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Targeting Factor XII (F12) with a novel delivery platform as a prophylactic treatment for thromboembolism

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#AHA16

Disclosures

- Financial Relationships
  - All Authors are employees and stockholders of Arrowhead Pharmaceuticals

F12 is an attractive target for RNAi therapeutics

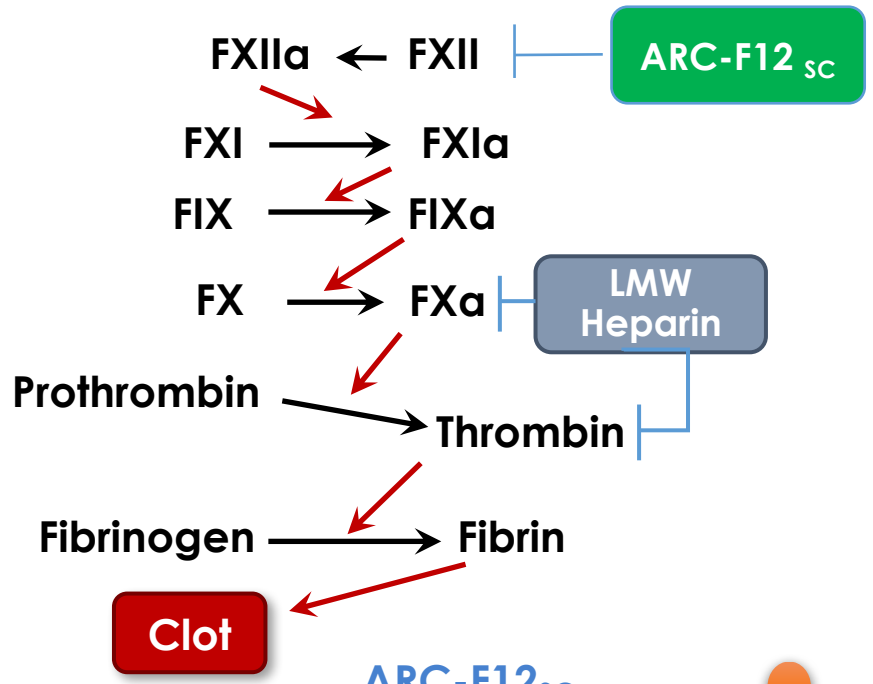
Factor XII (F12)

- Key component of contact activation pathway
- Predominantly expressed in the liver; circulates in blood

F12 inhibition is genetically validated

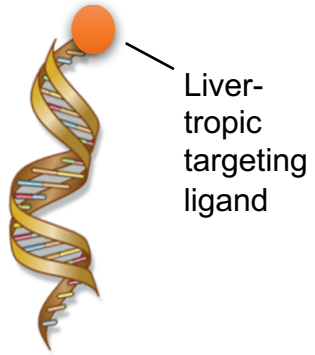
- F12-deficient mice:
  - viable and fertile[4]
  - do not show bleeding defects[4,5]
  - protected from thromboembolic disease (stroke, pulmonary embolism)[5]
- F12 deficiency in humans is *not* associated with either bleeding or thrombotic disorders[1,2,3]

Contact (intrinsic) coagulation cascade



ARC-F12$_{SC}$ RNAi trigger

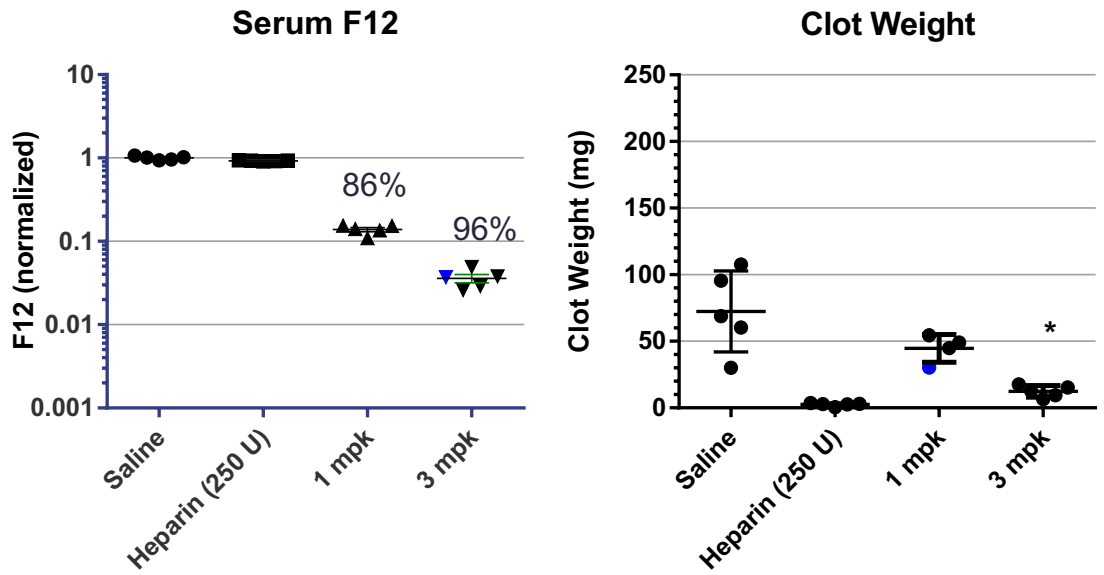
- Short dsRNA targeting F12 mRNA
- Liver-tropic targeting ligand
- Injected subQ



[1] Girolami A. *et al.* (2004) J. Thromb. Thrombolysis 17:139–143
[2] Koster A. *et al.* (1994) Br. J. Haematol. 87:422–424
[3] Zeerleder S. *et al.* (1999) Thromb. Haemost. 82:1240–1246
[4] Pauer, H. U., *et al.* (2004) *Thromb. Haemost.* 92:503
[5] Renne, T. *et al.* (2005) *J. Exp. Med.* 202:271
* Figure modified from Albert-Weissenberger, C., *et al.* (2014) *Front. Cell Neurosci.* 8:345

Rat arterio-venous shunt model – dose responsive

- ***Measure thrombus weight by collection from Tygon tubing shunt***
- ***Single dose ARC-F12$_{sc}$,14 days prior to assessment, n=5/group***

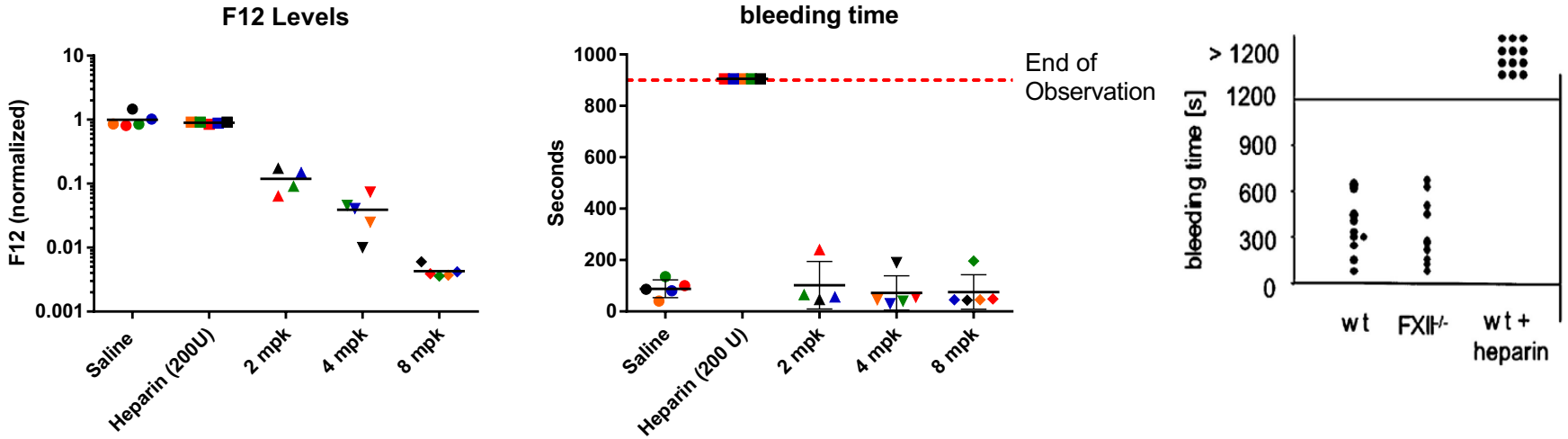


- **Dose response observed for serum F12 levels and thrombus weight**

- **Statistically significant reduction in thrombus weight at >95% F12 knockdown (p=0.002)**

No increase in bleeding risk in mouse model

- ***Transverse cut of tail vein, monitor time to clotting***
- ***Single dose ARC-F12, 7 days prior to assessment, n=5/group***



- **No increased bleeding observed, even with >99% knockdown of F12 levels**

- **Consistent with F12 $^{(-/-)}$ mice showing no increase in bleeding over wild type controls**

Right panel from: Renné T, et al. (2005) J. Exp. Med. 202:271-281

Summary

- **Arrowhead is developing a RNAi-based approach targeting F12 as a prophylactic treatment of thromboembolism**
- **Identified human/NHP/rodent cross-reactive RNAi trigger (ARC-F12$_{sc}$) that gave >95% knockdown of serum F12 levels with good duration of effect after a single subQ injection**
- **Rat arterio-venous shunt model showed statistically significant reduction in thrombus weight after a single injection of ARC-F12$_{sc}$**
- **No prolonged bleeding in ARC-F12 treated mice with up to 99% F12 knockdown**

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