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ONO

Discovery of ONO-5450598, a highly orally bioavailable small molecule factor XIa inhibitor: the pharmacokinetic and pharmacological profiles

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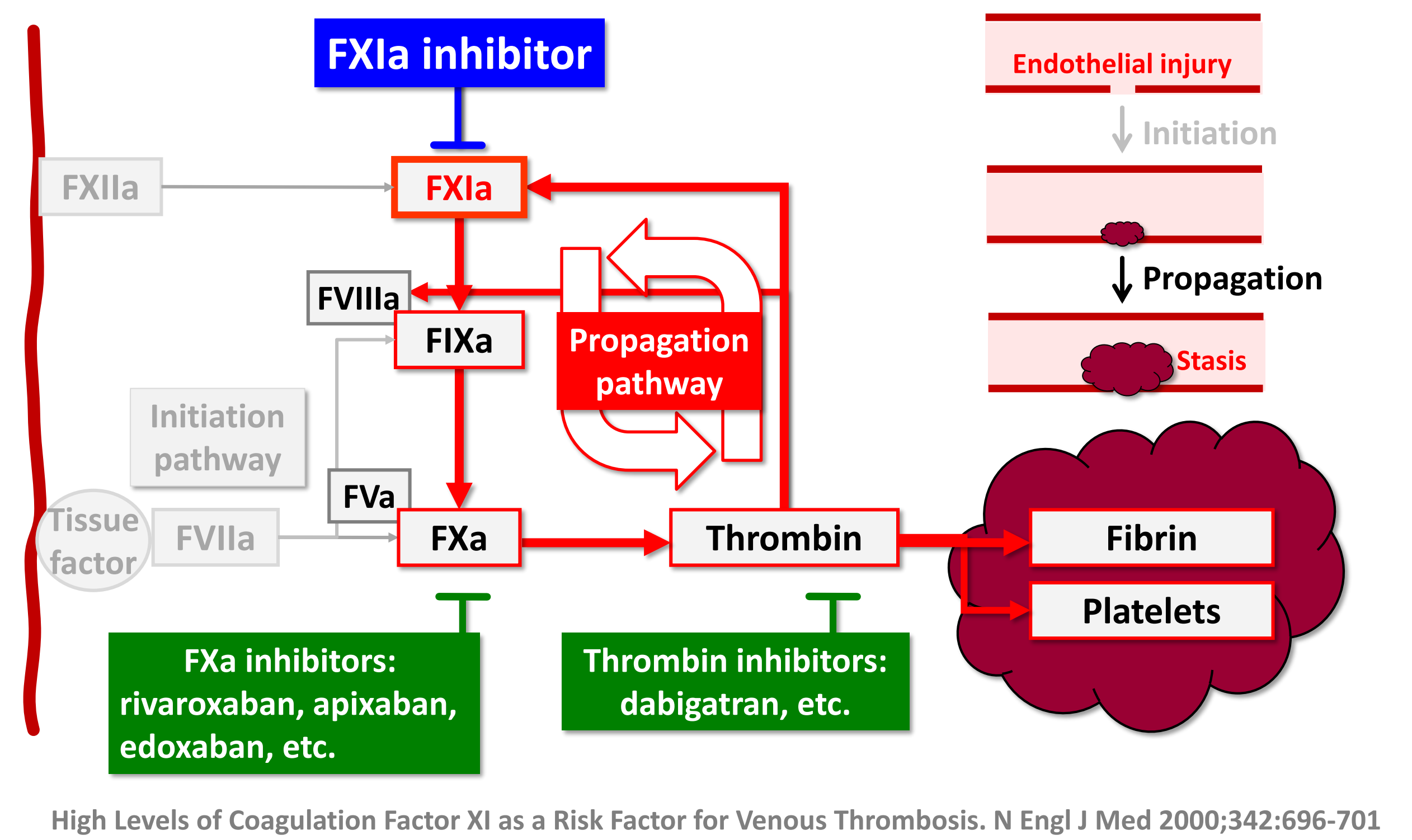
Conclusion

ONO-5450598 was identified to:

- Be a highly selective inhibitor of activated human blood coagulation factor XI.
- Have a high oral bioavailability in animals.
- Have potent antithrombotic efficacy in thrombosis models.
- Have a significantly lower bleeding risk than an activated factor X inhibitor, rivaroxaban.

Introduction

Activated blood coagulation factor XI (FXIa) is one of the serine proteases that is involved in the amplification of thrombin production. Inhibition of FXIa reduces thrombin generation and prevents occlusive thrombosis. Whilst congenital FXI deficiency is associated with bleeding, the symptom is less severe than those observed in patients with deficiency in other coagulation factors. Therefore, a highly selective FXIa inhibitor is considered to be a promising drug candidate for the treatment of venous thromboembolism with a significantly lower bleeding risk than existing anticoagulants.



Background

In ISTH2015, we reported that ONO-7750512 as a small molecule factor XIa (FXIa) inhibitor has an oral bioavailability (BA) of 22% in rats and has potent antithrombotic efficacy without a prolonged bleeding time in animal models. Recently, we have found a new small molecule FXIa inhibitor ONO-5450598, which is equivalent to ONO-7750512 in terms of the potent antithrombotic efficacy without a prolonged bleeding time and has even higher oral BA.

Aims

- Elucidation of the *in vitro* pharmacological profile
- Investigation of:
 - The oral BA in various animal species
 - The *in vivo* antithrombotic and hemorrhagic effects of ONO-5450598 in monkeys

There are no relevant conflicts of interest to disclose.
All the animal experiments were reviewed by the Institutional Animal Care and Use Committee and finally approved by the director of Ono Pharmaceutical Co., Ltd.

In vitro profile of ONO-5450598

Human enzymes	Ki (μmol/L)	Anticoagulant effects	APTT x2* / PT x2* (μmol/L)
FXIa	0.0020	Human	0.5-0.8 / >33
Plasma Kallikrein	0.021	Monkey	0.50 / >33
Thrombin, FVIIa, FIXa, FXa, FXIIa, plasmin, urokinase, t-PA	>10	Rabbit	0.46 / >33

*The final concentration of ONO-5450598 that doubles each coagulation time of the mixture of plasma and test reagents

