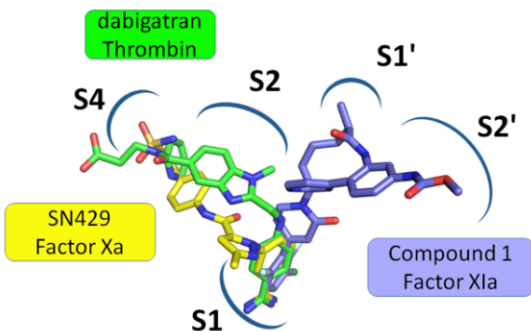
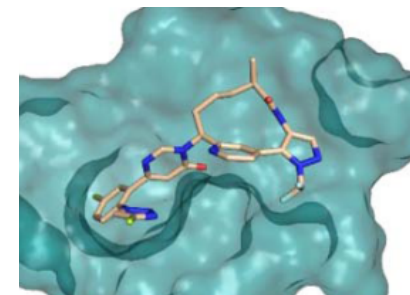
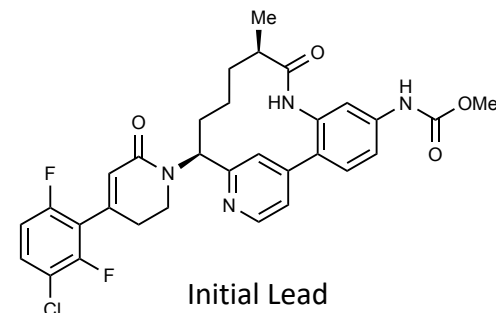


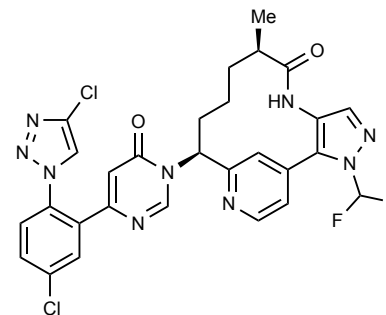
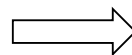
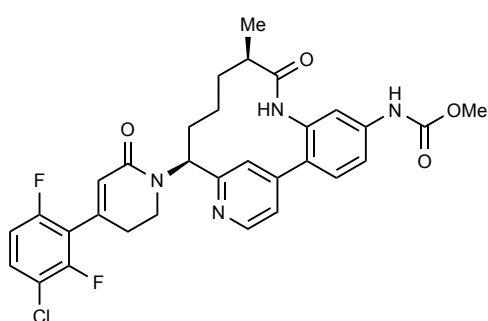
- 17.8 million global deaths due to cardiovascular diseases (CVD) in 2017
 - 21% increase in 10 years
- Blood thinners (anticoagulants) often prescribed to reduce risk of CVD
- Most anticoagulants are associated with increased bleeding
 - Therapeutic targets are often involved in hemostasis
- Hemostasis is the process the body uses to repair injury to blood vessels
- Coagulation Factor XIa is a new target that does not increase bleeding



Thrombin and Factor Xa inhibitors interact at S1 and S2
 Factor XIa inhibitors interact at S1, S1', and S2'
 S2' binding relies on Polar-Polar interaction
 S1' and S2' pocket is much larger, requires larger molecules
Challenge: balance pharmacokinetics (small, less polar)
 with potency (large, more polar)



High affinity for FXIa
 (0.26 nM)
 Poor bioavailability
 (0.7% free fraction
 in plasma)



Lower affinity for FXIa
 (0.87 nM)
 Poor bioavailability
 (7.1% free fraction)
 Better solubility
 100 min. half-life in liver cells

Discovery synthesis:

