction is HK dependent. HK is important for factor XIIa mediated activation of factor XI, it serves as a non-enzymatic cofactor in this reaction. The apple 2 domain is involved in the interaction between FXI and HK(15) and by interfering with this reaction, Ab 15F8.3 prevents factor XI activation and subsequent thrombus formation.

All three antibodies revealed superior effects in the in vitro experiments when compared to our previously described antibodies. The superior inhibitory capacities of these three antibodies are also reflected in the in vivo experiments. All three antibodies completely prevented thrombosis in the ferric chloride mouse model and this is comparable to the effects seen in factor XI knock out-mice(6). Taken together, the results from our in vitro and in vivo experiments indicate that Ab’s 34.2, 15F8.3 and PRO-01 completely block factor XI activity in plasma. Furthermore, the antibodies are as effective as LMWH and more effective than the previous antibodies we described, at least in this particular model. Interestingly, Ab 15F8.3, which inhibits the factor XIIa mediated activation of factor XI, also completely prevented vessel occlusion in the ferric chloride model, which indicates that this animal model is dependent on both FXI and FXII(16). However, the physiological role of FXII during coagulation in humans is not completely clear and therefore it is difficult to translate this observation to the human situation. Nevertheless, because Ab 34.2 interacts with the catalytic domain of factor XI, we think this antibody is the best candidate for future development. Clinical trials have to establish whether factor XI is indeed a good target for anticoagulation and if Ab 34.2 is as effective as the currently available anticoagulant drugs.

To our great surprise Ab PRO-01 significantly prolonged the bleeding time and the total amount of blood loss in the tail bleeding assay. Since FXI knock out-mice do not have an enhanced bleeding phenotype, this observation was highly unexpected. Also because of the fact that Ab 34.2, which is the murine variant of the antibody, did not prolong bleeding time. This indicates that the humanized form of the antibody has an additional effect on coagulation. We ruled out the possibility that Ab PRO-01 inhibits other clotting factors (e.g. FIXa), interacts with platelets or that the protein was contaminated with for instance heparin (data not shown). One possibility is that Ab PRO-01 is so potent that it induces nonspecific factor XI independent effects on coagulation. Additional (dose-finding) studies are necessary to understand this observation.

To study the anti-thrombotic effect of the inhibiting factor XI antibodies we used the well-established ferric chloride injury model. Ferric chloride induced thrombosis has several advantages. Application of ferric chloride to the vessel wall induces rapid thrombus formation in the underlying vessel in a highly reproducible manner(17). This makes it an excellent model to study anticoagulant drugs(18). However, the thrombi produced
by ferric chloride are histologically different from natural occurring thrombi in humans. Furthermore, ferric chloride is an artificial trigger, making the results difficult to directly translate to human VTE. Nevertheless, the ferric chloride model is a widely used animal model to study the effects of antiplatelet and anticoagulant drugs.

Future (clinical) studies on factor XI inhibition will learn whether factor XI indeed is a good target for anticoagulation. In this study we have chosen for an antibody approach, which has several advantages. First, the antibodies immediately start working unlike for instance vitamin K antagonists or factor XI antisense oligonucleotides which require 2 to 3 days before a maximum effect is reached(19). Second, the antibodies have a very high affinity for factor XI, combined with the relatively long half-life of factor XI (48 hours) a 2 to 3 times a week dosing regime is possible, probably improving patient compliance. Obviously, this has to be established in clinical trials.

In conclusion, we developed two new inhibitory FXI antibodies (Ab 34.2 and Ab 15F8.3), which prevent thrombosis comparable to LMWH, without causing a bleeding tendency. A humanized homologue of Ab 34.2 was prepared (Ab PRO-01) and showed similar effectiveness as the murine counterpart. However, this antibody did prolong the bleeding time in mice which is currently not understood. Ab PRO-01 is the first inhibitory factor XI antibody for administration to humans.
References