




The contact activation system as a potential therapeutic target in patients with COVID-19

Joseph J. Shatzel MD^{1,2}  | Emma P. DeLoughery BS³ | Christina U. Lorentz PhD^{2,4} | Erik I. Tucker PhD^{2,4} | Joseph E. Aslan PhD⁵   | Monica T. Hinds PhD² | David Gailani MD⁶ | Jeffrey I. Weitz MD, FRCP(C), FACP⁷ | Owen J. T. McCarty PhD, FAHA^{1,2} | Andras Gruber MD^{1,2,4}

¹Division of Hematology and Oncology, Oregon Health & Science University, Portland, OR, USA

²Department of Biomedical Engineering, Oregon Health & Science University, Portland, OR, USA

³Mayo Clinic Alix School of Medicine, Mayo Clinic, Rochester, MN, USA

⁴Aronora, Inc., Portland, OR, USA

⁵Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

⁶Vanderbilt University Medical Center, Nashville, TN, USA

⁷The Thrombosis and Atherosclerosis Research Institute and McMaster University, Hamilton, ON, Canada

Correspondence

Joseph Shatzel, MD, Division of Hematology and Oncology, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239.
Email: shatzel@ohsu.edu

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Abstract

Coronavirus disease 2019 (COVID-19) is predicted to overwhelm health care capacity in the United States and worldwide, and, as such, interventions that could prevent clinical decompensation and respiratory compromise in infected patients are desperately needed. Excessive cytokine release and activation of coagulation appear to be key drivers of COVID-19 pneumonia and associated mortality. Contact activation has been linked to pathologic upregulation of both inflammatory mediators and coagulation, and accumulating preclinical and clinical data suggest it to be a rational therapeutic target in patients with COVID-19. Pharmacologic inhibition of the interaction between coagulation factors XI and XII has been shown to prevent consumptive coagulopathy, pathologic systemic inflammatory response, and mortality in at least 2 types of experimental sepsis. Importantly, inhibition of contact activation also prevented death from *Staphylococcus aureus*-induced lethal systemic inflammatory response syndrome in nonhuman primates. The contact system is likely dispensable for hemostasis and may not be needed for host immunity, suggesting it to be a reasonably safe target that will not result in immunosuppression or bleeding. As a few drugs targeting contact activation are already in clinical development, immediate clinical trials for their use in patients with COVID-19 are potentially feasible for the prevention or treatment of respiratory distress.

KEYWORDS

ARDS, DIC, hemorrhage, inflammation, sepsis

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Essentials

- Patients with coronavirus disease 2019 (COVID-19) with severe infection suffer from inflammatory and thrombotic complications.
- Contact activation supports inflammation and thrombin generation.
- Inhibiting contact activation in infection models reduces inflammation and death.
- Contact activation inhibitors in clinical development could be tested in patients with COVID-19.

1 | INTRODUCTION

Patients with coronavirus disease 2019 (COVID-19) may succumb to a systemic cytokine release syndrome, which has prompted therapeutic trials of biologic agents targeting interleukin (IL)-6 (tocilizumab, sarilumab) and other inflammatory mediators. A single-arm study of tocilizumab in 20 patients with severe or critical COVID-19-related pneumonia undertaken during the outbreak in China reported a reduction in oxygen requirements and improvement in pulmonary imaging in 75% and 90% of patients, respectively.¹ The US Food and Drug Administration has since approved a phase 3 clinical trial of tocilizumab (Actemra, Genentech) in patients with COVID-19 with pneumonia.²

Dysregulated coagulation with hypercoagulability is common with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and can progress to disseminated intravascular coagulation (DIC). A retrospective analysis of patients admitted with severe SARS-CoV-2 infection found that 71.4% of patients who ultimately died from COVID-19 developed overt DIC compared with only 0.6% of survivors. On admission, nonsurviving patients presented with higher D-dimer levels and prolonged prothrombin times and activated partial thromboplastin times compared with surviving patients.³ Furthermore, recent retrospective analyses have suggested that anticoagulation with heparin may improve clinical outcomes in patients with critical COVID-19,⁴ and autopsy reports from patients who died from severe COVID-19-related respiratory failure note intra-alveolar fibrin accumulation, suggesting a loss of vascular integrity.⁵

Pathologic upregulation of inflammation and coagulation in response to SARS-CoV-2 infection has led to significant enthusiasm for mobilizing clinical trials targeting either pathway.⁶ In this paper, we propose that targeting contact activation is a rational target for clinical trials in patients with COVID-19 at risk for respiratory compromise based on (i) animal models showing that inhibiting contact activation prevents pathologic host inflammatory responses to certain infections or bacterial challenge; (ii) clinical rationale that inhibiting contact activation may be safe in critically ill patients and is unlikely to provoke significant bleeding or compromise the immune system; and (iii) several contact activation inhibitors are in clinical development and are potentially available for rapid clinical trial implementation.

2 | THE CONTACT PATHWAYS OF COAGULATION AND INFLAMMATION

The molecular complex of contact activation composed of factor XII (FXII), factor XI (FXI), prekallikrein, and high-molecular-weight

kininogen serves as a central node linking the coagulation and inflammation pathways (Figure 1). Contact activation not only leads to thrombin generation but also upregulation of the kallikrein-kinin system (KKS). Thrombin generation may also upregulate the KKS through feedback activation of FXII via thrombin-induced FXI activation. Kallikrein induces the generation of bradykinin, which interacts with the renin-angiotensin system and induces the release of inflammatory cytokines, leading to complement activation and enhanced fibrinolysis. As outlined below, knockout or selective inhibition of components of the contact activation system inhibits both fibrin generation and systemic inflammation in animal models. Recent clinical trials suggest that inhibition of FXI attenuates thrombosis with little effect on hemostasis, although the effect of inhibiting FXI in humans with infection is unknown.⁷

3 | ANIMAL MODELS TARGETING THE CONTACT SYSTEM IN INFECTION

Several studies have evaluated the effects of FXI knockout in murine models of bacterial challenge. FXI knockout mice develop a less severe coagulopathy and lower serum cytokine levels than wild-type mice when challenged with *Listeria monocytogenes*. Plasma inflammatory markers, including IL-6 and hepatic mRNA encoding IL-6 and IL-10, were significantly attenuated, correlating with improved survival (30% vs 67%).⁸

Likewise, in a cecal ligation and puncture model designed to mimic polymicrobial peritoneal sepsis, FXI knockout mice experienced less consumptive coagulopathy than wild-type mice.⁹ Prothrombin times increased significantly in wild-type mice but remained unchanged in FXI-deficient animals. Mice that lacked FXI clearly developed a less pronounced coagulopathy and relatively attenuated inflammatory response compared with wild-type controls, and this translated directly to a significant survival advantage (46% vs 13%). This experimental model was later replicated to further define the changes in inflammatory cytokine levels and coagulation profiles in FXI knockout mice. Compared with wild-type mice, FXI-deficient mice demonstrated significantly lower plasma levels of IL-1 β , IL-6, IL-10, and tumor necrosis factor- α (TNF- α) during the infection. Survival at 7 days was also significantly higher in the FXI knockout mice (39% vs 6%).¹⁰

However, pharmacological inhibition of FXIa or deficiency of FXI has the potential to impair hemostasis, which may already be compromised during some infections. Therefore, inhibition of other

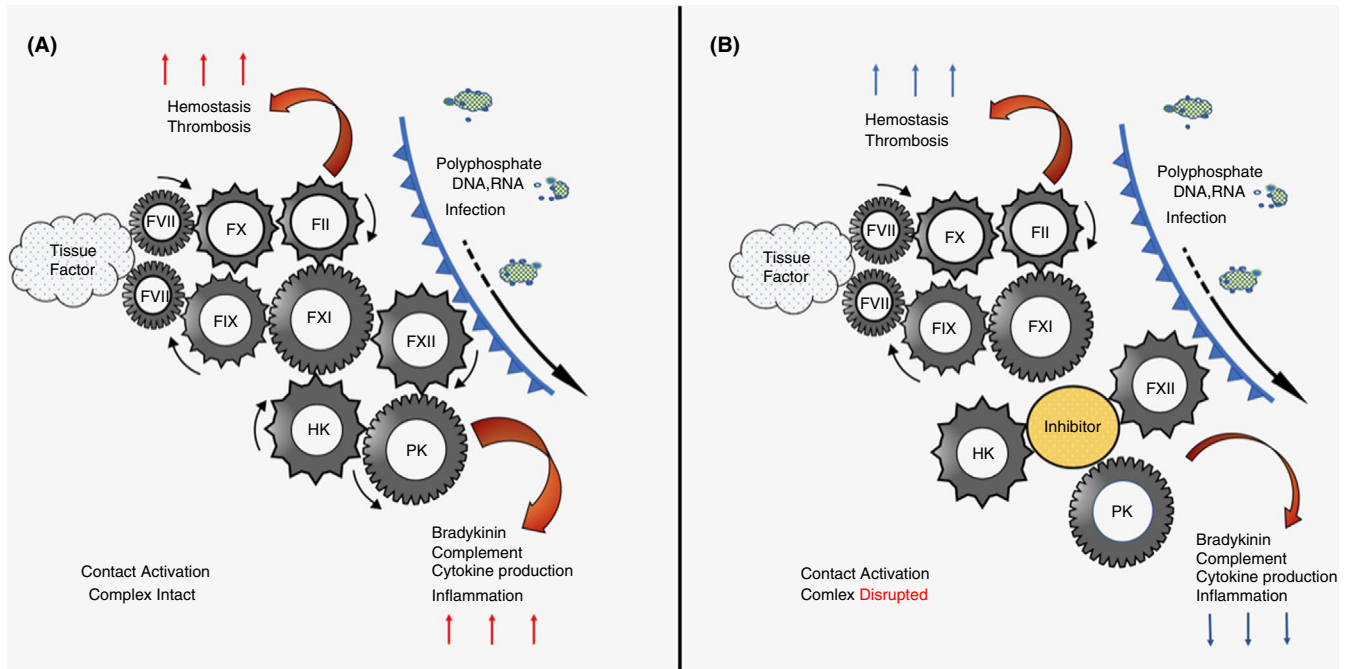


FIGURE 1 Schematic of pathologic thrombin and bradykinin generation in the absence (A) or presence (B) of a contact activation inhibitor. FII, factor II; FIX, factor IX; FVII, factor VII; FXI, factor XI; FXII, factor XII; HK, high-molecular-weight kinogen; PK, prekallikrein

components of the contact activation complex have been evaluated. The murine monoclonal antibody 14E11, which binds to the A2 domain of FXI and selectively disrupts reciprocal activation of FXI and FXII without affecting activation of FXI by thrombin or FIX activation by FXIa, had beneficial effects in the cecal ligation and puncture model described above, including significantly improved survival (80% vs 45%). On postmortem organ evaluation, only 40% of 14E11-treated mice had evidence of hepatic vascular microthrombi as compared with 75% of the control group. Levels of inflammatory cytokines, including TNF- α and IL-6, were significantly lower in the 14E11-treated mice.¹¹ Administration of 14E11 to *L monocytogenes*-infected mice also improved survival.⁸

Similarly, preclinical studies have evaluated the role of FXII in health and disease. FXII knockout mice are protected from experimentally induced thrombosis in numerous models while displaying normal hemostatic capacity.¹² Upregulated FXII activation is the cause of certain forms of hereditary angioedema and leads to excess bradykinin generation, complement activation, increased vascular permeability, and edema. The monoclonal antibody 3F7 that inhibits the activity of FXIIa has been shown to be protective against bradykinin generation and edema in mouse models of hereditary angioedema and to prevent bradykinin generation in plasma from humans with hereditary angioedema.¹³ The recombinant version of the antibody, CSL312, is currently under clinical development for treatment or prevention of hereditary angioedema.¹⁴ Finally, *Ixodes ricinus* contact phase inhibitor, a dual inhibitor of FXIa and FXIIa isolated from the saliva of *I ricinus* ticks, has been shown to attenuate thrombosis in animal models without apparent detriment to hemostasis.¹⁵ The effect of simultaneous inhibition of FXIa and FXIIa in humans remains unknown.

4 | ANIMAL MODELS TARGETING THE CONTACT SYSTEM IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Systemic inflammatory response syndrome (SIRS) can emerge after a variety of serious insults, including trauma, blood loss, amniotic fluid or fat embolism, and severe viral or bacterial infections, and can lead to organ failure and death. Inhibition of contact activation may attenuate development of SIRS and reduce mortality. Antibody-mediated inhibition of FXIIa improved outcomes in a baboon model of lethal *Escherichia coli* challenge.¹⁶ Rapidly developing fatal hypotension after infusion of cultured *E coli* was attenuated, with 1 in 5 (20%) survival in the group that received a FXIIa inhibitory antibody (C6B7). A later study demonstrated that baboons pretreated with C6B7 before *E coli* exposure also exhibited reduced complement activation, neutrophil degranulation, and levels of tissue-type plasminogen activator (t-PA) and IL-6 compared with untreated controls.¹⁷

More recent nonhuman primate work by Silasi et al¹⁸ investigated the effects of the recombinant monoclonal anti-FXI antibody 3G3 (AB023), a humanized variant of the mouse anti-FXI antibody 14E11, discussed above, in baboons that received an intravenous lethal dose of inactivated *S aureus*. All animals given prophylactic 3G3 survived to 7 days as compared with none in the untreated control arm. Administration of 3G3 reduced the consumptive coagulopathy as reflected by shorter partial thromboplastin times and resulted in fewer respiratory complications, less tachypnea, and reduced fever as compared with untreated controls. Serum biomarkers of end-organ dysfunction were also significantly decreased. Upon postmortem analysis, no microvascular thrombi were detected in the lungs, kidneys, and livers of the 3G3-treated baboons, and organs

appeared normal on histopathologic evaluation. In contrast, extensive microvascular thrombosis and organ damage were detected in untreated animals.¹⁸

Inhibition of reciprocal FXI and FXII activation with 3G3 resulted in a marked blunting of the cytokine storm usually associated with bacteremia and sepsis. Plasma levels of IL-6, IL-8, monocyte chemoattractant protein-1, granulocyte-macrophage colony-stimulating factor, and IL-1 β were lower in FXI-inhibited nonhuman primates. Treated animals also displayed decreased contact (prekallikrein), fibrinolytic (t-PA), and complement cascade activation, reflected by lower levels of circulating C3b and C5b-9 terminal complement complex.¹⁸ A more recent preliminary study with 5C12, an antibody that directly inhibits FXIIa, in the same baboon model of lethal SIRS yielded results similar to those observed with 3G3.¹⁹

5 | HUMAN AND ANIMAL DATA SUGGESTING THE POTENTIAL SAFETY OF CONTACT SYSTEM INHIBITION

While the contact activation system of coagulation leads to thrombin generation and appears to contribute to the development of thrombosis, it seems to be mostly dispensable for hemostasis. Epidemiologic data suggest that individuals with congenital FXI deficiency are largely protected against venous and arterial thrombosis while usually having only a mild bleeding diathesis with little or no spontaneous bleeding, and the bleeding with hemostatic challenge (trauma, major surgery) often does not require treatment. Importantly, congenital FXII deficiency, while rare, is not associated with abnormal bleeding.¹² The relative safety of reducing FXI activity in humans was demonstrated in a prospective clinical trial of an antisense oligonucleotide that reduced plasma FXI levels in surgical patients. Partial reduction in FXI levels was an effective method for prevention of postoperative venous thromboembolism in patients undergoing elective knee arthroplasty and was associated with a trend for less bleeding than traditional anticoagulation.²⁰ Similarly, antibody-mediated inhibition of FXIa was associated with a trend for less bleeding than that observed with low-molecular-weight heparin in a large prospective trial of thromboprophylaxis in patients undergoing elective knee arthroplasty.²¹ In a phase 1 trial, AB023 appeared to be safe without any notable drug-related adverse effects in healthy volunteers.²² While recent retrospective analyses have suggested anticoagulation with heparin products may improve clinical outcomes in patients with COVID-19,⁴ selective targeting of contact activation may offer a more refined approach, with no impact on hemostasis, and would likely be associated with fewer bleeding complications. However, the safety of inhibiting the contact activation system in patients with bacterial or viral infections has not been assessed.

Innate immunity does not appear to be compromised in humans with congenital FXI or FXII deficiency, although FXI deficiency has been associated with nasal infections in Holstein cattle.²³

Epidemiologic studies of humans with FXI deficiency reported identical rates of hospitalization for pneumonia and pneumonia-related outcomes as controls with normal FXI levels. To our knowledge, there are no reports linking human FXI deficiency with an immunocompromised phenotype.²⁴ Thus, while contact activation appears to contribute to proinflammatory and procoagulant pathways in humans, the absence of FXI does not seem to significantly compromise host defense or hemostasis. It should be noted that results from a study of a mouse model of pneumonia conflict with this premise. Thus, Stroo and colleagues^{25,26} showed that administering *Streptococcus pneumoniae* or *Klebsiella* into the lungs resulted in more inflammation and higher mortality in FXI-deficient mice than in wild-type mice. While raising a cautionary note, these findings may represent a species-specific effect like that observed in Holstein cattle. It is reassuring that the aforementioned epidemiologic study found no increase in the frequency of pneumonia in FXI-deficient humans compared with those with normal FXI levels. Furthermore, in those with pneumonia, there was no significant difference in severity or short-term mortality.²⁴ We posit that a strategy directly targeting FXII or targeting the link between FXII and FXI will not produce the same effect as complete deficiency of FXI and, importantly, leave the hemostatic function of FXI intact. However, it will be important to monitor the response when directly targeting or eliminating the function of the KKS in patients with pneumonia.

6 | CONTACT SYSTEM INHIBITORS CURRENTLY IN HUMAN TRIALS

Multiple agents targeting FXI, and one targeting FXII, have been evaluated in early-phase clinical trials. Inhibitors of FXI under evaluation include IONIS-FXI Rx, a FXI antisense oligonucleotide that inhibits hepatic synthesis of FXI; MAA868 (abelacimab), a monoclonal antibody that binds the catalytic domain of both FXI and FXIa; Osocimab (BAY1213790), a monoclonal antibody that only binds the catalytic domain of FXIa; BAY1831865, a monoclonal antibody that binds the A3 domain of FXI and prevents FXIa-mediated activation of FIX; and JNJ-70033093 and BAY2433334, which are small-molecule inhibitors of FXIa. More selective inhibitors of contact activation upstream of FXIa include AB023 (3G3), a monoclonal antibody that binds FXI and inhibits its activation by FXIIa and FXII activation by FXIa; and CSL312, a monoclonal antibody that inhibits FXIIa.^{14,27}

Preclinical data and rationale exist for preventing the activation of FXI and FXII while preserving some of the hemostatic FXI activity in patients with COVID-19. To our knowledge, of these drugs, only AB023 (3G3) has been tested in infection models and has shown promise in preventing the systemic inflammatory response, clinical decompensation, and death in a nonhuman primate model of lethal bacterial challenge. By targeting the reciprocal activation of FXI and FXII, AB023 breaks the connection between activation of FXII by foreign surfaces that may get exposed during bacterial and viral infections, thereby downregulating activation of FXI and the KKS. Moreover, selectively inhibiting the pathologic interaction between FXII and FXI

to prevent deleterious thrombin and kallikrein generation would still preserve the hemostatic function of FIX activation by thrombin-induced FXI activation. Therefore, FXI activation by FXIIa, by virtue of its position as an interface between contact activation and thrombin generation, may represent a unique target to safely prevent or treat COVID-19–related inflammatory complications including the cytokine response and the coagulopathy and to reduce associated mortality.

7 | CONCLUSION

The world is in the midst of a pandemic, the time course and resolution of which is unclear. In such times it is the responsibility of the scientific and medical community to quickly develop well-designed clinical trials rationally based on preclinical and clinical data. We propose the FXII ↔ FXI axis as a rational therapeutic target. A potential clinical trial could include prophylaxis against decompensation in COVID-19 patients with severe disease as evidenced by a reduction in the need for ventilator treatment, shorter time to ventilator weaning, or reduced progression to extracorporeal membrane oxygenation. The hemostatic safety and potential effects on the innate immune response will need to be monitored as part of this novel approach. In addition to these clinically relevant end points, which may free up vital resources, the available preclinical data suggest that inhibition of contact activation has the potential to improve survival in patients with SARS-CoV-2 infection–induced severe COVID-19.

RELATIONSHIP DISCLOSURE

AG, CUL, DG, EIT, Aronora, Vanderbilt University Medical Center, and Oregon Health Sciences University may have a financial interest in this study. JJS and JIW are consultants for Aronora, Inc. The remaining authors declare nothing to report.

AUTHOR CONTRIBUTIONS

JJS wrote the manuscript; AG conceived the concept; AG, CUL, EIT, MTH, and OJTM developed contact activation inhibitors; AG, DG, EPD, JA, JIW, and OJTM provided critical input for the manuscript; all authors read and approved the manuscript.

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ORCID

Joseph E. Aslan  <https://orcid.org/0000-0002-8873-0387>

TWITTER

Joseph J. Shatzel  @Clotmaster

Joseph E. Aslan  @JoePlatelet

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