



Fitusiran treatment modulates the ratio between alpha- and beta-antithrombin isoforms

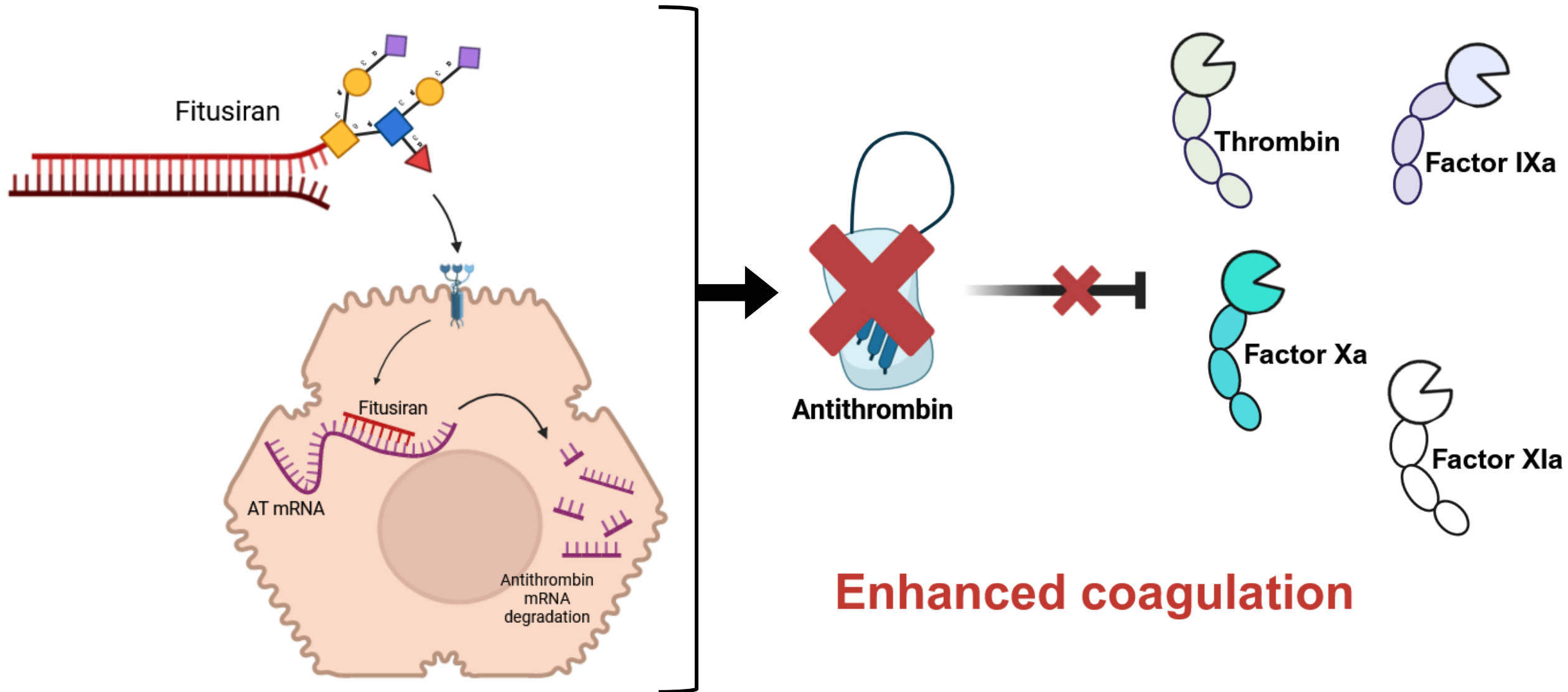
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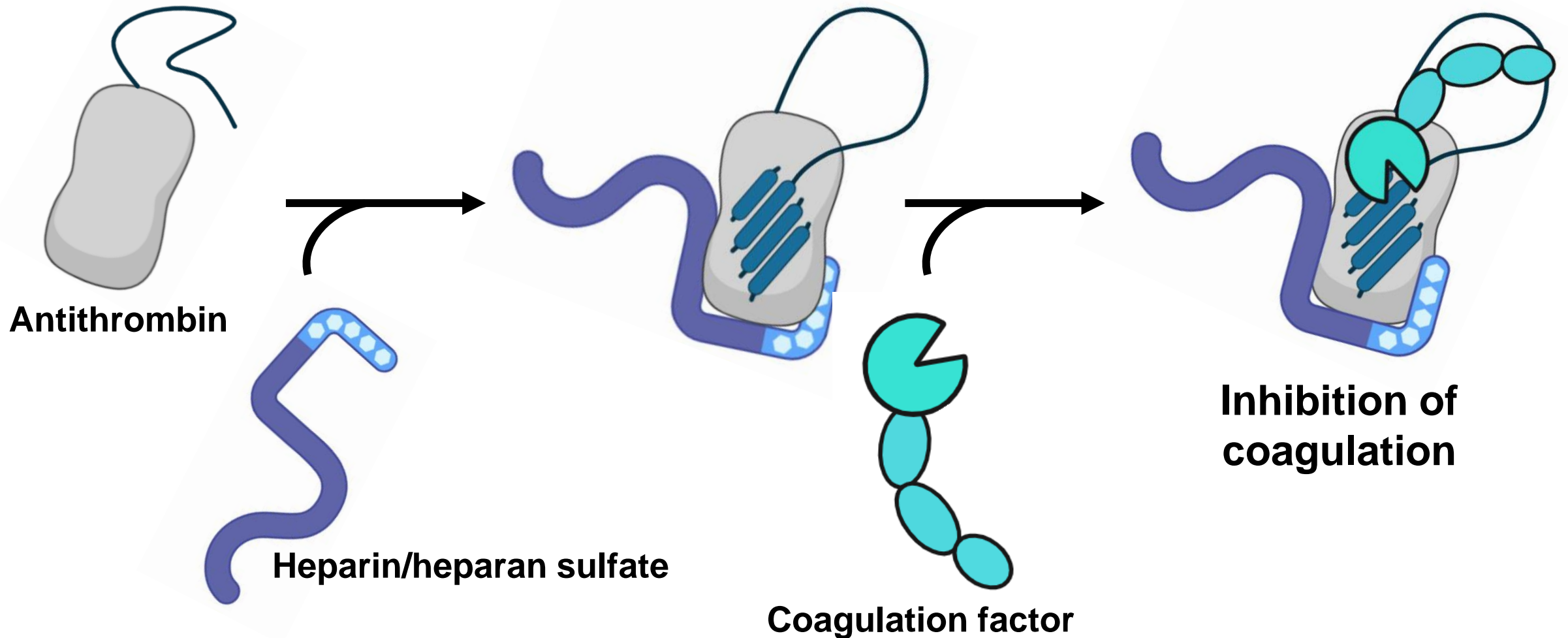
Disclosures

- Study supported by SANOFI

Fitusiran: an investigational siRNA targeting antithrombin

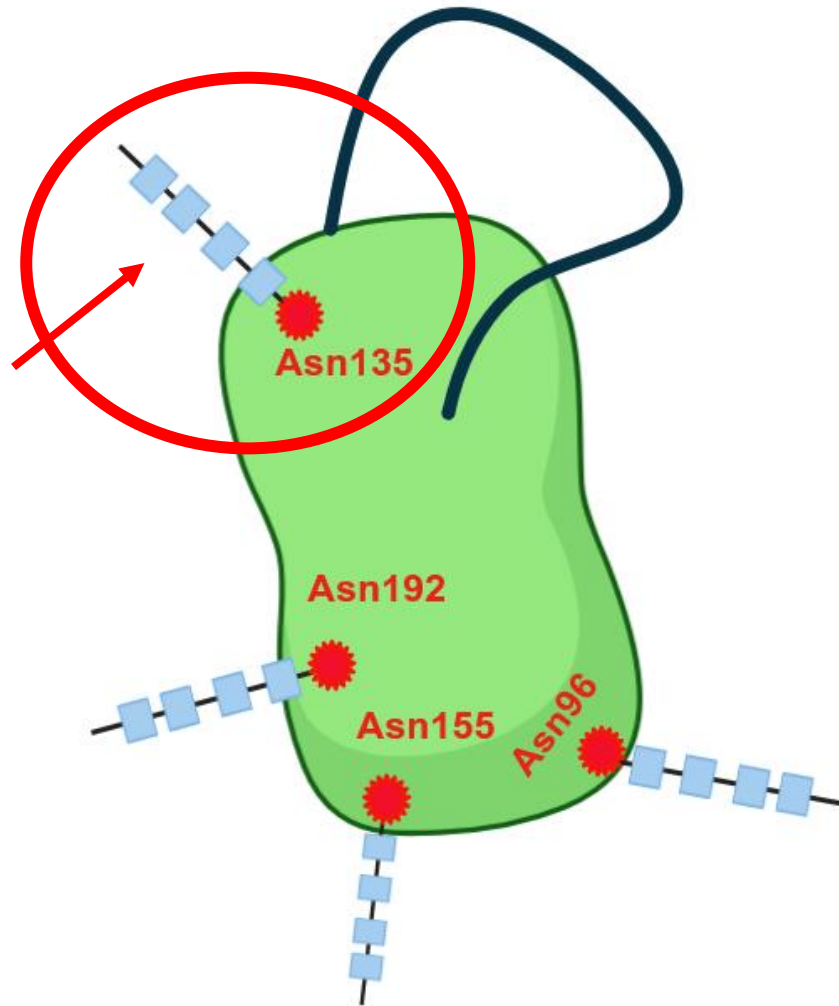


Antithrombin : a serine protease inhibitor

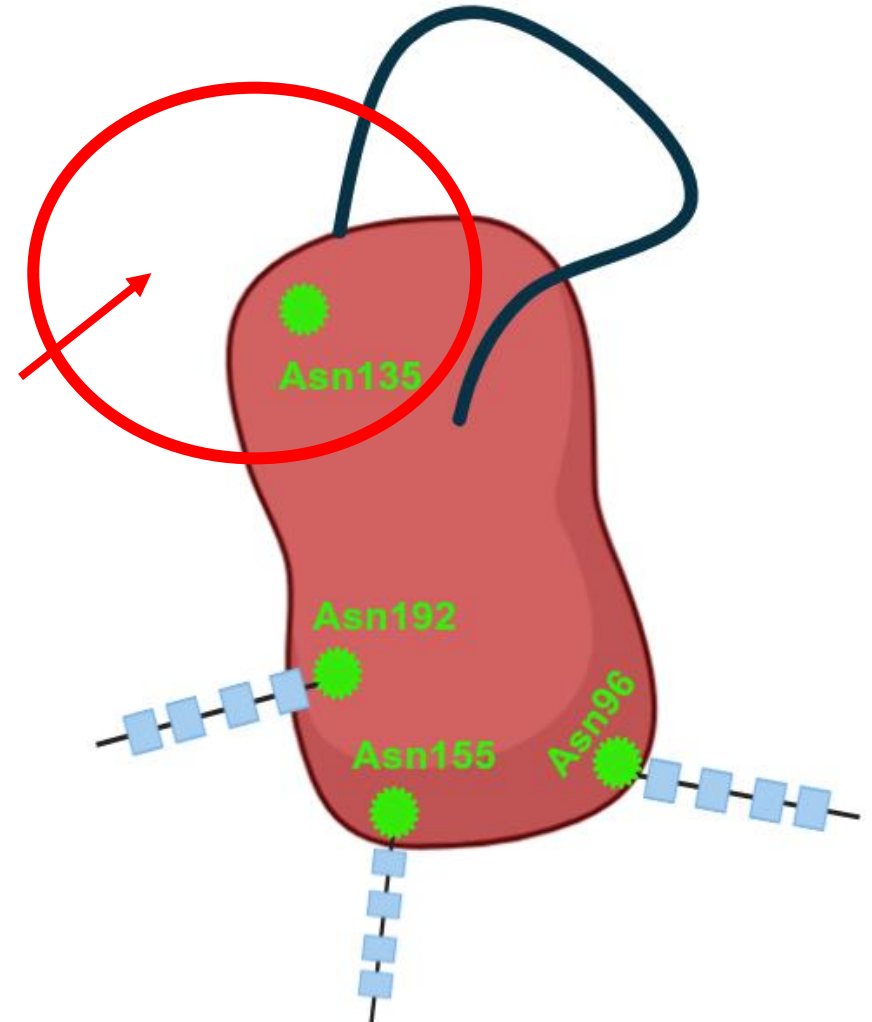


Antithrombin isoforms: β -antithrombin lacks the N-glycosylation at Asparagine135

ALPHA (α -AT)

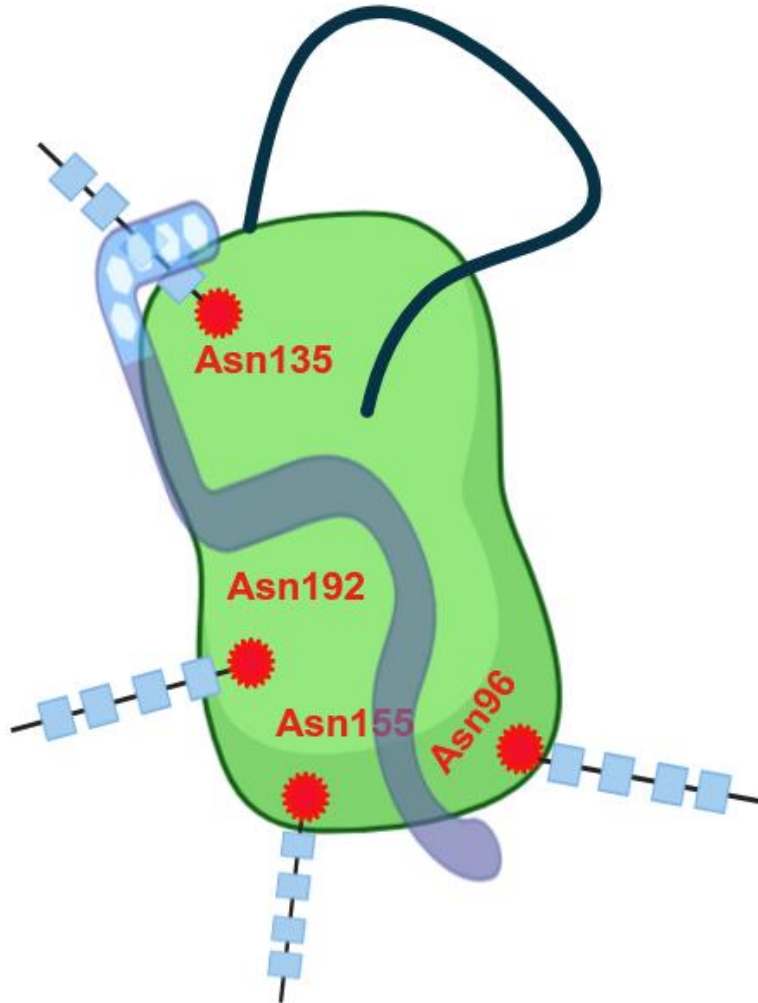


BETA (β -AT)



Antithrombin isoforms: β -antithrombin has higher activity than α -antithrombin

ALPHA (α -AT)

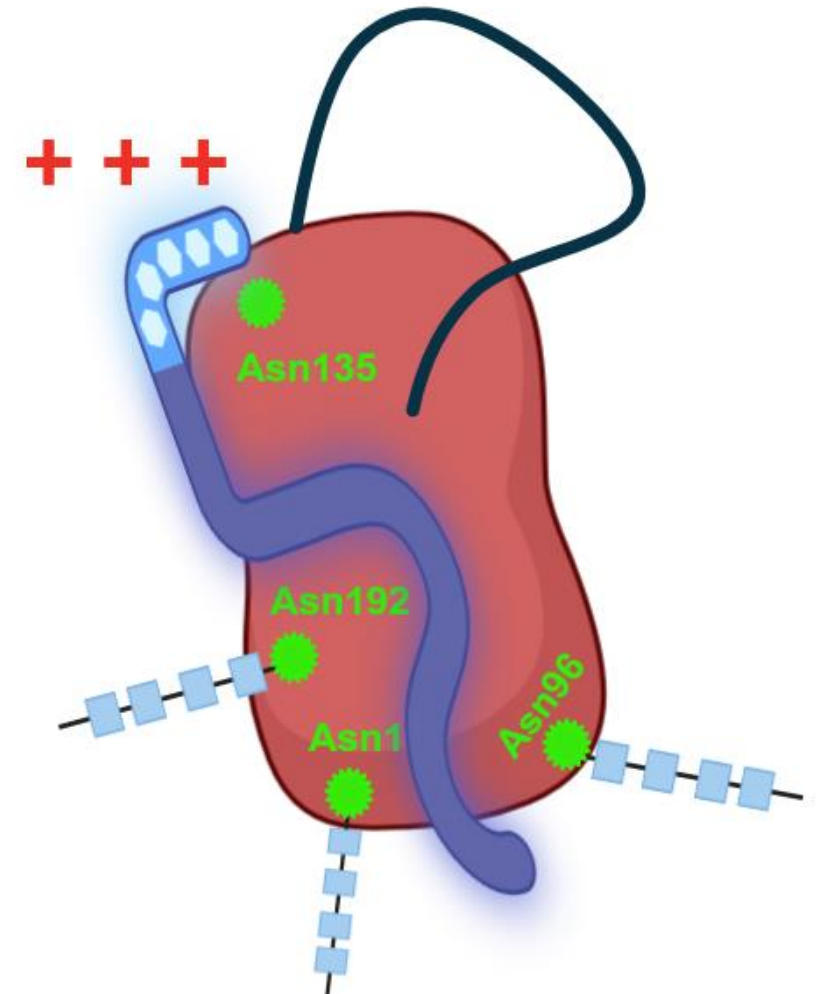


Higher affinity
for heparin

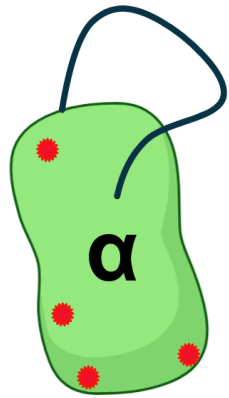
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Higher activity

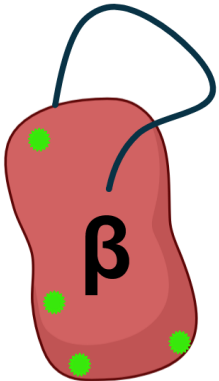
BETA (β -AT)



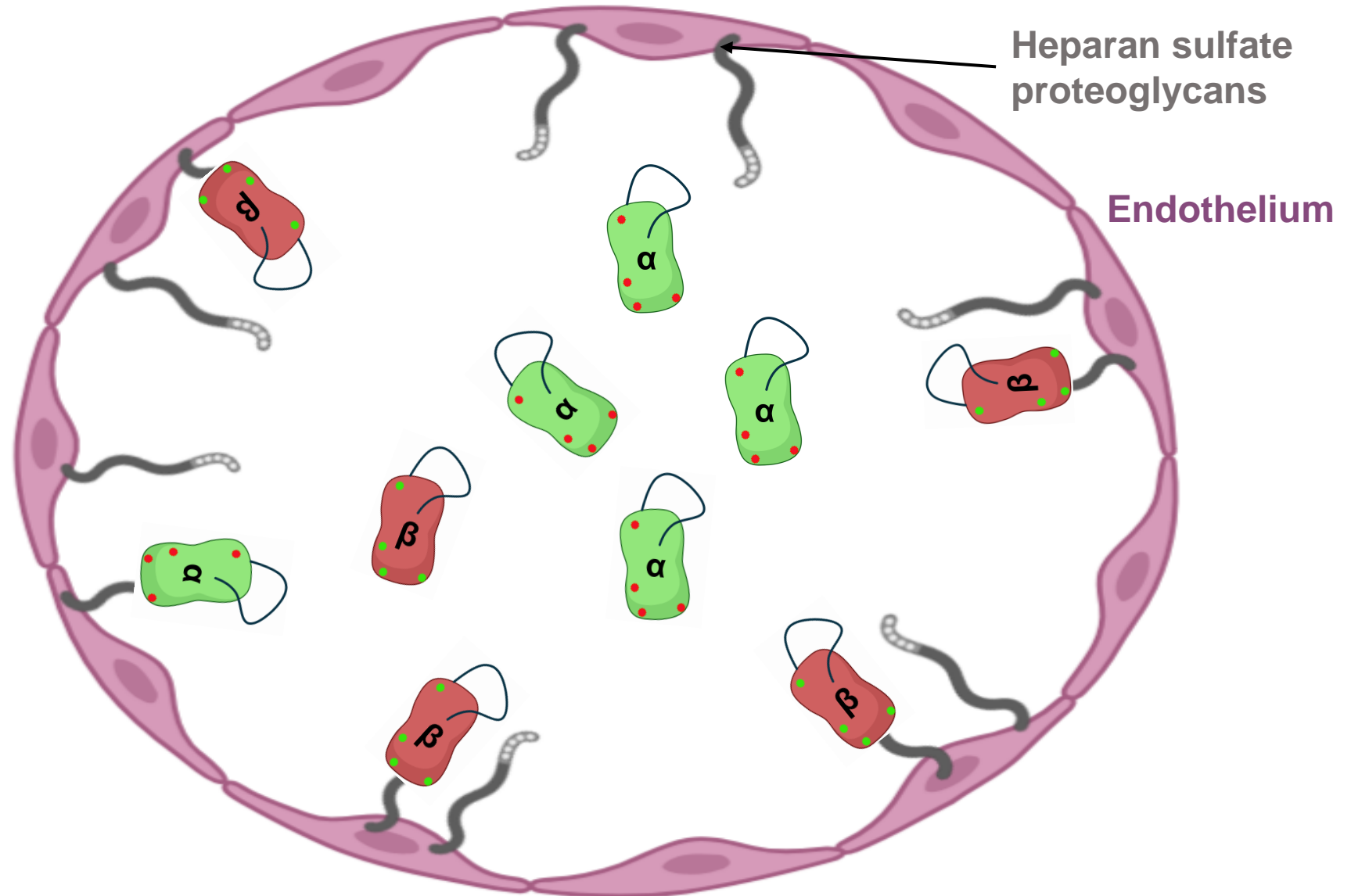
Antithrombin isoform distribution in circulation



α -AT:
85-95% in
circulation



β -AT:
5-15% in
circulation
Majority bound
to vessel wall

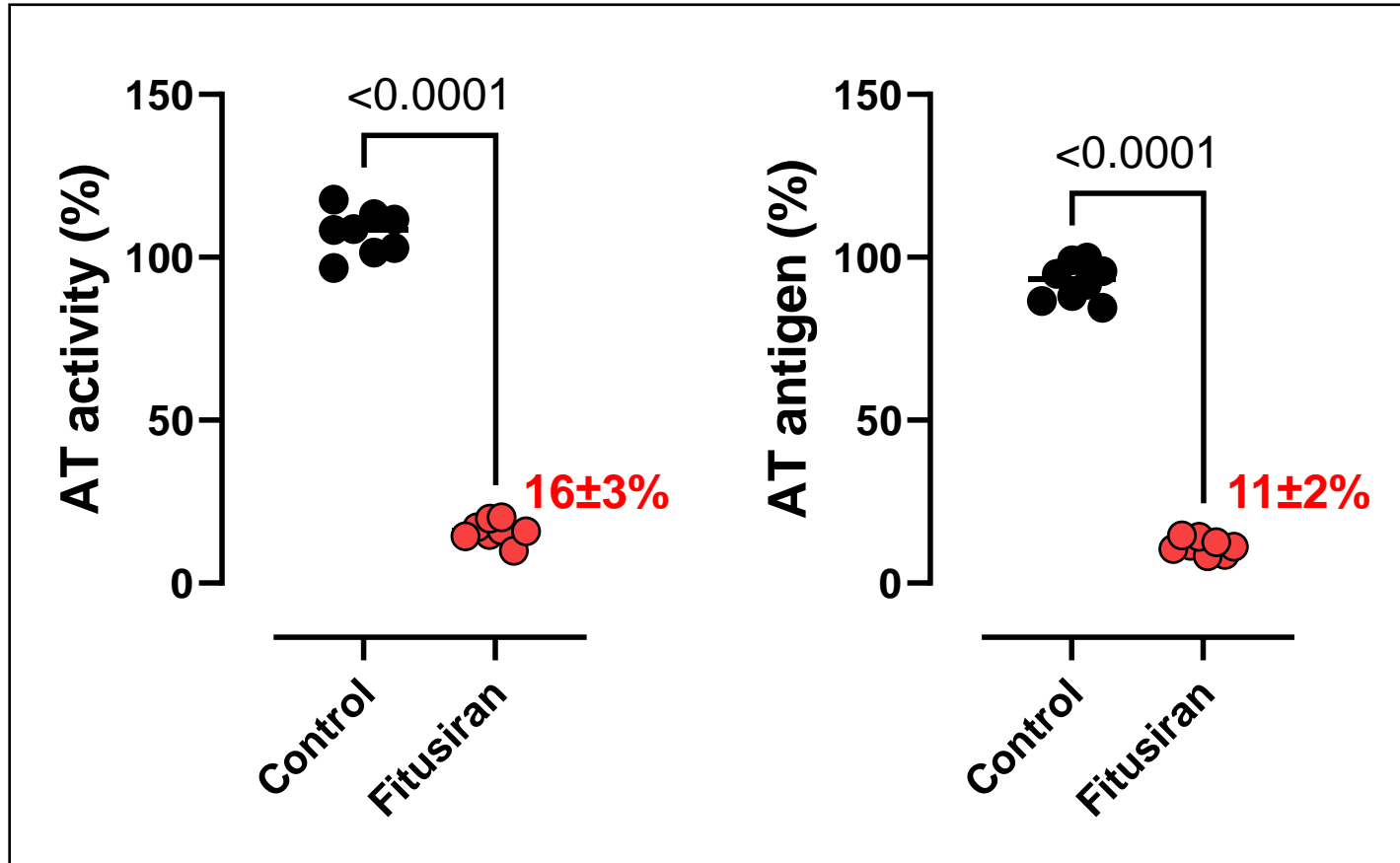


How are the alpha and beta isoforms of antithrombin affected after fitusiran treatment?

Objectives

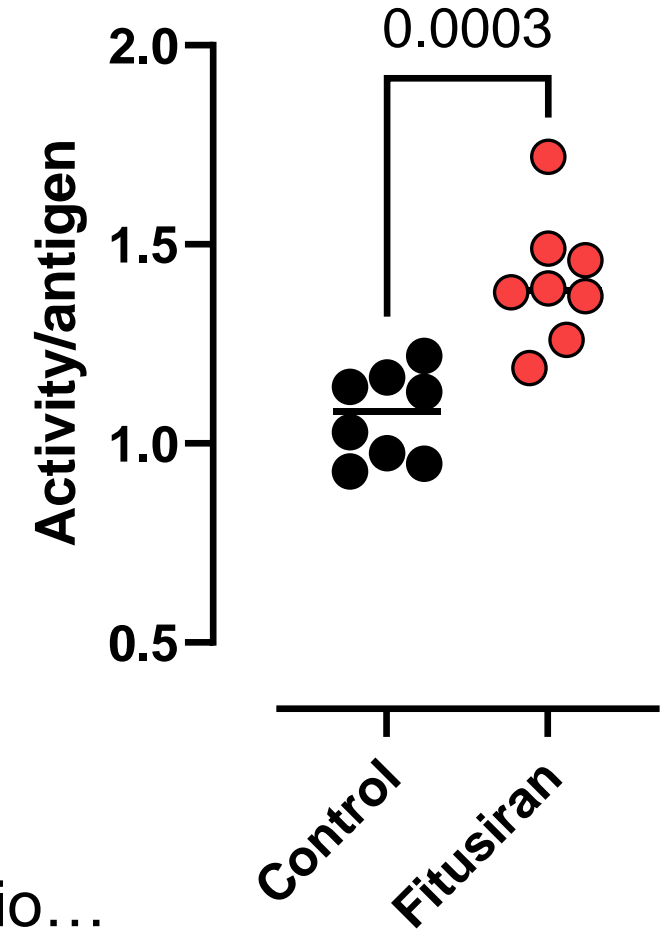
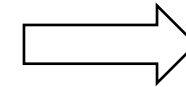
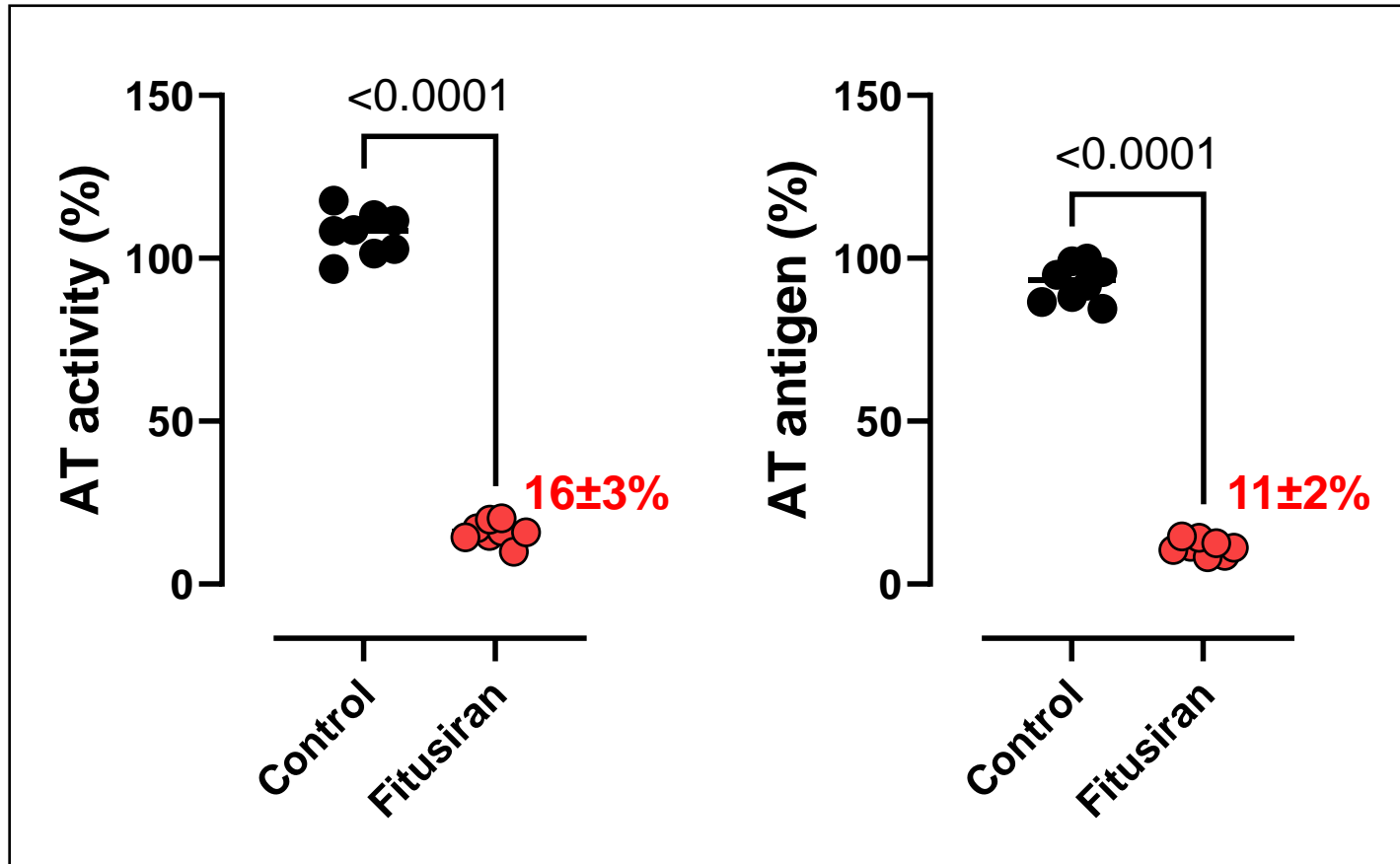
- Isoforms in fitusiran-treated hemophilia A (HA) patients
- Isoforms in fitusiran-treated F8 KO mice
- Does fitusiran affect the isoform alpha/beta ratio?

How fitusiran affects AT activity/antigen ratio in HA patients



Control: untreated

How fitusiran affects AT activity/antigen ratio in HA patients



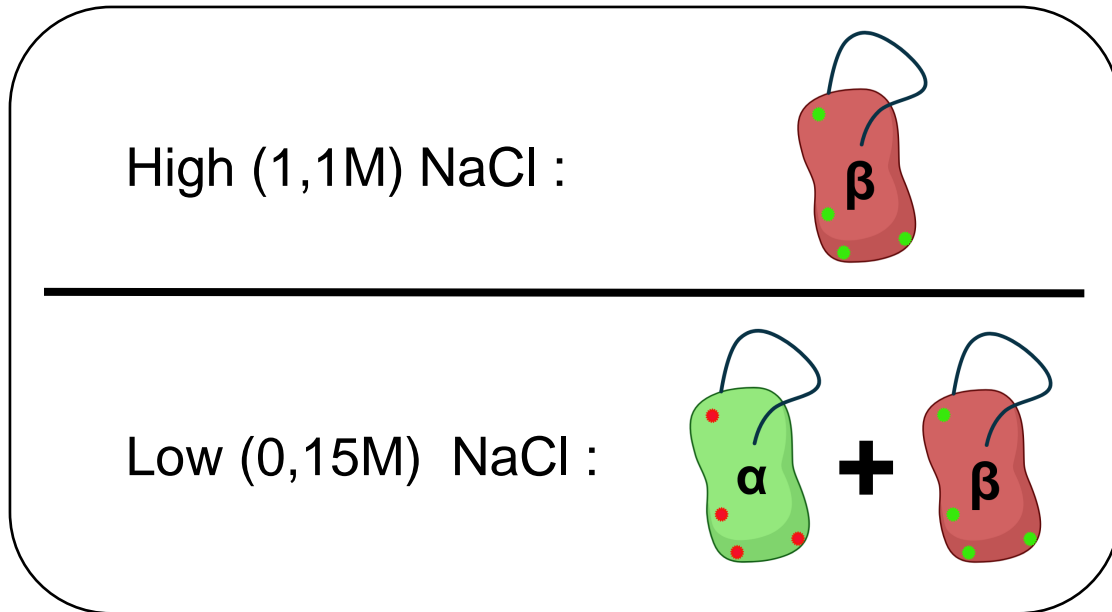
Fitusiran treatment increases antithrombin activity/antigen ratio...

... Indicating AT in fitusiran-treated plasma has a higher potency

Control: untreated

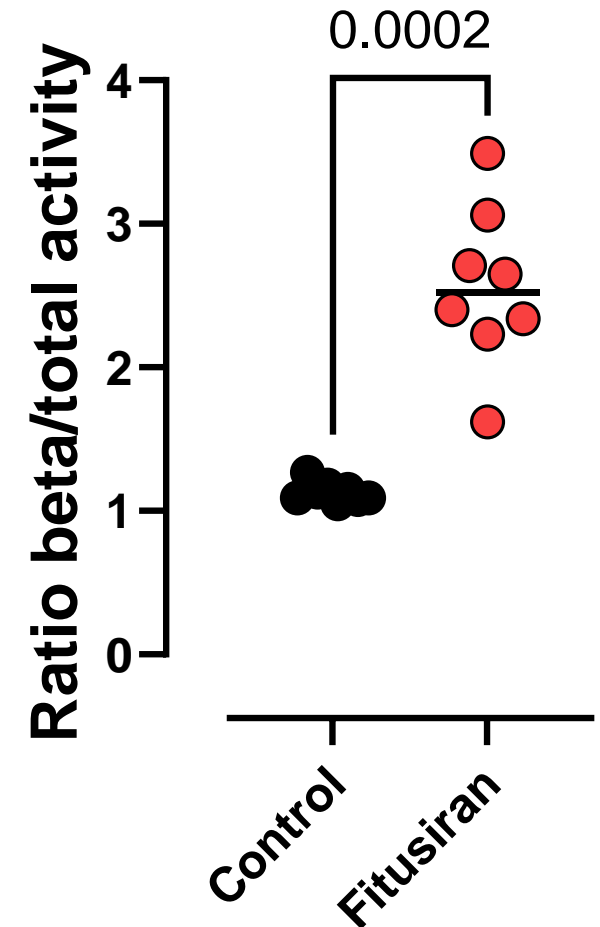
How fitusiran affects β -AT activity ratio in HA patients

Detecting β -AT activity in plasma



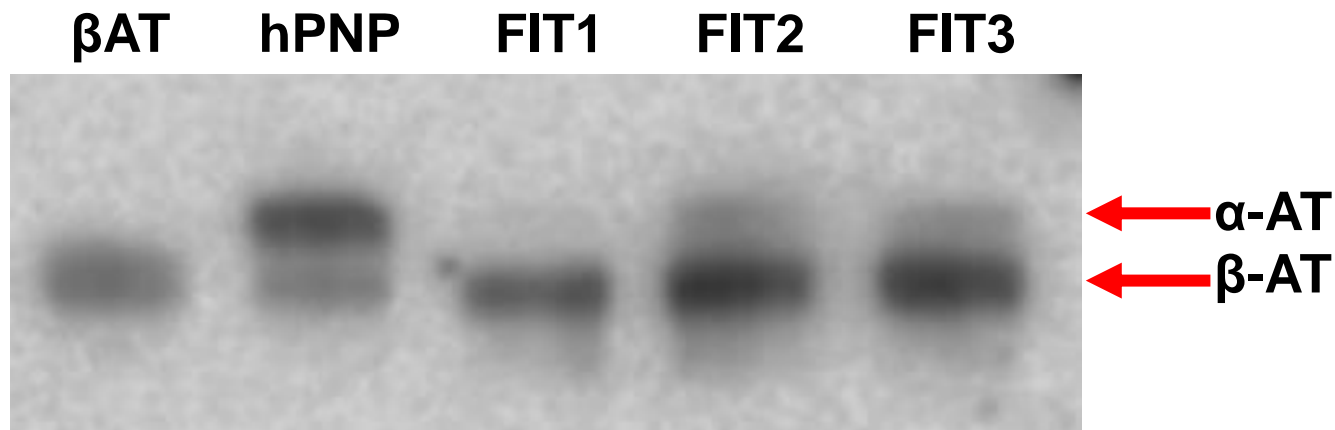
→ The relative ratio of beta/total AT activity is significantly higher in fitusiran-treated patients

→ Suggesting higher proportion of β -AT in circulation in patients



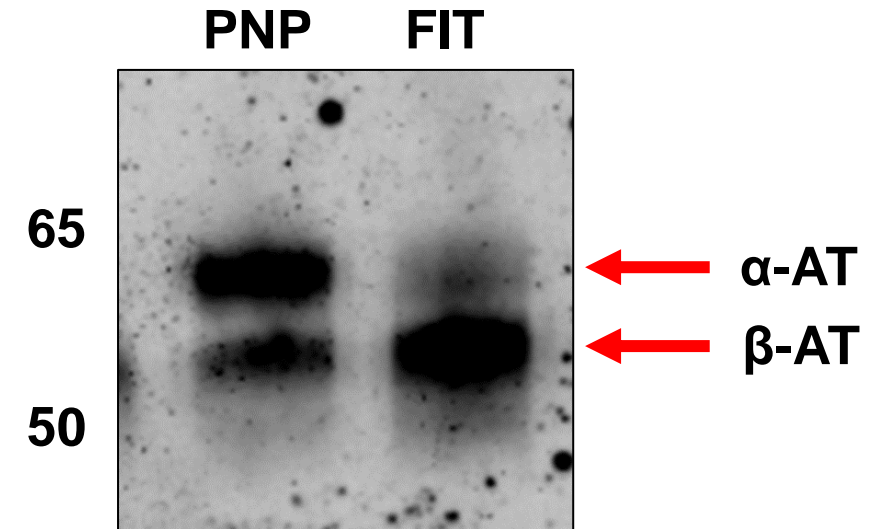
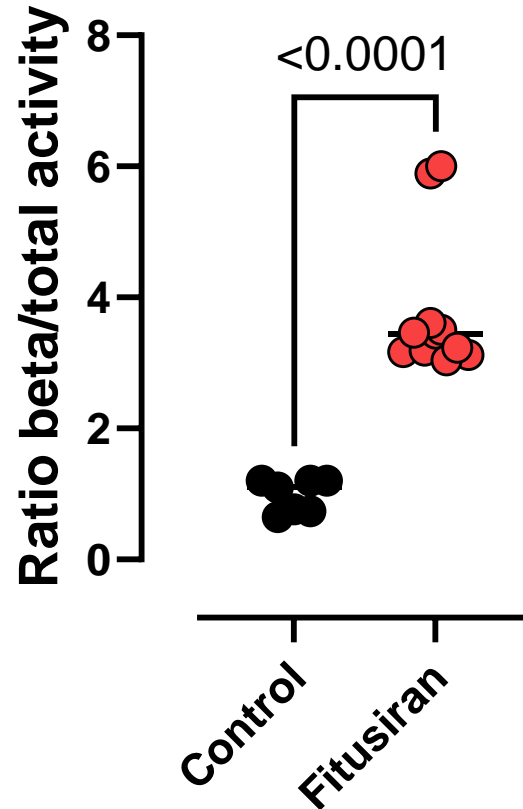
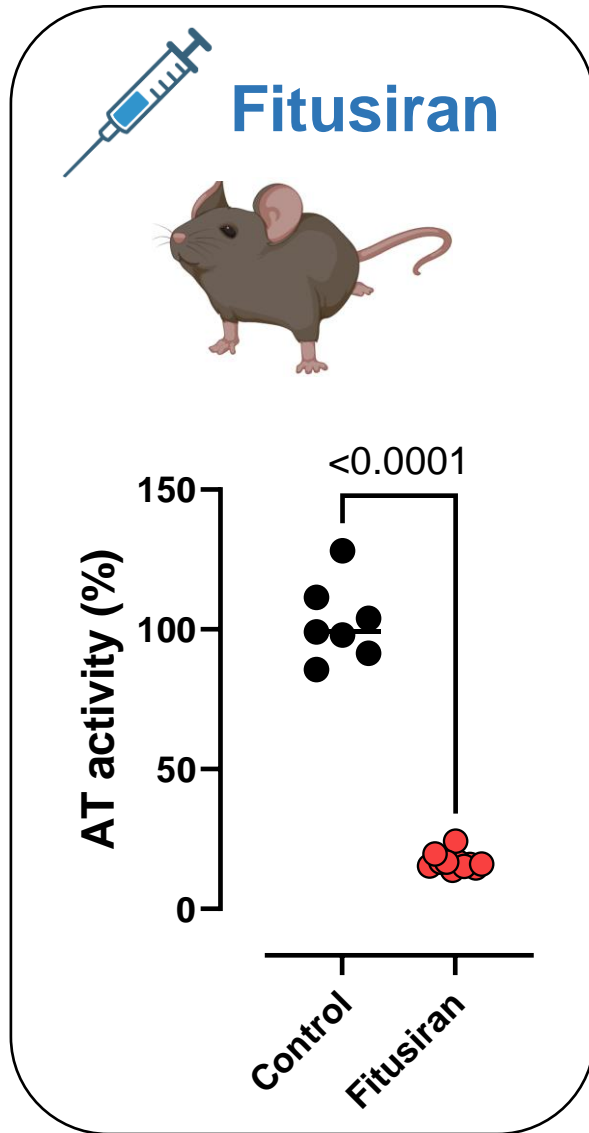
How fitusiran affects β -AT activity ratio in HA patients

hPNP: human pooled normal plasma
FIT1-3: fitusiran-treated patients



- The proportion of β -AT isoform is increased in fitusiran-treated patient plasma
- The distribution of α -AT and β -AT isoforms is altered after fitusiran treatment

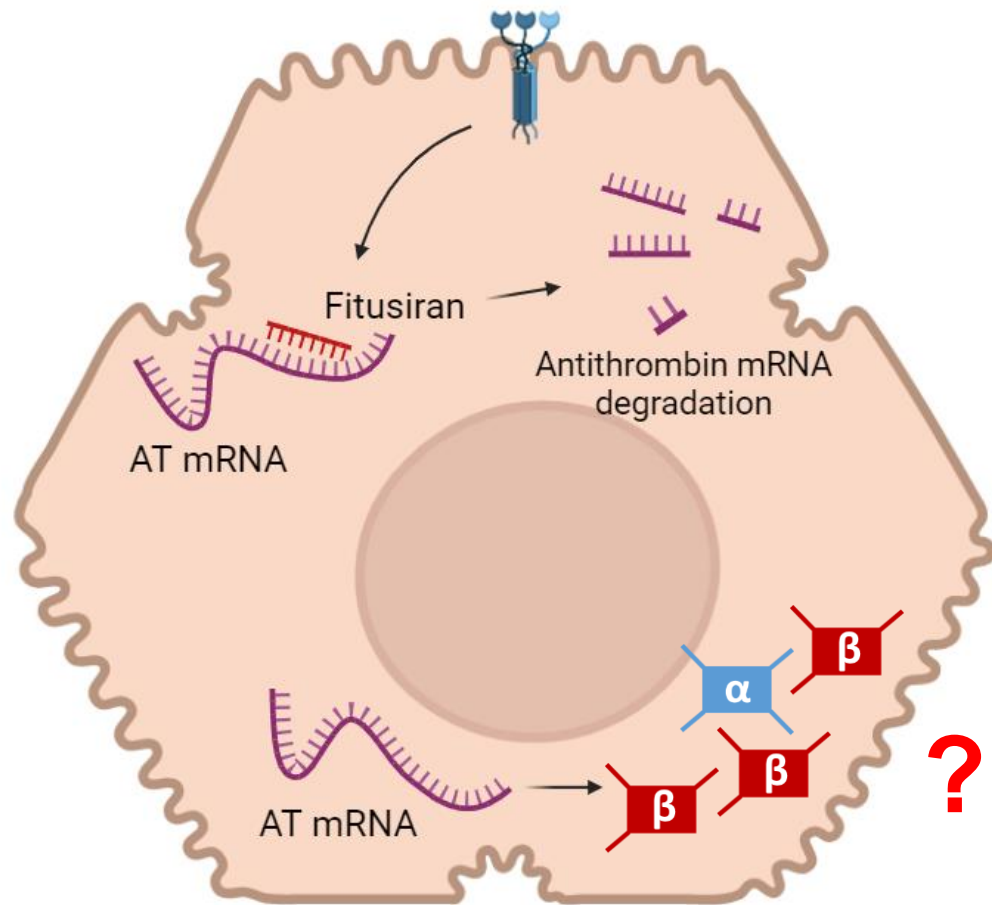
How fitusiran affects AT isoform ratio in HA (F8 KO) mice



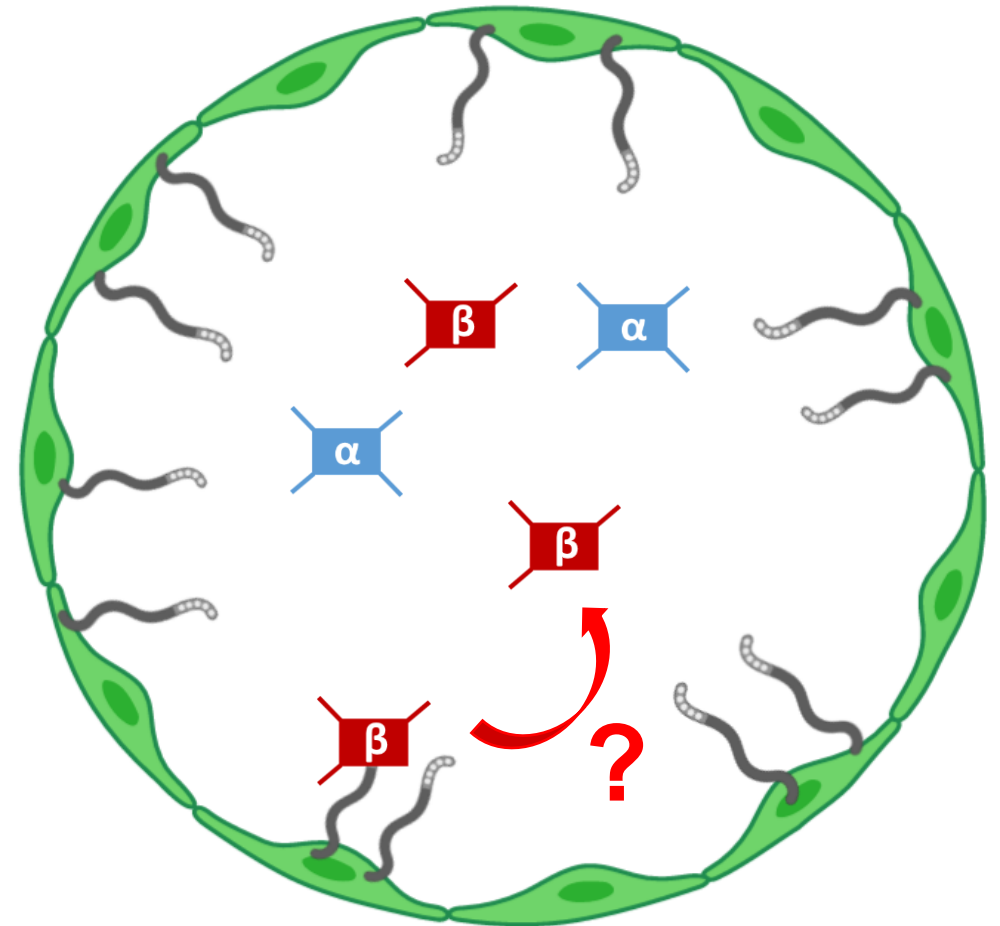
The ratio high/low increases in fitusiran-treated mice, pointing to a **higher proportion of β-AT in circulation compared to controls**

How is fitusiran affecting antithrombin isoform distribution?

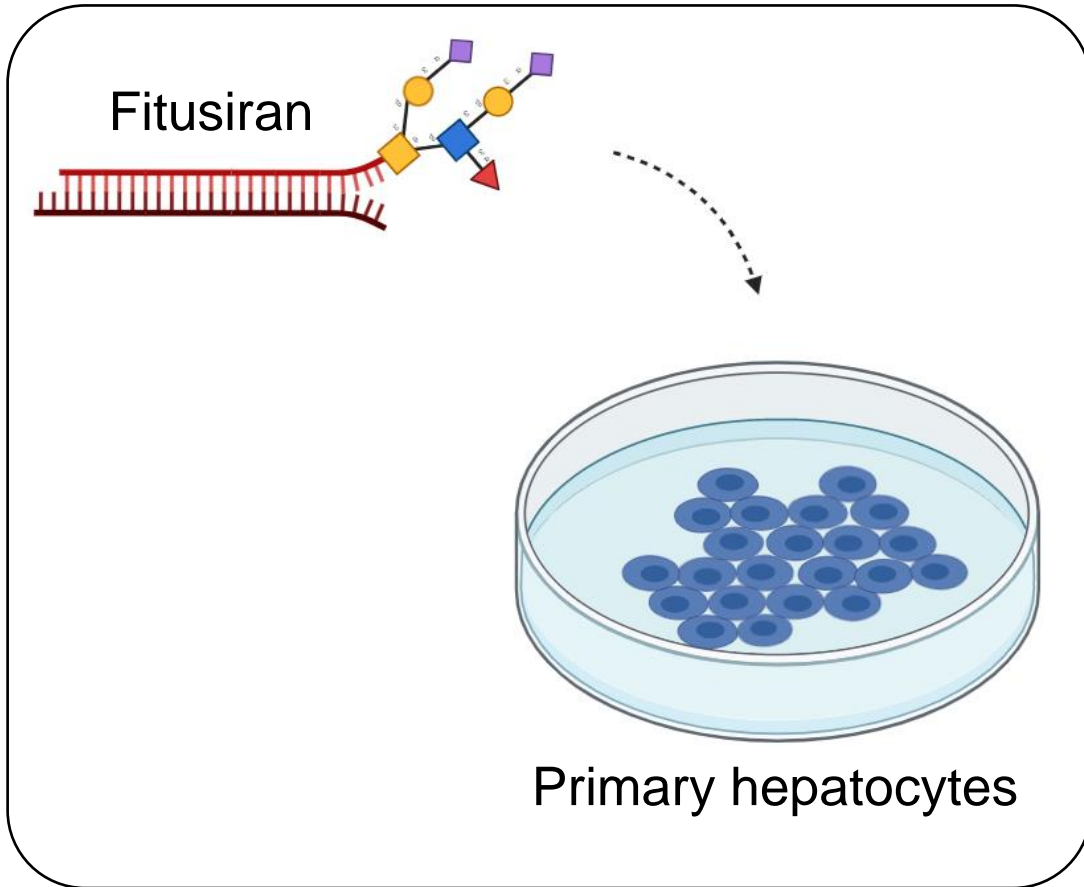
Synthesis of α -AT and β -AT isoforms where more β AT produced ?



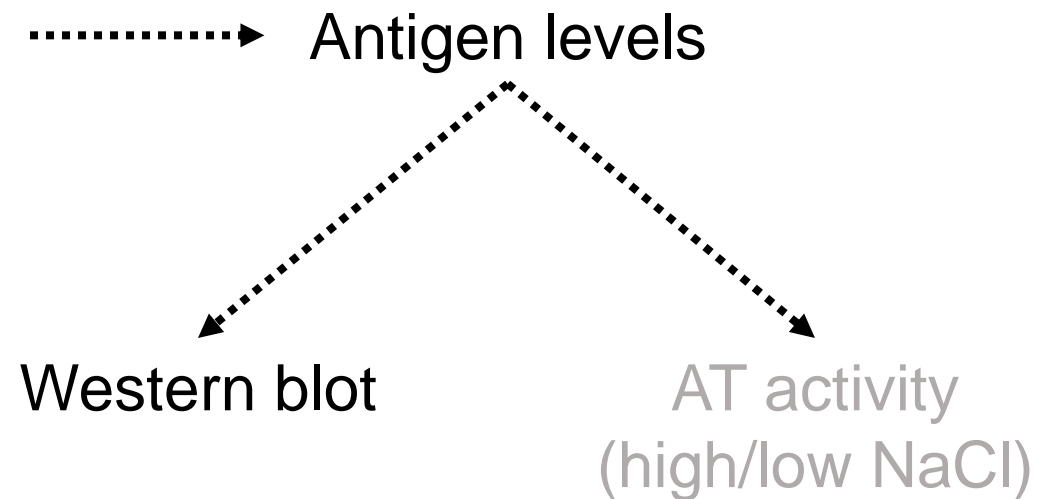
Biodistribution of endothelium-bound (β -AT) and circulating AT (α -AT) is modified ?



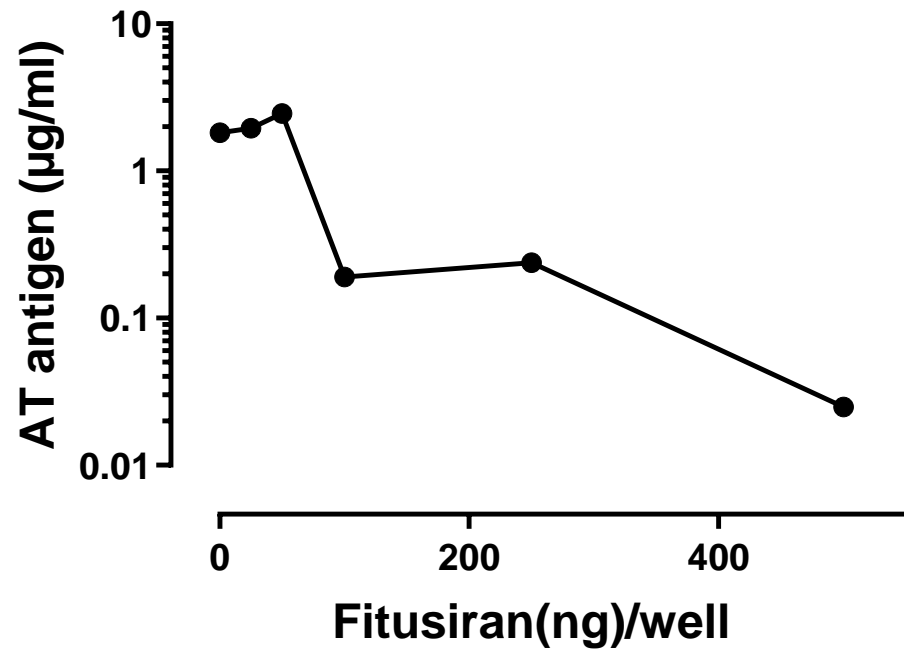
Does fitusiran affect the synthesis of antithrombin isoforms?



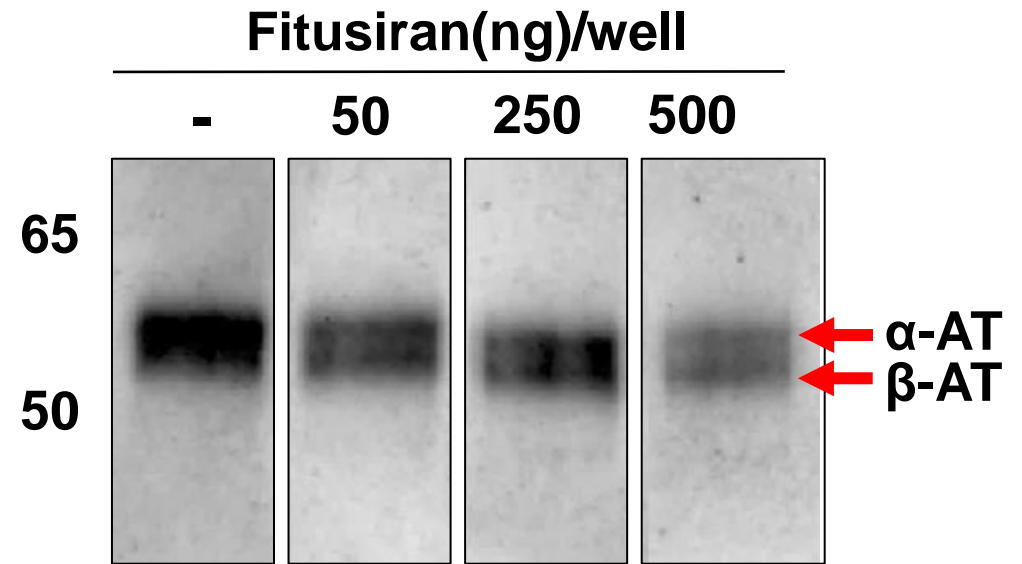
→ Detection of α -AT and β -AT when it is produced from the liver, before they are distributed in circulation



Does fitusiran affect the synthesis of antithrombin isoforms?



Fitusiran dose-dependently decreases antithrombin antigen production



Fitusiran does not affect the synthesis of the α -AT and β -AT isoforms from hepatocytes

Conclusions

- Fitusiran affects the isoforms of antithrombin by increasing the β -AT isoform proportion in circulation
- Fitusiran does not affect the synthesis of antithrombin isoforms
- Could fitusiran affect the biodistribution? Experiments are ongoing

Thank you for your attention!

