Published in final edited form as:

Expert Opin Ther Pat. 2020 January ; 30(1): 39–55. doi:10.1080/13543776.2020.1705783.

Factor XI(a) inhibitors for thrombosis: an updated patent review (2016-present)

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Abstract

Introduction: Anticoagulation without bleeding is an ideal goal in treating thrombosis, however, this goal has not been achieved. All current anticoagulants are associated with significant bleeding which limits their safe use. Genetic and pharmacological findings indicate that factor XIa is a key player in thrombosis, yet it is a relatively marginal one in hemostasis. Thus, factor XIa and its zymogen offer a unique opportunity to develop anticoagulants with low bleeding risk.

Areas covered: A survey of patent literature has retrieved more than 50 patents on the discovery of novel therapeutics targeting factor XI(a) since 2016. Small molecules, monoclonal antibodies, oligonucleotides, and polypeptides have been developed to inhibit factor XI(a). Many inhibitors are in early development and few have been evaluated in clinical trials.

Expert opinion: Factor XI(a) is being actively pursued as a drug target for the development of effective and safer anticoagulants. Although many patents claiming factor XI(a) inhibitors were filed prior to 2016, recent literature reveals a moderately declining trend. Nevertheless, more agents have entered different levels of clinical trials. These agents exploit diverse mechanistic strategies for inhibition. Although further development is warranted, reaching one or more of these agents to the clinic will transform the anticoagulation therapy.

Keywords

Thrombosis; safe anticoagulants; factor XIa; active site inhibitors; pyridine-*N*-oxide; oxopyridine; macrocyclic; β -lactam; monoclonal antibodies; aptamers

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Declaration of interest

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Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1. Introduction

1.1. Current anticoagulants and the need for new ones

Thrombosis is the pathological formation of blood clots in blood vessels and/or heart. Venous thrombosis and arterial thrombosis are significantly associated with high morbidity and mortality rates in developing as well as developed countries [1,2]. Venous thrombosis is manifested as deep vein thrombosis or pulmonary embolism, whereas arterial thrombosis is manifested as ischemic heart disease or stroke. Atrial fibrillation, unstable angina, and disseminated intravascular coagulation are also examples of thrombosis-related diseases. Treatment of thrombotic diseases entails the use of antithrombotics i.e. anticoagulants and antiplatelets. Current anticoagulants include the indirect conventional drugs and the direct novel ones. In one hand, the indirect anticoagulants include vitamin K antagonists (warfarin) and antithrombin activators (fondaparinux, low molecular weight heparins, and unfractionated heparin). In the other hand, the direct novel anticoagulants include thrombin inhibitors (dabigatran etexilate and argatroban) and factor Xa (FXa) inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban) [3–5]. Although currently available anticoagulants are effective in treating and/or preventing thrombosis, yet they continue to be associated with a host of drug-specific and drug-nonspecific complications [3,4]. One of the most life-threatening complications of current anticoagulation therapy is bleeding [5,6].

All clinically used anticoagulants block the coagulation process by directly or indirectly inhibiting serine proteases in the common coagulation pathway i.e. thrombin and/or FXa, and thus, they affect the three stages of the coagulation process i.e. initiation, propagation, and amplification. In other words, current anticoagulants do not distinguish between the pathological coagulation i.e. thrombosis and the physiological coagulation i.e. hemostasis. As a result, they are clinically effective, yet they also induce serious bleeding complications which limit their safe use in a wide range of thrombotic patients [7–12]. In fact, the risk of bleeding with the use of anticoagulants is further increased in certain patient populations. For example, patients with chronic kidney diseases, who are considered as a high-risk group for thrombosis, have platelet abnormalities which put them at higher risk of bleeding. Another special group of patients is those with atrial fibrillation. Because of the risk of bleeding, more than 30% of these patients fail to receive anticoagulant prophylaxis and among patients receiving anticoagulants, up to 50% are ineffectively treated [7–12]. Thus, new anticoagulants that address the need of these patients are urgently needed.

In fact, proteins other than those of the common coagulation pathway have been considered to develop new anticoagulants with minimal risk of bleeding [13]. This includes coagulation protein of the extrinsic pathway i.e. factor VIIa (FVIIa) [14] and coagulation proteins of the intrinsic pathway and contact activation pathway i.e. factors XIIa, XIa, and IXa [15–17]. This review will focus on the drug development for molecules that interfere with the physiological function(s) of factor XI(a) (FXI(a)) which is considered as one of the most promising drug targets for effective and relatively safer anticoagulants [5,6].

1.2. Structure and function of human FXI(a): the promise of a new anticoagulant target

Factor XI (FXI) is the zymogen of factor XIa (FXIa), a coagulation serine protease of human plasma. Structurally, FXI is a disulfide-linked homodimer of two identical subunits with a total molecular weight of about 160 kD and approximate plasma concentration of 30 nM. Its biosynthesis happens largely in hepatic cells, and to some extent in pancreatic and renal tubule cells. Although not fully understood, platelets have also been reported to contribute to FXI expression/biosynthesis. The activation of the zymogen FXI to the protease FXIa takes place by cleaving the peptide bond R369-Ile370. This activation takes place in the presence of FXIIa or thrombin. Auto-activation of FXI may also take place in the presence of polyanions including polymeric inorganic polyphosphates [18–20].

Structurally, human FXIa possesses an *N*-terminal heavy chain and a *C*-terminal light domain (Figure 1). The former chain consists of four repeats known as the apple domains and labeled as A1 through A4. The latter chain is a trypsin-like catalytic domain. The X-ray crystal structure of the zymogen FXI revealed that the catalytic and the apple domains form a ‘cup and saucer’ relationship [18–20]. In one hand, the apple domains of FXIa contain several binding sites for macromolecules that interact with FXI(a) system during its course of physiological actions. Specifically, there is a binding site for thrombin in A1 domain [21], high molecular weight kininogen in A2 domain [22], factor IX (FIX) [23], platelet glycoprotein-Ib [24], and heparin/heparan sulfate in A3 domain [25], and FXIIa in A4 domain [26]. In the other hand, the catalytic domain contains the active site with the catalytic triad of H413, D462, and S557 (the chymotrypsin residue numbering: H57, D102, and S195). As with other proteases, the architecture of FXIa active site involves multiple subsites (S4–S3–S2–S1–S1′–S2′–S3′–S4′) with unique structural features so as to achieve substrate specificity. For instance, the S1 specificity pocket is known to bind to the basic arginine residue in the physiological substrate, FIX, and contains an aspartate residue (D189) at the bottom of the subsite [6]. Furthermore, the S2 specificity pocket engages with threonine residue in FIX whereas the S1′ pocket prefers small and lipophilic residues involving alanine and/or valine. Subsites S3 and S2′ commonly recognize leucine or phenylalanine and glutamate or valine, respectively. Additionally, the catalytic domain also has an anion-binding site which has been implicated in the protease regulation by either charge neutralization or allosteric modulation [27].

Physiologically, the protease FXIa has multiple substrates. FXIa activates FIX to factor IXa (FIXa) in the coagulation process. In the activation event, FIX binds to an exosite on the A3 apple domain of FXIa. The key amino acids in the active site of FXIa then cleave the peptide bond of R145-A146 and then the peptide bond of A180-V181 resulting in the formation of FIXaβ, which eventually promotes thrombin generation and blood clotting [28,29]. Furthermore, several studies indicate that FXIa can activate other proteases that are important for the coagulation process as well as the kallikrein-kinin system. Particularly, FXIa was reported to activate factors V, VIII, X, and XII [30–35]. FXIa also promotes clot formation/stability by inhibiting other coagulation regulators including tissue factor pathway inhibitor [36] and the von Willebrand factor-cleaving metalloproteinase [37]. Moreover, studies also indicate that FXI binds to platelets, and thus, contributes to platelet activation and accumulation. FXI localized to platelets was found to promote coagulation and

inflammation in mice in a glycoprotein 1b-dependent manner [38]. FXI was also reported to bind to the platelet apolipoprotein E receptor-2 [39] suggesting that FXI binding to platelets may involve a complex process. FXI also interacts with the human recombinant laminin heterotrimers in the extracellular matrix of blood vessels and arteries [40]. The interaction was proposed to contribute to the FXIa-mediated activation of FIX and thrombin generation in the extracellular matrix following blood vessel injury [20]. Overall, given the multiple substrates that FXI(a) system interacts with, its role has been re-defined from a component in the intrinsic pathway in the waterfall hypothesis of coagulation to a key player that bridges the thrombin generation process via activating FIX and the host defense, inflammatory mechanism(s) via activating FXII (Figure 2).

Importantly, mounting clinical, experimental, and epidemiological evidence indicates that the protease FXIa fundamentally contributes to the amplification phase of blood clotting, rather than the initiation phase. Accordingly, FXIa has been considered to mainly contribute to the pathological blood clotting i.e. thrombosis, and to play a relatively minor role in the physiological blood clotting i.e. hemostasis. Along these lines, patients with hemophilia C (FXI genetic deficiency in humans) are linked to a relatively mild-to-moderate risk of bleeding compared to those with hemophilia A or B. These patients show a normal prothrombin time (PT), yet a relatively prolonged activated partial thromboplastin time (APTT) which indicates a specific defect in the amplification phase of the coagulation process [41–43]. Furthermore, reports indicate that patients with severe FXI deficiency exhibit a reduced risk of deep vein thrombosis [44] and/or ischemic stroke [45]. Epidemiological studies also revealed that increased levels of FXI may increase the risk of deep vein thrombosis [46], stroke [47–49], myocardial infarction [50], and cardiovascular diseases in women [51]. Moreover, testing of antisense oligonucleotides, monoclonal antibodies, and small molecules in animal models (mice, rats, rabbits, and baboons) of arterial thrombosis and venous thrombosis as well as in humans strongly support that agents targeting FXI(a) do provide a clinically relevant protection against thrombosis with no significant impact on bleeding times [5,6]. In particular, the antisense oligonucleotide ISIS 416858 [52,53], the monoclonal antibodies MAA868 [54,55], BAY1213790 [56], and AB023 [57], and the small molecules EP-7041 [58] and BMS-986177 [59] have finished various levels of clinical trials (Phase I and, in some cases, Phase II) with very promising results as anticoagulants with no bleeding complications. Corresponding sections below will provide details about patents and reported results relevant to small molecules and monoclonal antibodies. Patent and reported results relevant to the antisense oligonucleotide ISIS 416858 were recently reviewed [5].

2. FXI(a) inhibitors

Given the promise of FXI(a) as a drug target for effective and safe anticoagulants, several small molecule active site inhibitors [58,59], glycosaminoglycan mimetic allosteric inhibitors [17,60,61], monoclonal antibodies [54–56], antisense oligonucleotides [52,53], aptamers, and polypeptides have been developed, and many were recently reviewed [5,6]. Furthermore, patents claiming FXI(a) inhibitors until early 2016 were also recently reviewed [5]. In this review, we describe the patents claiming molecular entities that target FXI(a) system starting 2016 to the date of this review publication. Given its promise, a survey of

patents literature indicates that the number of published patents claiming molecular agents targeting FXI(a) system exceeds those reported to target any other coagulation factor including FIIa (thrombin), FXa, FIXa, FVIIa, or FXIIa (Figure 3(a)). Figure 3(b) shows the categories of agents targeting FXI(a) as well as the corresponding number of the patents that have been filed/approved since 2016. Parallel to the number of FXI(a)-related patents filed over the 2016–2019 period is the number of peer-reviewed publications pertaining to the same system (Figure 3(c)).

2.1. Small molecules

Several small molecules have been claimed by various pharmaceutical companies as selective, active site inhibitors of human FXIa or dual inhibitors of FXIa and plasma kallikrein. We chose to present the inhibitors according to their central structural domain which can be pyridine-*N*-oxide, oxypyridine, substituted phenylalanine, or β -lactam. Although macrocyclic FXIa inhibitors may include one of the above central domains, yet they are presented separately.

2.1.1. Pyridine N-oxide-containing inhibitors and their derivatives—In 2016, pyridine-*N*-oxide-containing molecules were claimed by Merck Co. to be FXIa inhibitors or dual inhibitors of FXIa and plasma kallikrein, and therefore, to be used singularly or in combination with other current anticoagulants to treat thromboses, embolisms, hypercoagulability, or fibrotic changes [62]. In the claimed inhibitors, the pyridine-*N*-oxide moiety is di-substituted at positions- 2 and –5 with the most frequent position-2 substituent is methine imidazole whereas position-5 is frequently substituted with chlorophenyl tetrazole moiety. Several derivatives were tested as racemic mixtures or pure enantiomers considering the stereochemistry of the methine carbon which was commonly substituted with benzyl or cyclopropyl methyl moiety. Example of molecules from this claim is inhibitor **1** (Figure 4) which inhibited FXIa and plasma kallikrein with IC_{50} values of 1.34 and 1.52 nM, respectively [62]. Potential binding mode is expected to be the active site where the chlorophenyl tetrazole group fits into the S1 subsite and the terminal methyl carbamate fits into the S2' subsite. In a similar claim by the same group, it was found that the replacement of the central imidazole moiety with a benzene ring, that is further substituted at position-3 with benzoic acid (carboxylic group is at position-3) as in inhibitor **2** (Figure 4), led to better inhibition potency to FXIa (IC_{50} = 0.46 nM) and better selectivity over plasma kallikrein (IC_{50} = 77.71 nM) [63]. Closer look at the structure-activity relationship of the above molecules indicated that using the (*S*)-stereochemistry may improve FXIa inhibition potency while changing the position of the carboxylic group of inhibitor **2** may decrease the potency [63].

In related patents, it was found that replacing the methyl (4-(5-chloro-1*H*-imidazol-4-yl)phenyl)carbamate moiety in inhibitor **1** with 1*H*-benzo[d]imidazole-5-carboxylic acid (inhibitor **3**) maintained high potency toward FXIa and good selectivity over plasma kallikrein [64]. Furthermore, it appears that the inhibition potency and selectivity were also retained following the bioisosteric replacement of the carboxylic acid group with fluorine atom as shown by inhibitor **4** [64]. The methyl (4-(5-chloro-1*H*-imidazol-4-yl)phenyl)carbamate moiety in inhibitor **1** can also be replaced with 3-amino-1*H*-indazole-6-

carboxamide as in inhibitor **5** which inhibited FXIa and plasma kallikrein with IC_{50} values of 0.9 and 25 nM, respectively [65]. The pyridine-*N*-oxide can also be rigidified in the form of cyclopenta[b]pyridine-*N*-oxide (inhibitor **6**) [66] or in the form of 5,6,7,8-tetrahydroquinoline-*N*-oxide (inhibitor **7**) [67], both of which possessed nanomolar inhibition potency toward FXIa and potentially significant selectivity over plasma kallikrein.

Other modifications were also introduced as demonstrated by inhibitor **8** (Figure 4). This molecule inhibited FXIa and plasma kallikrein with IC_{50} values of 2.1 and 79 nM, respectively, and demonstrated APTTEC1.5x of 1.16 μ M. Importantly, its (*R*)-enantiomer inhibited human FXIa only 47% at about 1000 μ M. The molecule exhibited drug clearance of 5 ml/min/kg, mean residence time of 2.5 hrs, and bioavailability of 56%. In fact, inhibitor **8** indicated that the S1-binding group can be chloro-4-(difluoromethoxy)-2-fluoro-benzene moiety rather than the frequently recruited chlorophenyl tetrazole moiety whereas S1'-binding group can be cyclopropyl methyl rather than benzyl [68].

2.1.2. Oxopyridine-containing inhibitors and their derivatives—A series of patents by Bayer Pharma described 2-oxopyridine-containing molecules as inhibitors of human FXIa and plasma kallikrein. The inhibitors were claimed for treating and/or preventing thrombotic or thromboembolic diseases, edemas, and ophthalmological diseases [69–76]. Figure 5 provides examples from seven patents showing the chemical structures of 8 inhibitors with demonstrated inhibition potency toward FXIa and plasma kallikrein in the nanomolar range. Structural analysis revealed that the 2-oxopyridine moiety is always substituted at positions-1, -4, and -5. The most frequent substituent at position-5 is methoxy whereas the most frequent substituent at position-4, which likely binds into S1 subsite in the active site of FXIa, is 5-chloro-benzonitrile-2-yl. Position-1 is connected to the rest of the inhibitor's chemical structure and bears two structural domains, one domain is frequently acyclic aliphatic and potentially binds to the S1' subsite (inhibitors **9–11** and **14–16**) and the second is frequently carboxylated aromatic and potentially binds to the S2' subsite (inhibitors **9, 11, 15, and 16**).

Likewise, 2-oxopyridine-containing molecules **17** and **18** (Figure 6) were claimed by Chinese companies (Jiangsu Hengrui Medicine Co. and Shanghai Hengrui Pharmaceutical Co.). The two molecules inhibited FXIa with IC_{50} value of 34 nM [77] and 6.4 nM [78], respectively. Inhibitor **18** was also claimed as cyclo-butyl prodrug in another patent [79]. Inhibitor **19** was also claimed by the same Chinese companies. It inhibited FXIa with IC_{50} value of 92 nM [80]. Lastly, similar molecules that are oxo-pyrimidine derivatives were claimed by Bristol-Myers Squibb Co. as novel substituted glycine derivatives, and inhibitors of FXIa and/or plasma kallikrein for the prophylaxis or treatment of thromboembolic disorders, or for the treatment of retinal vascular permeability associated with diabetic macular edema and diabetic retinopathy [81]. Example of Bristol molecules is represented by molecule **20** (Figure 6), a pyrimidine-2-one derivative which inhibited FXIa and plasmin kallikrein with IC_{50} values of 2.5 and 189 nM, respectively, and affected the APTT at a concentration of 1.74 μ M [81].

2.1.3. Macrocyclic derivatives—Cyclization of peptide-based molecules is widely used strategy in the design of enzyme inhibitors. Potential gains are improved drug-like

properties, particularly target affinity, metabolic stability, and oral bioavailability [82,83]. Following this concept, Bristol-Myers Squibb has filed several patents claiming macrocyclic FXIa inhibitors starting 2016 [84–90]. The macrocyclic molecules were claimed as inhibitors of FXIa and/or plasma kallikrein for the prophylaxis or treatment of thromboembolic disorders or for the treatment of retinal vascular permeability associated with diabetic macular edema and/or diabetic retinopathy. An example of these molecules is represented by the tri-amide macrocyclic inhibitor **21** (Figure 7) which was reported to inhibit FXIa in vitro with IC_{50} value of 17.89 nM. In this inhibitor, the *p*-chlorophenyl tetrazole moiety appears to bind to the S1 subsite in the active site of FXIa. Subsequently, inhibitor **22** (Figure 7) was claimed by the same company [84]. Rewarding modifications represented by introducing the pyrimidinone moiety to the P1 domain and by incorporating two heteroaromatic systems i.e. pyridine and *N*-substituted pyrazole into the macrocyclic domain led to FXIa IC_{50} value of 0.1 nM [85]. The molecule also inhibited plasma kallikrein with IC_{50} of 28 nM and increased the APTT in citrated normal human plasma by 1.5-fold at a concentration level of 0.5 μ M. The solubility of its crystal form was claimed to be 6 μ g/mL at pH = 6.5 and its free fraction of human plasma protein binding was about 9%. Likewise, inhibitor **23** inhibited FXIa and plasma kallikrein with K_i values of 2 and 179 nM, respectively [86]. Other examples include inhibitors **24** [87] and **25** [88], as well as the macrocyclic spiro-carbamate inhibitor **26** [89] (Figure 7).

Similarly, Merck Sharp & Dohme Corp. has filed for multiple patents claiming the FXIa inhibitory activity of large number of macrocyclic derivatives (Figure 8). Specifically, inhibitors **27** [91] and **28** [92] were reported to inhibit both FXIa and plasma kallikrein. Other macrocyclic FXIa inhibitors were also claimed by Chinese companies. Inhibitor **29** [93] and inhibitor **30** [94] (Figure 9) were claimed by Sunshine Lake Pharma Co. and Sichuan Kelun-Biotech Biopharmaceutical Co., respectively. The former inhibited FXIa with IC_{50} value of 44.7 nM, whereas the latter inhibited FXIa with IC_{50} value of 0.59 nM.

2.1.4. 4 -substituted phenylalanine derivatives—Several patent applications were filed by Bayer Pharma since 2016 in which substituted phenylalanine derivatives were claimed as FXIa inhibitors for the treatment and/or prophylaxis of fibrinolytic and thromboembolic diseases, in particular blood loss in the cases of hyperfibrinolytic states, organ transplants, or heart surgery interventions, or as a constituent of a fibrin adhesive [95–97]. The inhibitors **31–33** (Figure 10) have tripeptide-like structures in which the *N*-terminal residue is tranexamic acid which likely fits into S1 pocket of FXIa, the central residue is *p*-substituted phenylalanine which likely fits into S2 or S1' pockets, and the *C*-terminal residue is variable and seems to bind to S2' pocket. In one hand, inhibitors **31** and **32** have the *C*-terminal residue of 5-phenyl-triazole that is substituted with tetra-fluorinated propionic acid at position-2. The two inhibitors exhibited IC_{50} values in the nanomolar range of 0.5 and 0.34 nM, respectively. Furthermore, inhibitor **32** was also reported to inhibit plasmin with IC_{50} value of 0.87 nM, to inhibit plasma kallikrein with IC_{50} value of 7.2 nM, and to prolong the APTT at 0.06 μ M. The patents list other experiments establishing the inhibitors' selectivity, effects on clot lysis, and their *in vivo* activity.

Inhibitor **33** (Figure 10) is structurally different as the *para*-substituent of the phenylalanine moiety is 4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the C-terminal is chlorinated benzamide. Inhibitor **33** was found to inhibit FXIa, plasmin, and plasma kallikrein with IC_{50} values of 21.5, 1.0, and 8.5 nM, respectively. The inhibitor prolonged the APTT at 0.7 μ M. The patent lists other experiments establishing its selectivity, effect on clot lysis, and *in vivo* activity.

It is important to mention here that the patents [95–97] that claim 4-substituted phenylalanine derivatives as FXIa inhibitors provide the inhibitory activity for the (*S*)-enantiomer since the synthesis was started from L-phenylalanine. Generally speaking, the potency of the pure (*S*)-enantiomers appears to be superior to that of the racemic inhibitors or even those with pure (*R*)-stereochemistry.

2.1.5. β -lactam derivatives—Prior to 2016, multiple β -lactam-containing inhibitors (azetidine derivatives) were patented by Bristol Myers Squibb, Exithera Pharmaceuticals, and Daiamed [5,6]. In 2018 and 2019, more β -lactam-containing molecules were claimed by Exithera Pharmaceuticals to inhibit FXIa or plasma kallikrein for preventing or treating thrombosis or angioedema. Example of these molecules are represented by inhibitors **34** and **35** (Figure 11) [98,99]. Particularly, inhibitor **34** inhibited human FXIa with IC_{50} value of 10–100 nM and selectivity index of at least 100-fold over FXa, thrombin, and trypsin. The inhibitor's solubility was reported to be 10–100 μ M in PBS with significant Caco-2 permeability and plasma protein binding of >95% [98]. Mechanistically, some of β -lactam molecules may act as covalent inhibitors of FXIa as a result of the interaction between Ser195 of FXIa and the β -lactam moiety of the inhibitors, as reported previously [5,6]. Moreover, their guanidine group (or 2-aminopyridine group as in inhibitors **34** and **35**) may bind into the S1 pocket of FXIa.

Importantly, EP-7041 (Exithera Pharmaceuticals) [100], a potentially β -lactam-based, parenterally acting FXIa inhibitor was recently tested in Phase I trial [58]. Although reports describing its structure and mechanism have not been published, yet EP-7041 appears to be active site inhibitor of FXIa. This inhibitor may structurally look similar to those listed in Figure 11. It may potentially have a carboxylic group at position-2 of the β -lactam ring and 2-aminopyridin-4-yl-methyl moiety at position-3. In Phase I trial, healthy individuals received IV injections of single ascending doses of EP-7041 (0.01 mg/kg up to 1.0 mg/kg) or continuous IV infusions for 5 days (0.01 mg/kg/h up to 0.6 mg/kg/h). The investigators indicated that there were no serious adverse events. Mild events of infusion site bruising and headache were reported in 7% and 23% of subjects, respectively. EP-7041 exhibited dose-proportional pharmacokinetics with rapid onset, fast off-set, and predictable dose-dependent increases of APTT with no effect on PT. The study concluded that selective inhibition of FXIa with EP-7041 promotes anticoagulant and profibrinolytic effect with minimal risk of bleeding.

2.1.6. Miscellaneous—Lastly, other chemotypes of FXIa inhibitors were reported by Chinese pharmaceutical companies. This includes pyrrolidine-amide derivative **36** [101] and 3-(4-fluorophenyl)-ethyl propanoate derivative **37** [102] (Figure 12), both of which demonstrated nanomolar potency of FXIa inhibition.

2.2. Macromolecules

2.2.1. FXI(a) monoclonal antibodies—Several companies and academic institutions reported on the preparation and/or the use of monoclonal antibodies to target FXI(a) system for the treatment and/or the prevention of thrombosis. This includes Novartis AG (2016 and 2018) [103–105], Bayer Pharma (2018) [106,107], the regents of the University of California (2017) [108], Prothix BV (2017) [109], Merck Sharp & Dohme Corp (2017) [110], and a couple of patents by Shanghai Benemae Pharmaceutical Corp [111,112]. Specific monoclonal antibodies that have been pharmacologically exploited to target FXI(a) and have shown promising results in clinical trials include MAA868 (Novartis) [54,55], BAY1213790 (Bayer) [56], and AB023 (Aronora) [57,113].

Considering MAA868, the phage display technology was initially exploited to generate a fully humanized antibody NOV1090 which, upon expression as Fab, showed a high binding affinity to the zymogen FXI with a K_D value of 163 ± 24 pM and to the protease FXIa with a K_D value of 244 ± 96 pM. NOV1090 Fab inhibited FXIa with an IC_{50} value of 2.8 nM, yet it did not affect other human serine proteases including thrombin, FVIIa, FIXa, FXa, FXIIa, and plasma kallikrein. MAA868 was subsequently produced by transforming NOV1090 Fab into a full-length human immunoglobulin G1 and by making its primary structure sequence similar to a human germline sequence. Mechanistically, MAA868 traps FXI(a) in an inactive, zymogen-like conformation. Binding affinity studies indicated that MAA868 binds to the catalytic domains of human FXI with a K_D value of 1.3 ± 0.3 pM and human FXIa with a K_D value of 4.7 ± 2.1 pM as well as to cynomolgus monkey FXI with K_D values of 4–6 pM and cynomolgus monkey FXIa with K_D values of 6–9 pM [54,55].

In APTT assay, MAA868 prolonged the clotting time of human plasma in a dose-dependent fashion ($APTT_{EC2x} = 0.015$ μ M). In thrombin generation assay, MAA868 decreased the amount of thrombin in human plasma in a concentration-dependent fashion with an IC_{50} value of 0.024 μ M. MAA868 had no effect on the PT clotting time up to 1.3 μ M. In a model of FXI knockout mice reconstituted with human FXI, the administration of 0.6 mg/kg MAA868 significantly decreased the formation of FeCl₃-induced occlusive carotid artery thrombi. In a dose-escalation pharmacodynamic study in cynomolgus monkeys, both IV and SC administration of 3 mg/kg MAA868 led to a significant increase in APTT and ~90% decrease in free FXI levels with no bleeding or other adverse events up to 13 weeks including at the highest tested dose of 100 mg/kg/week [54,55].

In a Phase I, randomized, blinded, placebo-controlled trial (funded by Novartis), the safety, the pharmacokinetics, and the pharmacodynamics of MAA868 were examined in 61 healthy adult subjects by administering single ascending doses (5 mg up to 240 mg; SC). Vital signs, physical examination, blood biochemistry, hematology, and ECG were normal in placebo and MAA868 groups. No incidents of injection site reactions or hypersensitivity reactions were reported in those treated with MAA868. There were 9 adverse events considered to be potentially related to MAA868. Yet, the adverse events were of mild intensity with headache being the most common [54,55].

Considering the pharmacokinetic results, MAA868 exposures were dose-proportional with low-to-moderate intersubject variability. The median time-to-peak plasma concentrations

was in the range of 7–21 days. Levels effective to prolong APTT by >2-fold were achieved by 24 hours. The terminal elimination half-life was from 20.1 to 28.6 days. With respect to the pharmacodynamic aspects, dose- and time-dependent prolongation of APTT and reduction in free FXI levels and FXI coagulation activity were observed. In fact, a statistically significant prolongation of APTT started with the 50 mg dose but was maintained >2-fold only at higher doses of 150 mg dose (up to Day 29) and of 240 mg dose (up to Day 57). Exposure-response modeling indicated that maximal APTT prolongations of ~2.5 fold were observed at plasma levels of >30 nM of MAA868. The maximal inhibition was achieved on Day 2 with a mean FXI coagulation activity of 3% of baseline in the 150 mg dose cohort and 240 mg dose cohort. Importantly, no changes were observed in PT or thrombin time (TT). Lastly, exposure to MAA868 and duration of FXI inhibition were moderately lower in obese individuals. This could be because of the relatively large volume of distribution of MAA868 and/or its marginally rapid clearance. Novoseven, a commercially available recombinant FVII, was found to be effective in reversing MAA868 anticoagulation effects [54,55].

The second monoclonal antibody of interest is BAY1213790. The phage display technology was exploited to produce a fully human immunoglobulin G1 monoclonal antibody which was named as BAY1213790 [56]. Mechanistic analysis indicated that BAY1213790 is allosteric inhibitor of FXIa. The antibody binds to a specific region in the catalytic domain of FXIa that is adjacent to the enzyme active site. The antibody's binding event appears to cause a substantial disruption in the active site leading to enzyme inhibition. In animal studies, BAY1213790 reduced thrombosis in a mouse carotid artery FeCl₃-induced thrombosis model and did not increase bleeding times in rabbit liver-incision model [114].

Given the initial *in vitro* activity of BAY1213790, its safety, pharmacokinetics, and pharmacodynamics were evaluated in a Phase 1, single-center, randomized, single-blind, parallel-group, placebo-controlled, dose-escalation trial (funded by Bayer) in 83 healthy Caucasian men [56]. Nine doses were used in the range of 0.015–10 mg/kg and the follow-up visits continued to Day 150 following administration.

The study revealed that single IV doses of BAY1213790 were well tolerated with 54 of 81 volunteers in the antibody group reported at least one treatment-emergent adverse event. The most frequently observed events were headache (18.5%) and nasopharyngitis (17.3%), yet no relationship was indicated between the antibody dose and causality or intensity of adverse events. All adverse events were of mild to moderate intensity. Likewise, no signs of potential hypersensitivity reactions, bleeding, or thrombocytopenia were detected during the course of the study. There were no treatment-related severe adverse events or deaths in any group. Vital signs, laboratory tests, ECG, and physical examinations were normal. Dose-dependent increases in APTT were significantly observed following all doses except the lowest dose of 0.015 mg/kg. Following the administration of the highest dose of 10 mg/kg, the maximal mean increases in APTT in relative to the baseline were 1.85–2.17-fold. For doses of 0.6 mg/kg or higher, APTT was elevated above the baseline for at least 20 days. Minimal interindividual variability was also observed for all doses [56]. Furthermore, a significant dose-dependent reduction in apparent FXI activity was recorded for doses of 0.15 mg/kg or higher. FXI activity was maximally inhibited directly after the drug administration

and slowly returned to near baseline values in about 55 days, with a moderate level of interindividual variability. Interestingly, bleeding times did not increase and were similar across all study doses during the first 6 days. Moreover, ROTEM whole blood clotting time remained elevated in a dose-dependent fashion for at least 144 hours after all study doses. No significant increase in thrombosis biomarkers was observed throughout the study [56].

Considering BAY1213790 pharmacokinetics, there was a dose-dependent increase in measurable exposure to the antibody for all doses of 0.06 mg/kg or higher. The median time to maximum concentration of the antibody was between 1.05 hrs and 4 hrs, and the mean elimination half-life was ~30–44 days. The mean clearance and mean steady state volume of distribution were in the range of 0.13–0.29 L/day and 4–11 L, respectively [56].

The third monoclonal antibody of interest is AB023 (Xisomab 3G3) [57,113]. The antibody AB023 was produced by complementarity determining region-grafting technology from the monoclonal mouse anti-human FXI antibody 14E11. In previous studies, 14E11 was shown to significantly prolong carotid artery patency in mouse carotid artery FeCl₃-induced thrombosis model as well as to significantly prolong the time to breathing cessation in a model of thromboplastin-induced pulmonary embolism. Prolongation of APTT was not accompanied with an increase in bleeding in those models [115].

AB023 is a humanized, immunoglobulin G2b monoclonal antibody which mechanistically binds to the A2 apple domain of FXI with a K_D value of 3.66 nM. This binding event inhibits FXIIa-mediated activation of FXI. Likewise, AB023 binds the A2 apple domain of FXIa with a K_D value of 1.38 nM which eventually blocks interactions between FXIa and high molecular weight kininogen [113]. Interestingly, the antibody does not appear to affect the active site of FXIa or thrombin-mediated activation of FXI. AB023 prolonged the APTT of plasma from normal rats, baboons, cynomolgus monkeys, and humans in a concentration-dependent fashion. In a baboon acute vascular graft thrombosis model, a single IV pre-treatment with 1.0 mg/kg of AB023 reduced total platelet accumulation and total fibrin deposition within the collagen-coated vascular grafts and in the region that is 10 cm downstream of the graft. APTT was prolonged following the antibody treatment at 30 and 60 minutes after injection and continued to be elevated beyond 24-hour post-treatment without any effect on PT [57].

Motivated by the *in vivo* pre-clinical results, the safety, the pharmacokinetics, and the pharmacodynamics of AB023 were evaluated in a Phase 1, randomized, double-blind, placebo-controlled, single ascending bolus dose study at a single site (funded in part by US National Heart Lung and Blood Institute) in 21 subjects. Doses used were 0.1, 0.5, 2.0, and 5.0 mg/kg. AB023 was found to be safe and well-tolerated in the healthy volunteers with no effect on mean bleeding time or PT. There were no serious adverse events with a total of 20 treatment-emergent adverse events. The most common treatment-emergent adverse event was a productive cough which was considered by the investigators as unrelated or unlikely treatment-related event [57].

In the pharmacokinetic studies, plasma exposure was found to increase with increasing the AB023 doses. Median values of time to maximum concentrations were in the range of 0.08–

0.65 hrs. Mean elimination half-life values appeared to increase with increasing AB023 doses and ranged from ~1.3 hrs following the 0.1 mg/kg dose to ~121.5 hrs following the 5.0 mg/kg dose. The mean plasma clearance appeared to decrease with increasing AB023 doses and was in the range of 0.094–0.014 L/hrs. Steady state volume of distribution appeared to increase with increasing the antibody dose and was in the range of 2.5–4.3 L. The maximum APTT prolongation was achieved at doses of 0.5 mg/kg. Mean APTT values were highest or close to at 0.25–24 hrs post-administration at all concentrations tested. The APTT values returned to baseline by 24 hrs, 336 hrs, or 672 hrs for most or all subjects at dose levels of 0.1 mg/kg, 0.5 mg/kg, or 2.0–5.0 mg/kg, respectively [57].

Lastly, University of California and Pfizer Inc. developed a series of human immunoglobulin Gs that inhibited FXIa by targeting its active site and did not affect its zymogen or other coagulation proteases [108,116]. The immunoglobulins were produced via phage display technology with the most potent being C24 and DEF. In FXIa fluorogenic substrate hydrolysis assay, C24 inhibited human, cynomolgus macaque, and rabbit FXIa with IC_{50} values of 0.22–0.26 nM [108,116]. The K_D binding value to human FXIa was 0.0152 nM (C24 Fab). Furthermore, C24 did not bind to thrombin, FVIIa, FIXa, FXa, FXIIa, or plasma kallikrein, at concentrations 100-fold larger than those required to saturate FXIa in an ELISA-based assay. Likewise, C24 showed at least 80-fold inhibitory selectivity to small-substrate cleavage by FXIa over thrombin, FVIIa, FXa, FXIIa, plasma kallikrein, or activated protein C. C24 did not inhibit the proteolytic activation of FX by FIXa [108,116]. In human plasma, C24 inhibited the FXIIa-mediated peak thrombin generation with an IC_{50} value of 34 nM. In an intrinsic pathway-triggered clotting assay in human plasma and whole human blood, C24 led to half-maximal prolongations of clotting times at concentrations of ~69 nM and 21 nM, respectively. Using IV doses of 2–35 mg/kg, C24 inhibited FeCl₃-induced arterial thrombosis in FXI-humanized mouse [108,116].

To improve C24's drug-like properties, DEF monoclonal antibody was generated with similar activity, selectivity, and mechanism of action. In FXIa fluorogenic substrate hydrolysis assay, DEF inhibited human, cynomolgus macaque, and rabbit FXIa with IC_{50} values of 0.22–0.24 nM [108,116]. The K_D binding value to human FXIa was 0.0339 nM (DEF Fab). DEF (0.1 and 1.0 mg/kg; IV) decreased venous thrombus formation in a rabbit model in a dose-dependent fashion. The effect correlated with APTT prolongation. DEF did not affect the extrinsic pathway or the common pathway functions as indicated by the lack of effect on PT at a dose as high as 10 mg/kg. Furthermore, treatment with DEF did not increase cuticle bleeding in rabbits (10 mg/kg; IV) or spontaneous bleeding in cynomolgus macaques (20, 75, and 266.5 mg/kg; IV), whereas APTT was maximally or near maximally prolonged and PT was unaffected. Interestingly, the DEF activity *ex vivo* in human plasma and *in vivo* in rabbits was rapidly reversed using a human immunoglobulin labeled as revC4 which exhibited an apparent K_D value of 3 nM to DEF Fab [108,116].

2.2.2. DNA & RNA aptamers—Aptamers are single-stranded oligonucleotides. They are typically isolated from combinatorial libraries of nucleic acids using an *in vitro* selection process known as systematic evolution of ligands by exponential enrichment (SELEX) [117]. Generally speaking, aptamers can recognize a target protein or nucleic acid with high affinity and specificity which makes them very useful therapeutic, diagnostic, or research

tools. Aptamers that target different coagulation factors have been developed including those targeting FIX(a), FXI(a), and FXII(a) [118–125].

Specifically, FXIa-targeting aptamers were claimed in the year of 2017 to be used in the prevention, treatment, or alleviation of the symptoms of thrombosis. The aptamers were also claimed to be used for the detection or purification of FXIa [123]. The patent provided information on the structural aspects of the aptamers and provided information regarding the aptamers' anticoagulant activities. Briefly, the patent claimed aptamers with general formula of 5'-5W-C-3W-3' in which the 5' wing nucleotide sequence was 5'-GAATTCTAATACGACTCACTATA whereas the 3' wing nucleotide sequence was GCGTCCAACACATCG-3'. The core C represented the hypervariable central sequence [123].

In peer-reviewed reported results, a library of single-stranded DNA aptamers was screened for FXIa-binding using multiple cycles of negative and positive selection. Ultimately, 6 sequences out of 89 sequences were identified to inhibit the chromogenic substrate S2366 cleavage by FXIa (Figure 13). The most active aptamer was identified as Factor ELeven Inhibitory APtamer (FELIAP) which possessed a hypervariable central sequence of 5'-AACCTATCGGACTATTGTTAGTGATTTTATAGTGT-3' [124]. Kinetic studies indicated that FELIAP is a competitive inhibitor of FXIa-mediated hydrolysis of S-2366 with an estimated K_i value of 29 μ M. Not only that, but 10 μ M FELIAP also inhibited the FXIa-mediated activation of FIX to FIXa as well as the heparin-mediated interaction between FXIa and antithrombin. A K_D value of 1.8 ± 0.1 nM was measured for FELIAP using surface plasmin resonance. Furthermore, 30 μ M FELIAP prolonged the lag time of thrombin generation in recalcified diluted plasma. Likewise, FELIAP significantly reduced the endogenous thrombin potential by 3.2-fold as well as significantly increased the mean time to peak thrombin by 1.5-fold. These effects were eliminated when FXI-depleted plasma was exploited. Accordingly, FELIAP was put forward as a lead to develop DNA-based aptamers that target FXI(a) for clinical use [124].

Along these lines, two RNA aptamers, identified as 12.7 and 11.16, were reported to inhibit FXIa with the former binding to both the protease FXIa and the zymogen FXI and the latter binding only to the protease FXIa [125]. Besides, the two aptamers did not bind to a panel of coagulation factors. In the S-2366 chromogenic substrate hydrolysis assay, the two aptamers were shown to be noncompetitive inhibitors targeting the anion-binding sites on the catalytic domain, the A3 domain, and/or the autolysis loop. The K_i values for the aptamers were 60 ± 20 and 63 ± 22 nM, respectively. The two aptamers also significantly delayed FXIa-mediated activation of FIX. Aptamer 12.7 increased the APTT from 28.4 ± 6.3 sec to 56.3 ± 14.6 sec, whereas aptamer 11.16 increased the APTT to only 36.4 ± 5.3 seconds. Accordingly, the two aptamers were proposed to serve as leads to further develop RNA-based aptamers that target FXI(a) for clinical use [125].

2.2.3. Polypeptides—Prior to 2016, few polypeptides were reported to influence FXIa activity. The most recognized ones were fasxiator, desmolaris, AcaNAP10, and Ir-CPI [5,6,126,127]. In 2018, a polypeptide named Sj13 from *Schistosoma Japonicum*, a parasite causing schistosomiasis, and its mutants were reported to exert anticoagulant activity by

inhibiting FXIa [128]. The amino acid sequence of Sj13 polypeptide was identified. The recombinant Sj13 polypeptide and its mutants were also obtained by genetic engineering technology. The *in vitro* anticoagulant activity of the polypeptide and its mutant was established in APTT, PT, and TT tests. Their anticoagulant activities were attributed to inhibiting FXIa as well as FXa. They also inhibited the antifibrinolytic plasmin. In the mice model of FeCl₃-induced carotid artery thrombosis, it was shown that Sj13, at doses of 1.0 mg/kg and 0.5 mg/kg, led to reductions in clot weights comparable to those achieved by heparin. The polypeptide was reported to be associated with low bleeding risk [128].

3. Conclusion

In the above discussion, we provided an overview of the most recent patents by industrial as well as academic institutions in which molecular entities that target FXIa or its zymogen FXI have been claimed to promote anticoagulant activity with minimal bleeding complications. In combination with our previous surveys of patent and peer-reviewed literatures [5,6], this patent update reveals that the agents that have been claimed and/or confirmed to inhibit FXI(a) are structurally and mechanistically diverse. These agents include small molecule inhibitors [5,6,17,60], monoclonal antibodies [54–57,113], antisense oligonucleotides [52,53], aptamers [119–121], and polypeptides [126,127]. Some of these agents target the protease FXIa whereas others target both the protease FXIa and its zymogen FXI. Some of these agents are competitive inhibitors and others are noncompetitive inhibitors. In addition, they are also diverse with respect to their pharmacokinetic aspects including the route of administration (oral vs parenteral), the onset of action (fast vs delayed), the duration of action (short vs extended), and the clearance (hepatic and/or renal dependent vs hepatic and/or renal independent). As a result, we expect the structural and the mechanistic diversity of molecular entities targeting FXI(a) system to increase the likelihood of one or more of these agents to entering the clinic.

4. Expert opinion

The anticoagulation therapy has significantly improved over the last decade. This can partially be attributed to the approval of the novel direct oral anticoagulants, particularly FXa inhibitors [129]. Furthermore, the approval of new reversal agents including idarucizumab for dabigatran [130] and andexanet alfa for FXa inhibitors [131] has permitted a better management of the anticoagulant-induced bleeding complications. Yet, none of the currently available anticoagulants fulfill the pursuit of an ‘ideal’ anticoagulant. In fact, all current anticoagulants continue to be associated with an elevated and variable risk of bleeding, which could become very serious in patients with moderate-to-severe renal dysfunction, atrial fibrillation [7–12], or those who are at the extremes of body weights [132–134], among others. From the standpoint of clinical practice, even minor bleeds may become problem because patients tend to stop their treatments; not only their anticoagulant treatment, but other life-saving therapies as well. Moreover, the clearance of most of the clinically used anticoagulants is dependent on hepatic and/or renal function which perhaps demands dose adjustment in patients with compromised hepatic and/or renal function [135,136]. Therefore, the search continues for an ideal anticoagulant that is (1) not associated with a risk of bleeding or severe toxicity in general; (2) safe in compromised

patient populations such as those with chronic kidney failure, hepatic dysfunction, atrial fibrillation, or extreme body weights; (3) available in inexpensive oral and/or parenteral dosage forms; (4) exhibiting predictable pharmacokinetics; and (5) rapidly reversed by effective and inexpensive reversal agents [5].

Mechanistically, all anticoagulants in use today directly or indirectly inhibit thrombin and/or FXa, two serine proteases in the common coagulation pathway. This mechanistic aspect is the reason for their efficacy, but it is also the reason for the bleeding complications. Therefore, a rationale strategy to address the problem of bleeding has been to consider other proteins in the coagulation process. Nevertheless, with the advancement in our understanding of hemostasis and thrombosis as well as that of complications associated with the genetic deficiencies of clotting factors in humans, a compelling rationale for targeting FXI(a) to treat and/or prevent thromboembolism without inducing hemorrhagic complications has emerged and has been further advanced by many pre-clinical and clinical studies [5,6].

Although the number of patents claiming agents to inhibit/target FXI(a) has declined since the year of 2016 (Figure 1(b)), yet the number of agents advanced into clinical trials have significantly increased (Table 1). In Phase I trials, the tested agents (ISIS 416858, MAA868, BAY1213790, AB023, and EP-7041) demonstrated no serious adverse effects and prolonged APTT with no effect on PT. Furthermore, in a Phase II trial, the antisense oligonucleotide ISIS 416858 lowered FXI levels in patients undergoing elective unilateral total knee arthroplasty to a level that was sufficient to prevent postoperative venous thromboembolism without inducing bleeding complications [52,53]. Moreover, BMS-986177 (JNJ-70033093) completed multiple Phase I trials in healthy subjects, subjects with hepatic dysfunction, subjects with renal impairment, subjects with renal impairment on hemodialysis, subjects using aspirin, and subjects having potentially interacting medications. Thus far, the results of pre-clinical and clinical studies indicate that targeting FXI(a) of the intrinsic coagulation pathway is a powerful strategy toward achieving anticoagulation that is effective and significantly safer considering the bleeding complications.

Further development for the above agents is undergoing. A Phase I trial is recruiting to examine the tolerability and safety of BAY1213790 in subjects with end-stage renal disease on hemodialysis ([NCT03787368](#)). A Phase II FOXTROT trial, to compare BAY1213790 to current therapies (enoxaparin or apixaban) for the prevention of blood clotting and safety in patients undergoing total knee arthroplasty, was completed ([NCT03276143](#)). A Phase II trial of the orally bioavailable BMS-986177 in combination with clopidogrel or aspirin is currently enrolling ([NCT03766581](#)) to determine the efficacy and the safety of the combination therapy in relative to the standard therapy in secondary ischemic stroke prevention. A study of BMS-986177 versus subcutaneous enoxaparin in participants undergoing elective total knee replacement surgery (AXIOMATIC-TKR) is also currently recruiting ([NCT03891524](#)). Furthermore, a subcutaneously administered ISIS 416858 is in a Phase II trial to examine its safety, pharmacokinetics, and pharmacodynamics in patients with end-stage renal disease on chronic hemodialysis ([NCT03358030](#)). Likewise, AB023 (xisomab 3G3) is under consideration for a Phase II trial in patients with end stage renal disease on chronic hemodialysis to evaluate its safety and efficacy for reducing dialysis

circuit thrombosis ([NCT03612856](#)). A two-part study to assess the tolerability, safety, pharmacokinetics, and pharmacodynamics of ONO-7684 [137,138] (ONO-5450598; oral FXIa inhibitor that is being developed by Ono Pharmaceutical Co., Japan) in healthy adult volunteers is recruiting ([NCT03919890](#)).

Although further development is warranted, reaching one or more of the above FXI(a) targeting agents to the clinic will fundamentally transform the anticoagulation therapy. Potential indications for FXI(a) inhibitors include (a) prophylaxis against stroke in atrial fibrillation patients who are at a high bleeding risk; (b) cardiovascular events prevention in patients with chronic kidney disease or those undergoing hemodialysis; (c) thrombosis prophylaxis in patients with venous thromboembolism who are at increased risk of recurrent thrombosis following anticoagulant therapy cessation; (d) clotting prophylaxis in extracorporeal membrane oxygenation circuits; (e) prevention of cardiac devices-triggered thromboembolic events; and (f) prevention of stent thrombosis in acute coronary syndrome patients who require anticoagulant therapy besides the antiplatelet therapy [5,6]. Overall, the new anticoagulant therapy is expected to benefit thrombotic patients for who current therapy is limited in safety and/or efficacy.

Funding

This work was supported by NIGMS under award number [SC3GM131986] and by IDeA program from NIGMS under grant number [P20GM103424]. The content is solely the responsibility of the author and does not necessarily represent the official views of NIH.

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Article highlights

- Factor XIa is a homodimeric coagulation serine protease which continues to be an attractive drug target for effective and relatively safer anticoagulants.
- Small molecules and monoclonal antibodies dominate the drug development arena for factor XI(a) inhibition.
- The past 3 years have witnessed an increase in the number of clinical trials that evaluate the efficacy and safety of factor XI(a) inhibitors.
- Small molecules offer the convenience of oral administration, whereas monoclonal antibodies provide the benefits of monthly dosing and the independence of the drug clearance process from hepatic and renal systems.

Figure 1. Cartoon depiction of monomeric human FXI structure (PDB ID: 2F83). (a) Back view showing the four apple domains: A1 (red) involving binding sites for thrombin and high molecular weight kininogen; A2 (orange) with some residues important for high molecular weight kininogen; A3 (cyan) involving binding sites for FIX, platelet glycoprotein-Ib, and heparin; and A4 (blue) involving FXIIa binding site. (b) Side view showing the cup-saucer relationship between the catalytic domain and the apple domains, respectively.

Figure 2.

The key role of human FXIa. The role of FXIa has been re-defined from a component in the intrinsic pathway of coagulation in the waterfall hypothesis of coagulation to a key player that bridges the thrombin generation process via activating FIX and the host defense, inflammatory mechanism(s) via activating FXII. HKa is cleaved high molecular weight kininogen.

Figure 3.

(a) A histogram shows the number of patents filed for molecules targeting different clotting factors over the 2016–2019 period. The highest number is for new molecular entities targeting FXI(a). Patents that involve FIIa and FXa inhibitors are generally to improve the manufacturing or the delivery method of approved drugs. No significant patents were retrieved for agents targeting FIXa or FVIIa. (b) A histogram shows the number of patents filed for molecular entities targeting the FXI(a) system per year starting 2016. The histogram also shows the type of molecular entities that have been claimed (small molecules, monoclonal antibodies, aptamers, and polypeptides). The claimed agents are predominantly small molecules. There is a declining trend in the number of patents filed over the 2016–2019 period, yet the number of FXI(a)-based agents that are being evaluated in clinical trials

is increasing. (c) A histogram shows the number of peer-reviewed publications for topics involving FXI(a) system. The histogram highlights the most recognized areas of research. The overall declining trend in the number of FXIa publications is similar to that of patents, although publications in the areas of medicinal chemistry and biochemistry has remained steady. Data in histograms (a) and (b) were retrieved from SciFinder whereas data in histogram (c) were retrieved from Web of Science.

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Figure 4.

The chemical structures of pyridine-*N*-oxide-based inhibitors of FXIa (**1–8**) filed by Merck Sharp & Dohme Corp., US. Provided are the FXIa and plasma kallikrein (PK) IC_{50} values (nM) and the concentrations required to double clotting time in APTT assay (μ M) for inhibitor **8**.

Figure 5.

The chemical structures of 2-oxopyridine-based inhibitors of FXIa (**9–16**) filed by Bayer Pharma, Germany. Provided are the FXIa and PK IC_{50} values (nM).

Figure 6.

The chemical structures of 2-oxopyridine-based inhibitors of FXIa (**17–19**) filed by Shanghai Hengrui Pharmaceutical Co. and its partner, China, as well as the chemical structure of inhibitor **20** which was claimed by Bristol-Myers Squibb Co., US. Provided are the FXIa and PK IC_{50} values (nM).

Figure 7.
The chemical structures of macrocyclic inhibitors of FXIa (**21–26**) filed by Bristol-Myers Squibb Co., US. Provided are the FXIa and PK IC_{50} values (nM) and/or K_i values (nM).

Figure 8.
The chemical structures of macrocyclic inhibitors of FXIa (**27** and **28**) claimed by Merck Sharp & Dohme Corp, US. Provided are the FXIa and PK K_i values (nM).

Figure 9.

The chemical structures of macrocyclic inhibitors of FXIa (**29** and **30**) claimed by Sunshine Lake Pharma Co. and Sichuan Kelun-Biotech Biopharmaceutical Co., respectively, from China. Provided are the FXIa IC_{50} values (nM).

Figure 10.

The chemical structures of 4-substituted phenylalanine-based inhibitors of FXIa (**31–33**) filed by Bayer Pharma, Germany. Provided are the FXIa IC_{50} values (nM).

Figure 11.

The chemical structures of β -lactam-based inhibitors of FXIa (34 and 35) filed by Exithera Pharmaceuticals, US.

Figure 12.

The chemical structures of miscellaneous inhibitors of FXIa (**36** and **37**) filed by international companies. Provided are the FXIa IC_{50} values (nM).

FELIAP	5`-5W-AACCTATCGGACTATTGTTAGTGATTTTTATAGTGT-3W-3`	+++
APT10_A	5`-5W-AACCTATCGGACTATTGTTAGTGATTTTTATAGTTT-3W-3`	++
APT10_B	5`-5W-AACCTATCGGACTATTGTTAGTGATTTTTATATTGT-3W-3`	++
APT10_D	5`-5W-AACCTATCGGACTATTGTTAGTGATTTTTAGAGTG*-3W-3`	+
APT10_E	5`-5W-TGTCACCTCTGATCAAAAATTTGTAGTCATCTTGTTATGC-3W-3`	+
NRMAPT1	5`-5W-TACGTGGTTCTTTTTTTAGGGAGTTCGATCCTGAGGCCT-3W-3`	+

Figure 13.

The nucleotide sequences of the hypervariable core domains of the six active aptamers identified in references 123 and 124. The most active aptamer was FELIAP. The positive signs on the right is indicative of activity against FXIa as determined in S-2366 chromogenic substrate hydrolysis assay. +++ = most active, ++ = moderately active, + = slightly active. Highlighted nucleotides indicate differences among the first four aptamers. '*' in the fourth aptamer indicates that the last nucleotide is missing.

Table 1.

Pharmacodynamic and pharmacokinetic characteristics of molecules targeting FXI(a).

	Small molecules	Polypeptides	Monoclonal antibodies	Aptamers	Antisense oligonucleotides
Pharmacodynamics					
Mechanism of action	Competitive & noncompetitive inhibitors of FXIa	Competitive inhibitors of FXIa	Competitive & noncompetitive inhibitors of FXIa; some target FXI	Competitive & noncompetitive inhibitors of FXIa	FXI mRNA
Selectivity	Significant selectivity has been achieved by all classes				
Pharmacokinetics					
Route of administration	Oral and/or parenteral	Parenteral			
Onset of action	Fast				Delayed
Duration	Relatively short (hours), but can be extended using specific formulation or drug delivery system		Relatively long (days or months)		
Clearance	More likely to be dependent on renal and/or hepatic systems	Less likely to be dependent on renal and/or hepatic systems			
Clinical trials	EP-7041 and BMS-986177 (Phase I)	None	MAA868, BAY1213790, and AB023 (Phase I)	None	ISIS 416858 (Phase II in postoperative VTE prevention)