# Hemophilia Program
Unmet Need and Product Opportunity

RNAi to treat hemophilia

- Hemophilias are recessive X-linked monogenic bleeding disorders
  - » Hemophilia A defined by loss of function mutations in Factor VIII
    - – >40,000 Patients in EU/US
  - » Hemophilia B defined by loss of function mutations in Factor IX
    - – ~9,500 Patients in EU/US
- Hemophilia A "inhibitor" patients define segment of highest unmet need and cost*
  - » ~1/3 Patients with severe hemophilia A
  - » >6 Bleeds/patient/year
  - » >5 in-hospital days/patient/year
  - » >$300,000/patient/year
  - » Very poor quality of life
- Only available therapies: rFVIIa (NovoSeven™) and FEIBA
  - » Short half-life, requiring frequent dosing
  - » Not optimally effective
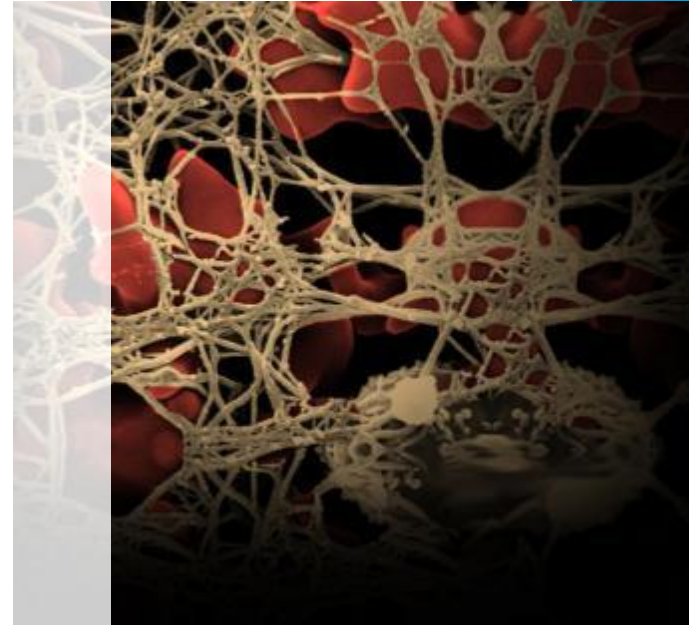
*Gringeri *et al., Blood* 2003

Alnylam
PHARMACEUTICALS

Protein C Target and ALN-APC Program

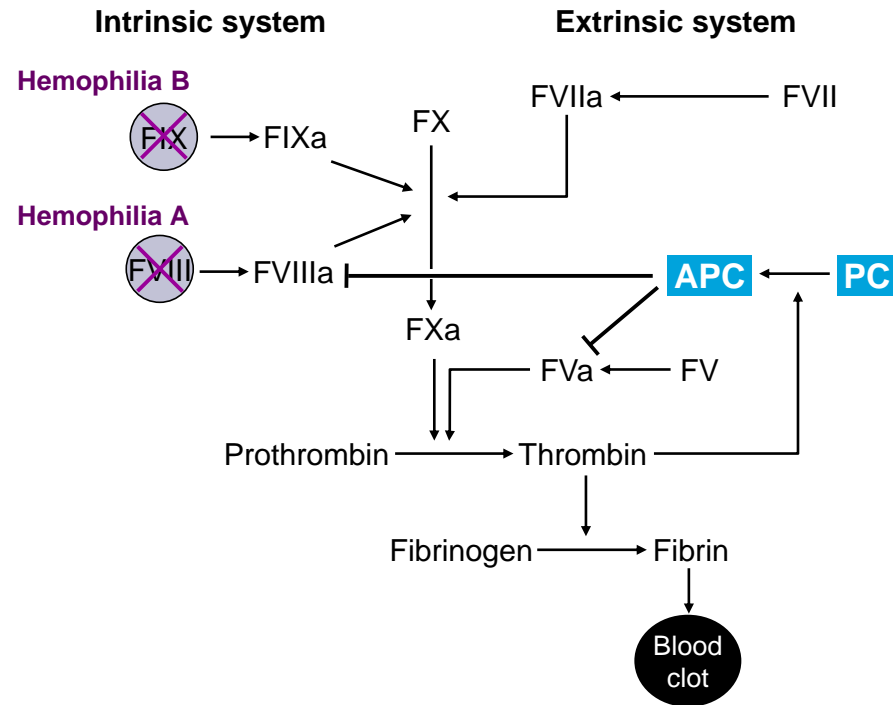## Protein C (PC) is genetically defined target

- Activated Protein C (APC) defines key natural anticoagulant pathway
  - » Inactivates factors Va and VIIIa
  - » Attenuates thrombin generation
- Heterozygous PC deficiency associated with increased thrombin generation
- Expressed in liver; circulates in plasma

APC Resistance (i.e., Factor V_{Leiden})

- Co-inheritance associated with milder bleeding in hemophilia patients

	No Co-Inheritance	With Co-Inheritance
First bleed age (range)	0.9 (0.1– 4.0)	1.5 (0.5 – 7.1)
Annual bleeding frequency (range)	6.0 (0 – 30)	1.8 (0 – 7)

Intrinsic system   **Extrinsic system**

Hemophilia B

Hemophilia A

FIX → FIXa   FX   FVIIa ← FVII

FVIII → FVIIIa ⊣   APC ← PC

FXa

FVa ← FV

Prothrombin → Thrombin

Fibrinogen → Fibrin

Blood clot

ALN-APC in R2D

- siRNA optimization
- *In vivo* efficacy in pre-clinical animal models
- IND Filing 2013

Kurnik *et al.*, Hematologica, 2007