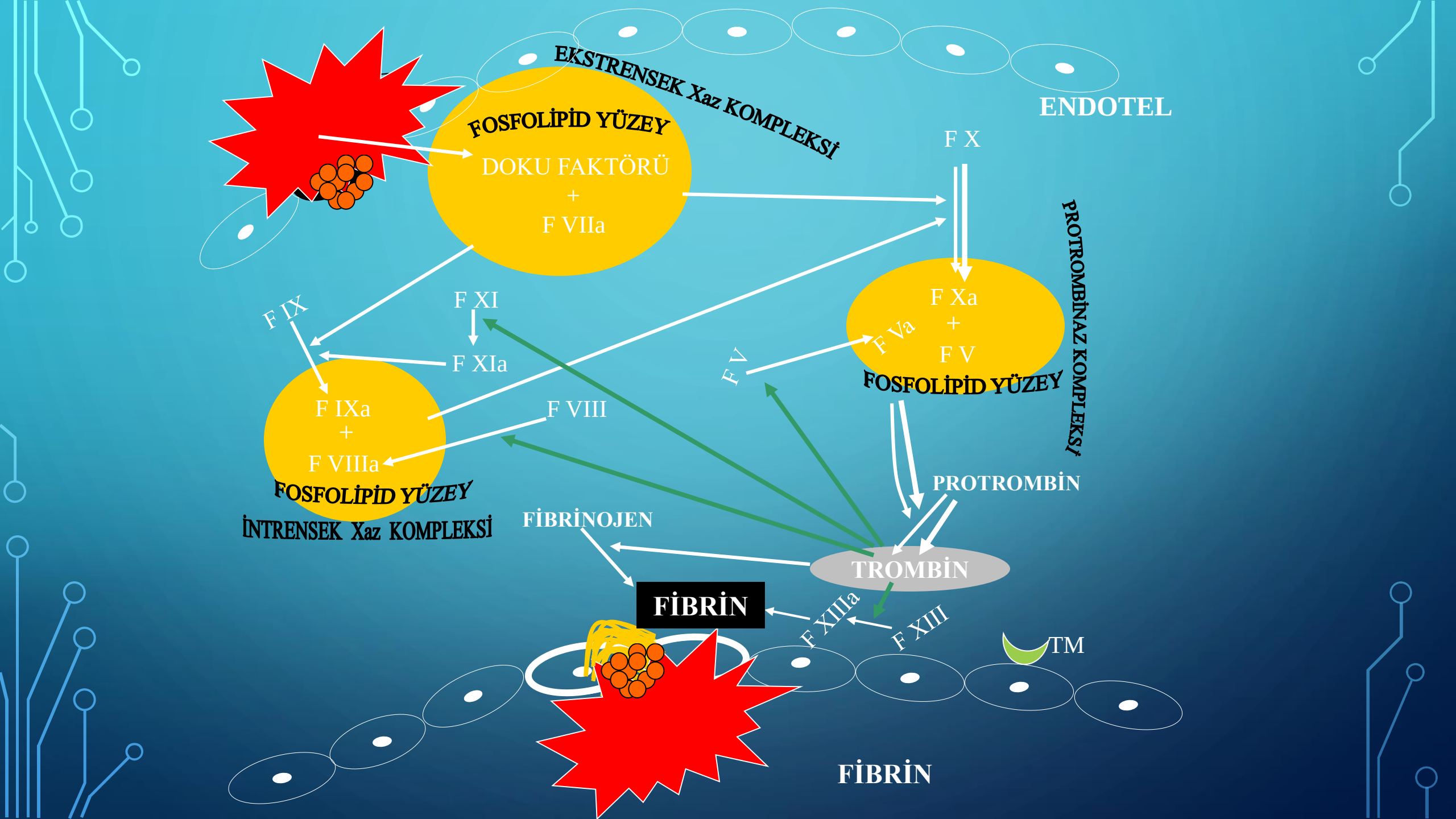
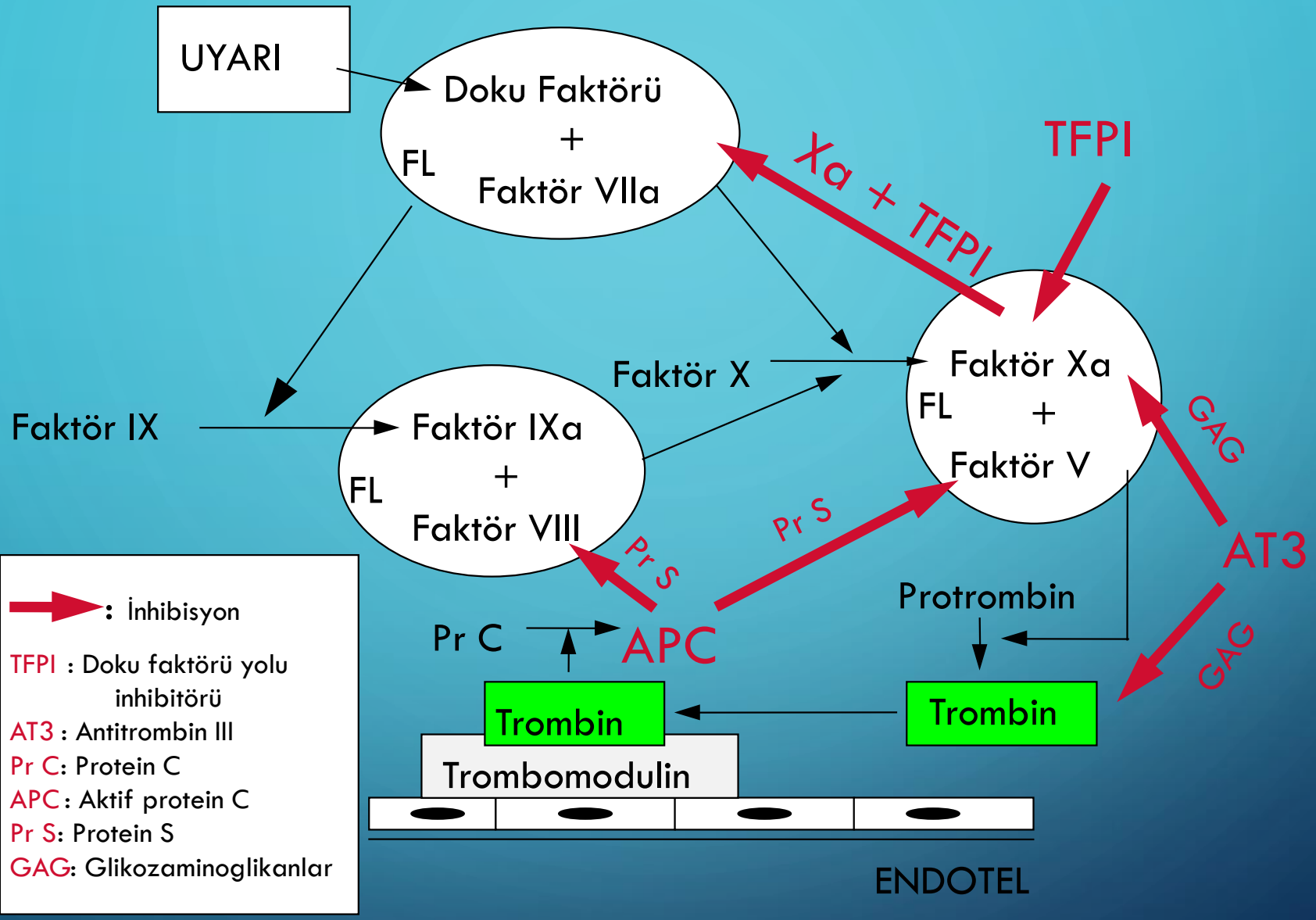
# HEMOFİLİDE YENİ TEDAVİ YAKLAŞIMLARI

PROF. DR. SALİH AKSU

HACETTEPE ÜNİVERSİTEİ

ERİŞKİN HEMATOLOJİ BL.


EKSTRENSEK Xaz KOMPLEKSİ
FOSFOLİPİD YÜZEY
DOKU FAKTÖRÜ
+
F VIIa
ENDOTEL
F X
F IX
F XI
F XIa
F IXa
+
F VIIIa
FOSFOLİPİD YÜZEY
İNTRENSEK Xaz KOMPLEKSİ
F VIII
F V
F Va
F Xa
+
F V
FOSFOLİPİD YÜZEY
PROTROMBİNAZ KOMPLEKSİ
PROTROMBİN
FİBRİNOJEN
TROMBİN
FİBRİN
F XIIIa
F XIII
TM
FİBRİN




Şekil. Doğal antikoagülanlar ve etki mekanizmaları

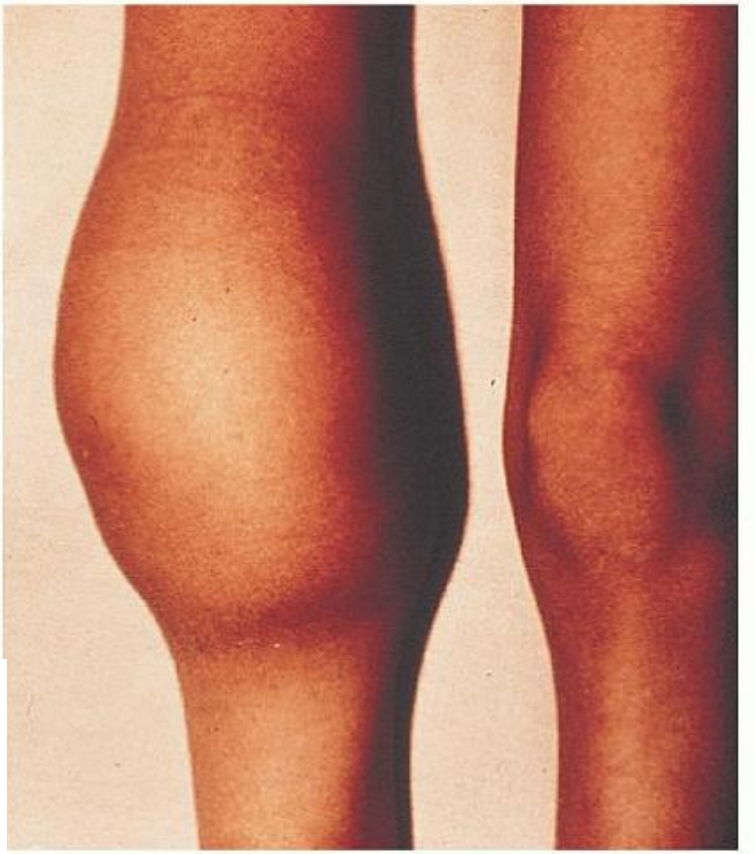
# HEMOFİLİ

- Eski Mısır'da tarif edilmiş
- 1940 tarihinde laboratuvar tanısı
- Kraliçe Victoria'nın kızları ile Avrupa kraliyet ailesinde olgular(özellikle Rus kraliyet ailesinde;Rasputin gibi büyücü sihirbazlar)
- Kan bankacılığındaki tekniklerin gelişmesi ile plazmada bir faktörün eksik olduğu anlaşıldı
- Taze donmuş plazma tedavisi(sıvı yüklenmesi)
- Cryoprecipitate(1960)
- FVIII konsantreleri

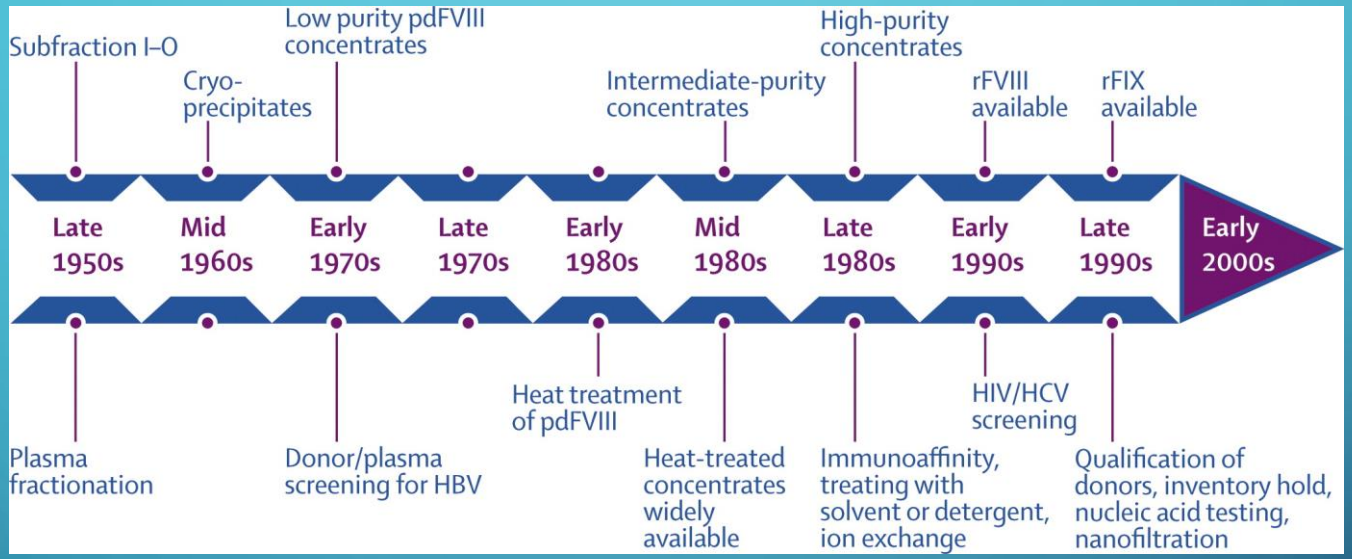







# Figure

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# KARŞILANMAMIŞ İHTİYAÇLAR

- 1940 öncesi: Kanamayı durdurma
- 1950 öncesi: Yüksek volüm
- 1980 öncesi: İnfeksiyonlar
- 1999 öncesi: İnhibitörlü hastalar
- 2005 öncesi: Hemofili morbiditeleri (Eklem vs.)
- 2017 öncesi:
  - Damar yolu
  - Kısa faktör yarı ömrü
  - Proflaksiye rağmen kanama

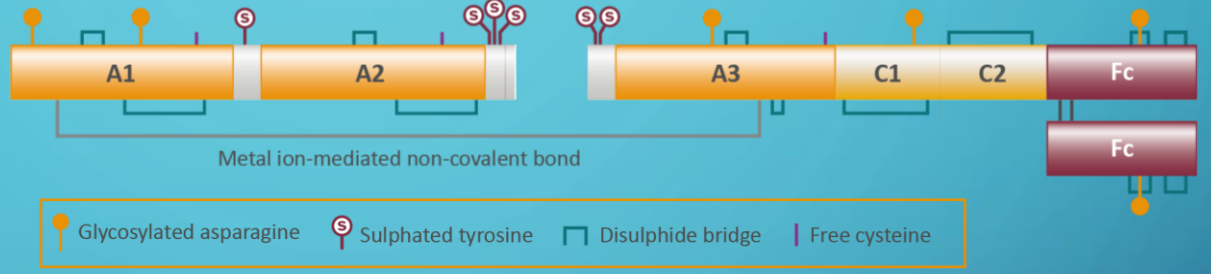
**Table 1: Novel Therapeutics for Hemophilia**

| Product | Mechanism | Advantages | | | Limitations | | | Status |
|---|---|---|---|---|---|---|---|---|
| | | Dosing Frequency | Route | Relative ease of compliance | Immuno-genicity | Monitoring | Study pop-ulation | |
| **EHL-rFVIII** | | | | | | | | |
| Efmoroctocog alfa (BDD-rFVIII-Fc, Eloctate)[7] | IgG1-Fc fusion | every 3-5 days | IV | Low | 3% NNA | Standard | PTP | Approved |
| Rurioctacog alfa pegol (BAX 855, Adynovate)[8] | 20 kDa site specific pegylation, | twice weekly | IV | Low | 4% NNA | Standard | PTP | Approved |
| BAY 94-9027[4] | 40 kDa site specific pegylation, | every 3-7 days | IV | Low | 3% NNA 0.6% anti-PEG | Chromogenic* | PTP | Phase 3 |
| Turoctocog alfa pegol (N8-GP)[5] | 60 kDa site specific pegylation, | every 4 days | IV | Low | 0.6% NNA 0.6% NAb[∞] | TBD | PTP | Phase 3 |
| **EHL-rFIX** | | | | | | | | |
| rFIX-Fc (Alprolix)[9] | IgG1-Fc fusion | every 7-10 days | IV | Medium | 0.8% NNA | Standard* | PTP | Approved |
| rFIX-FP (Idelvion)[10] | Albumin fusion | Weekly to bimonthly | IV | Medium | 0% NNA | Standard* | PTP | Approved |
| Nonacog beta pegol (N9-GP, Rebinyn)[13] | 40 kDa site specific pegylation, | weekly | IV | Medium | 4% NNA | Chromogenic* | On demand only in USA | Approved |
| **Non-Factor Therapies** | | | | | | | | |
| Emicizumab[30-32] | Bispecific antibody FVIIIa-mimetic | Weekly | SQ | Medium | 3% NNA | TBD | HA with inhibitor | Phase 3 |
| Fitusiran[36,37] | AT siRNA | Weekly to monthly | SQ | Medium | 4% NNA | TBD | HA/HB without inhibitor | Phase 1/2 |
| Concizumab[39] | TFPI monoclonal antibody | TBD | IV/SQ | TBD | 0% | TBD | HA/HB without inhibitor | Phase 1/2 |
| **Gene Therapy** | | | | | | | | |
| SPK-9001[60] AMT-060[57] BMN270[58] | Endogenous expression with AAV vectors | Vector dependent | IV | High | 0% | Standard | HA/HB without inhibitor; no NAb to vector | Phase 1/2 |

[∞]One patient developed inhibitor (initially low titer then high at 13.5 BU) after 93 exposure days to N8-GP in Phase III trial. *Differing results may be obtained with specific aPTT reagents, for detailed information on performance of standard vs chromogenic assays with these products, see Kitchen et al.[76] *Abbreviations: HA*, hemophilia A; *HB*, hemophilia B, NAb, neutralizing antibodies; *NNA*, non-neutralizing antibodies; *TBD*, to be determined; *PTP*, previously treated patients.

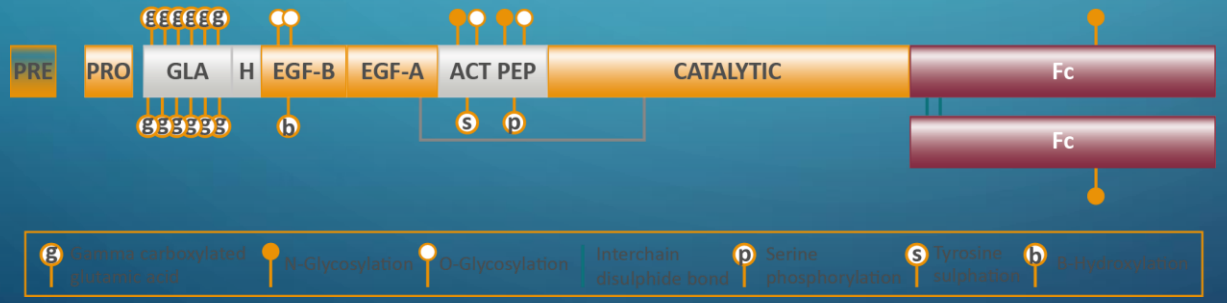
# FC FÜZYON TEKNOLOJİSİ

- rFVIIIFc bir BDD FVIII molekülünün Insan IG1 in Fc domainine ara bağlayıcı olmadan kovalent bağlanması ile oluşan rekombinant bir proteindir.[1-3]




rFVIIIFc 'nin biyokimyasal ve fonksiyonel karakteristikleri

- rFIXFc bir FIX molekülünün Insan IG1 in Fc domainine ara bağlayıcı olmadan kovalent bağlanması ile oluşan rekombinant bir proteindir[3-5]




rFIXFc' nin biyokimyasal ve fonksiyonel karakteristikleri

I. IgG domain'ne doğal Fc'nin ko

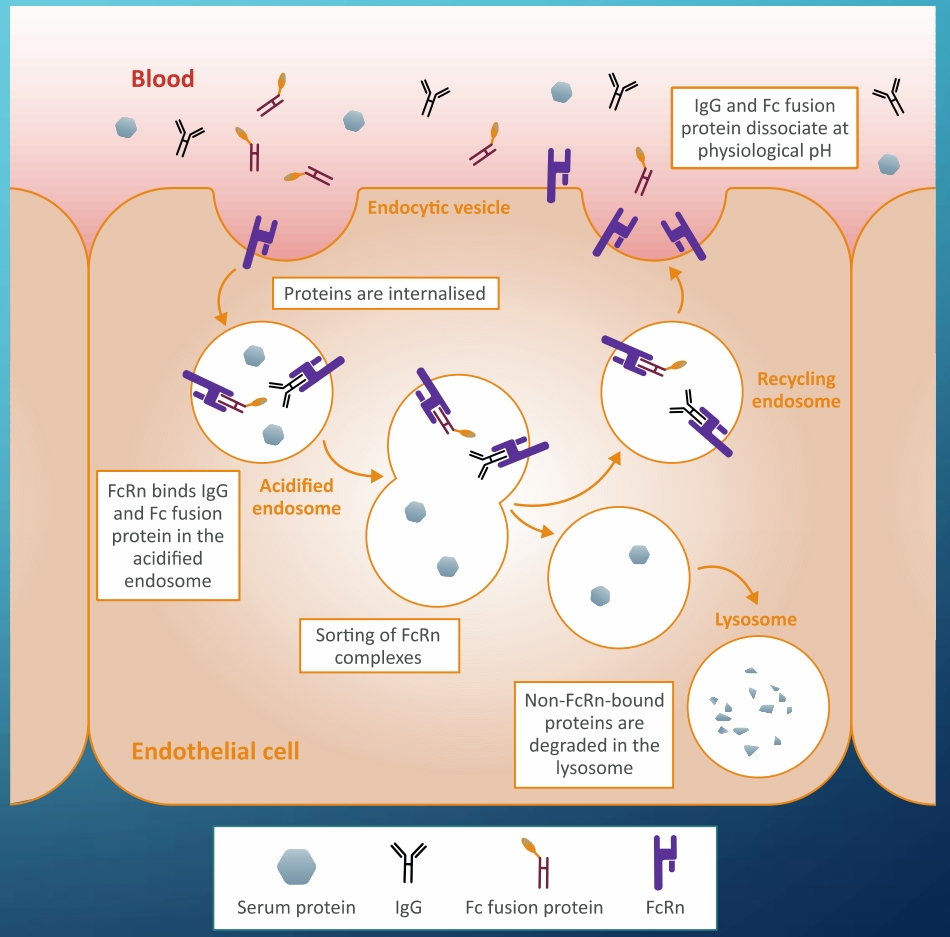


**1.** PETERS ET AL. *J THROMB HAEMOST* 2013 **2.** DUMONT ET AL. *BLOOD* 2012 **3.** ADAPTED FROM JAYANDHARAN & SRIVASTAVA. *J GENET SYNDR GENE THER* 2011 **4.** PETERS ET AL. *BLOOD* 2010 **5.** SHAPIRO ET AL. *BLOOD* 2012

# FC FÜZYON TEKNOLOJİSİ

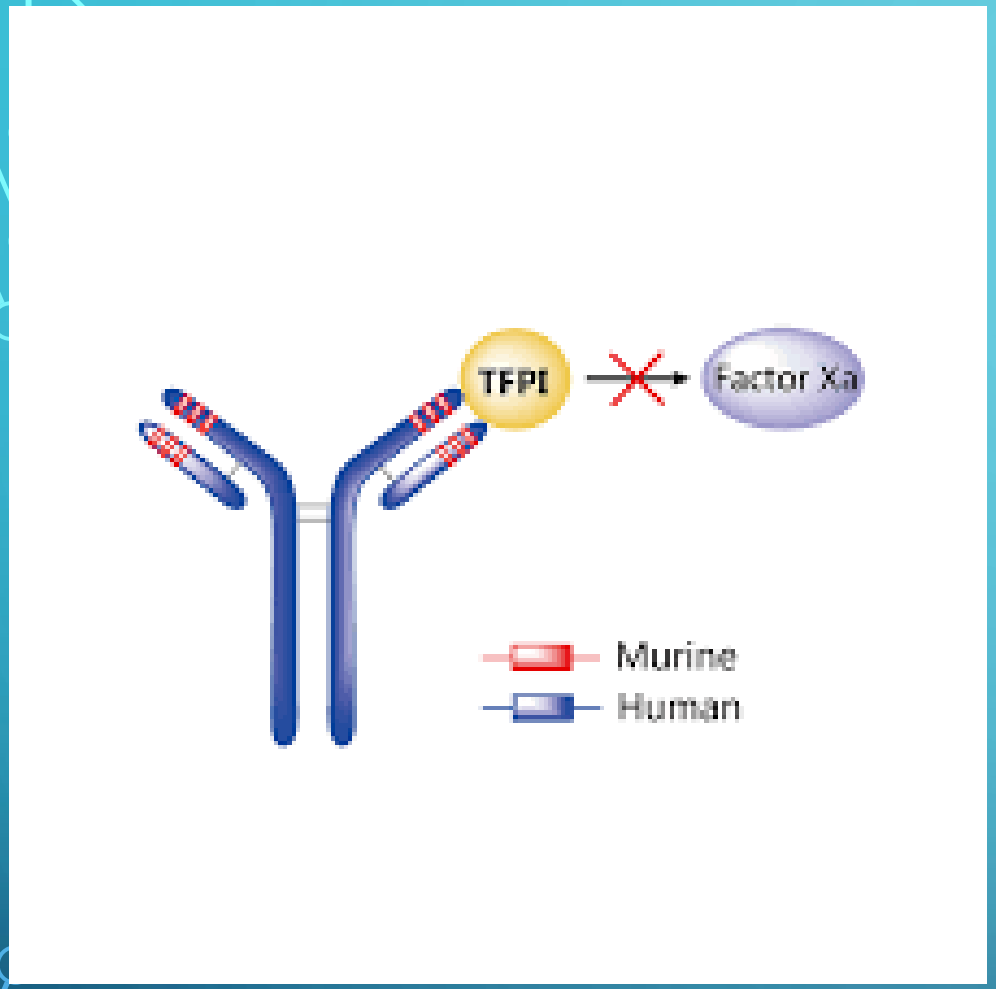
II. FVIII ve FIX' un yarılanma ömrünü uzatmak için doğal bir yol kullanılmıştır.

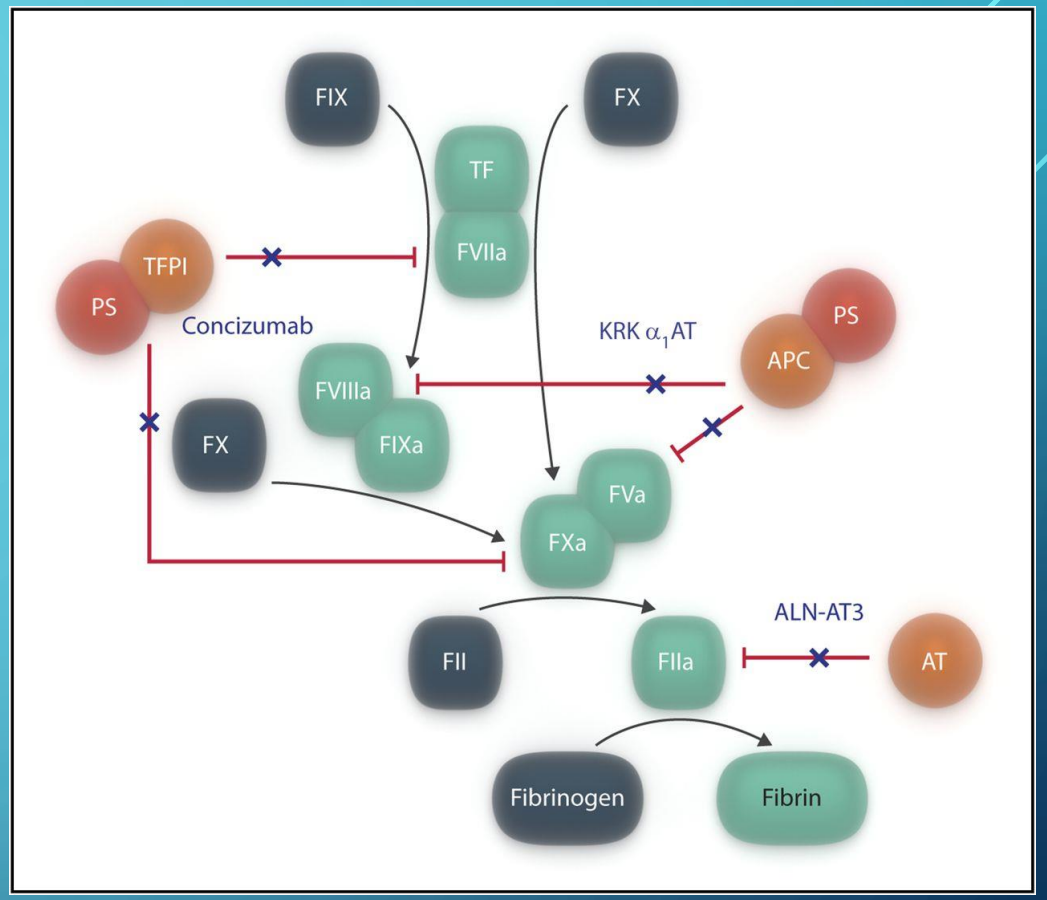
- Yenidoğan Fc reseptörü (FcRn), IgG ve Fc içeren proteinlerin lizozomal yıkımlarını geciktirerek dolaşımdaki yarılanma ömrünün uzamasından sorumludur[1,2]
- FcRn, rFVIIIFc bağlanarak dolaşıma geri dönmelerini sağlar [3-6]

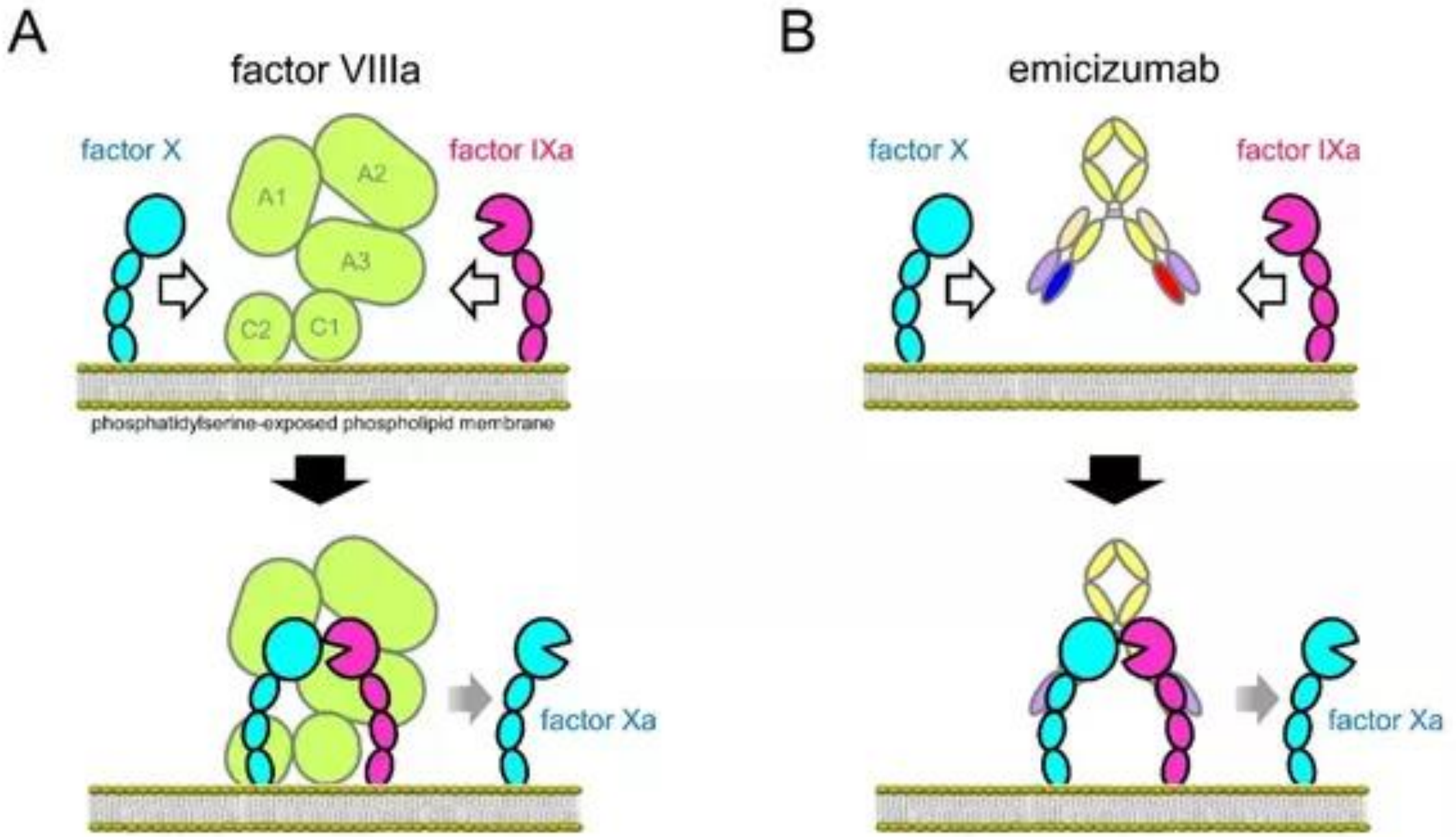


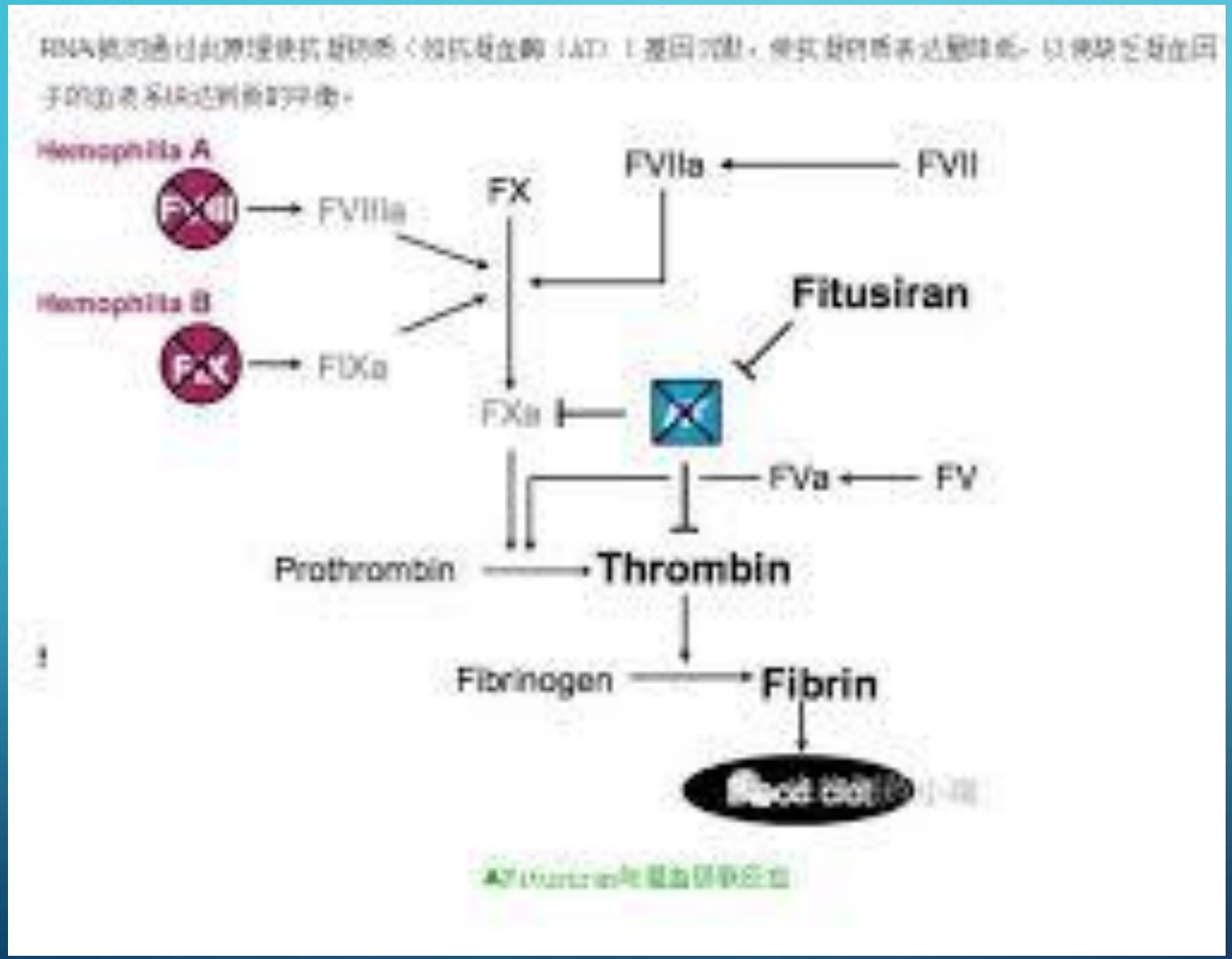


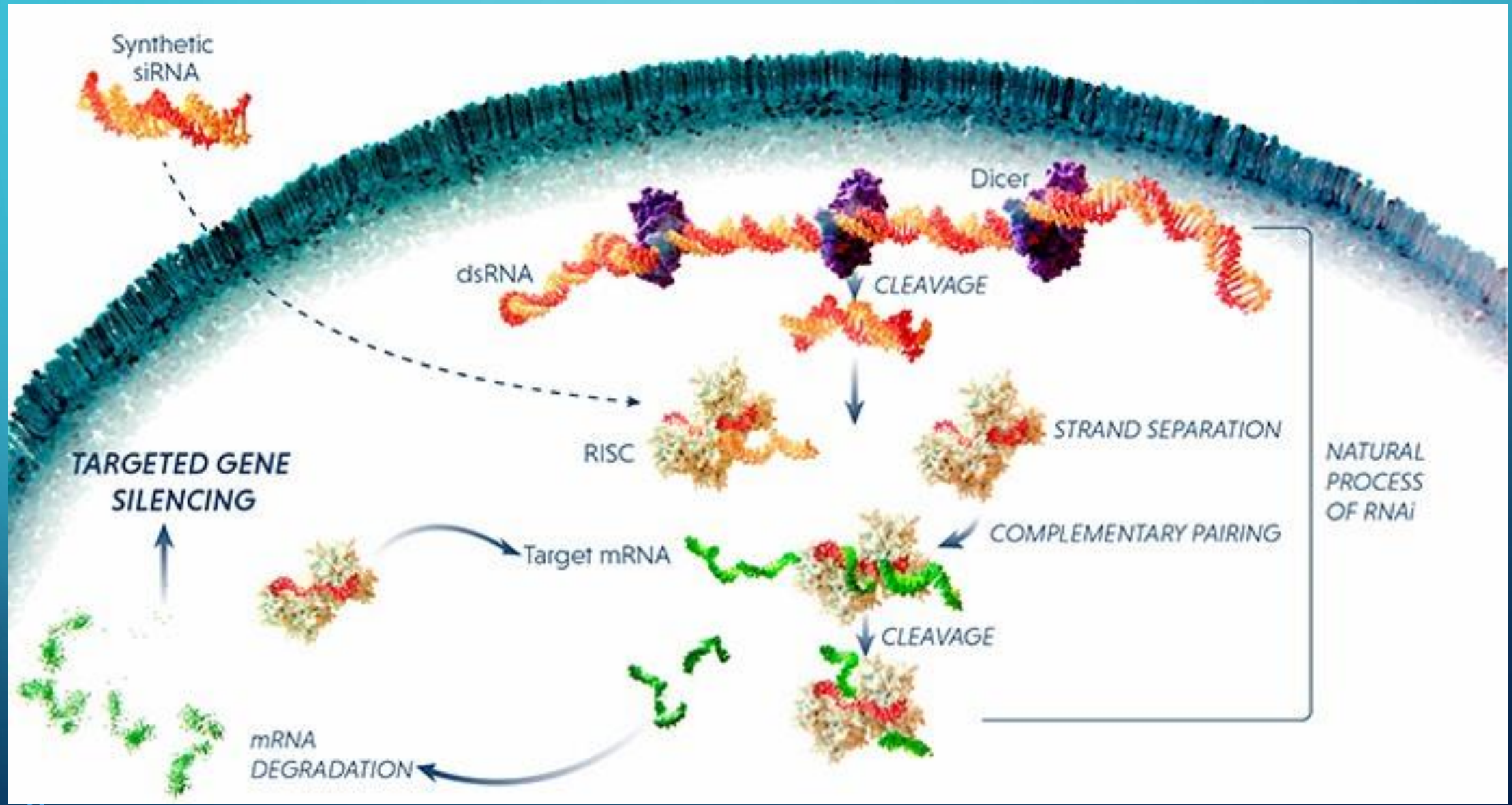

**1.** ADAPTED FROM ROOPENIAN & AKILESH. *NAT REV IMMUNOL* 2007 **2.** ADAPTED FROM SHAPIRO. *EXPERT OPIN BIOL THER* 2013 **3.** PETERS ET AL. *J THROMB HAEMOST* 2013 **4.** DUMONT ET AL. *BLOOD* 2012
**5.** PETERS ET AL. *BLOOD* 2010 **6.** SHAPIRO ET AL. *BLOOD* 2012

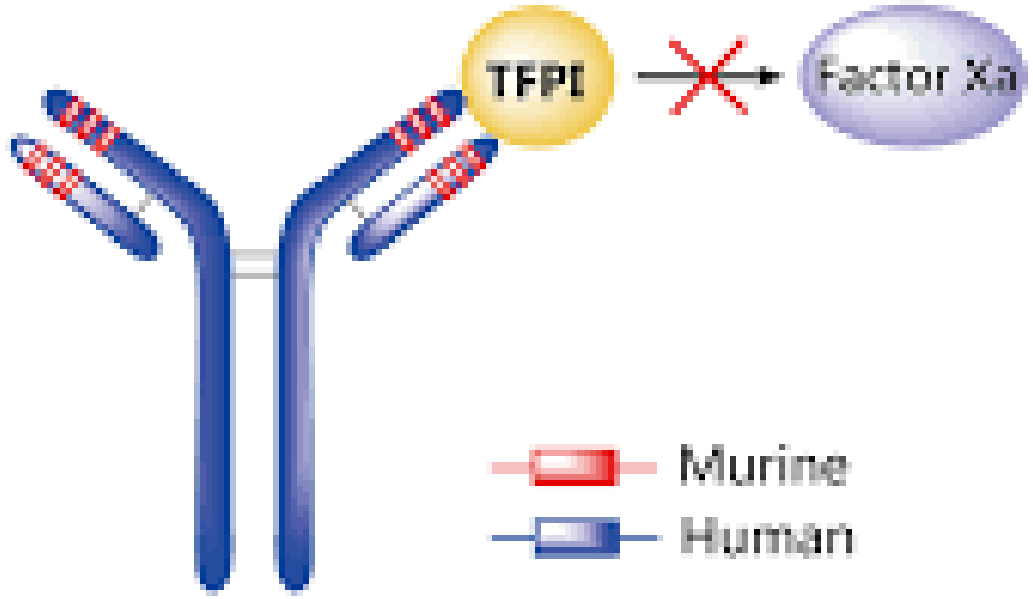

TFPI
Factor Xa
Murine
Human

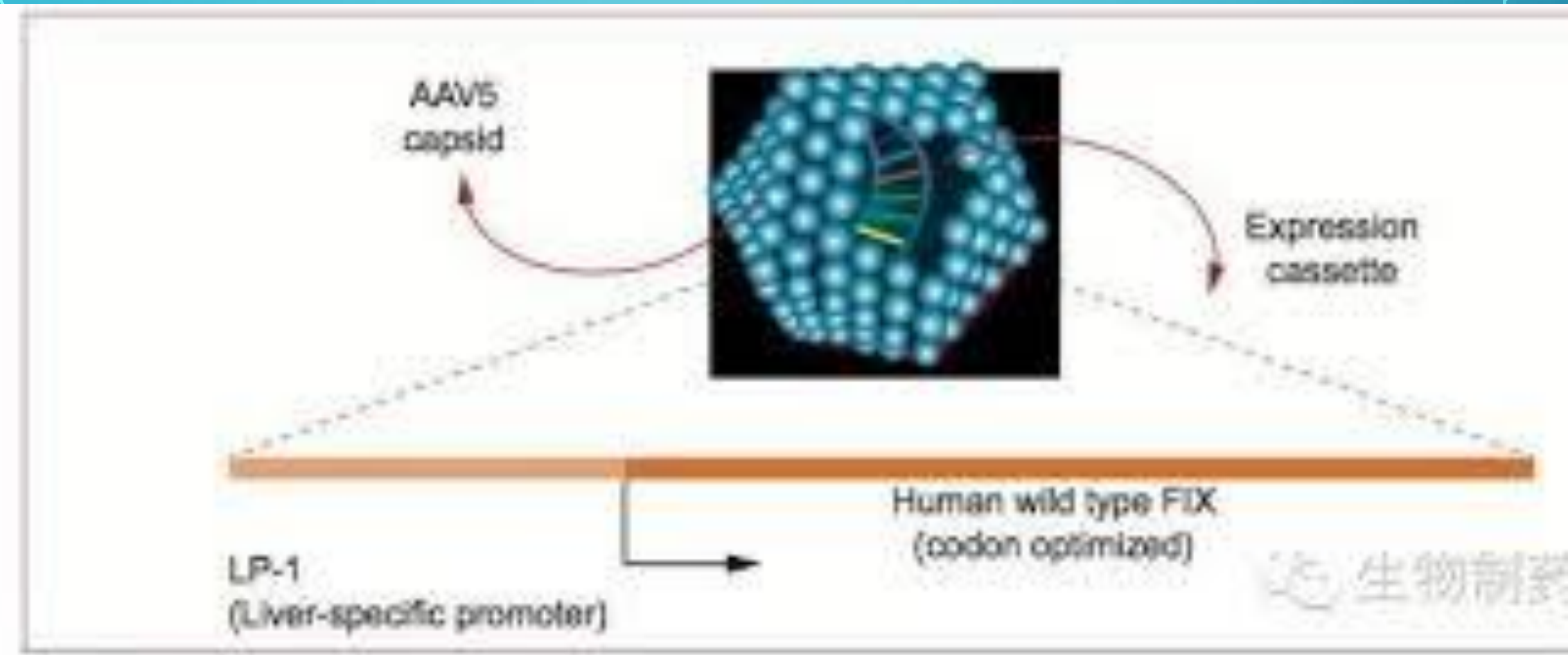

FIX
FX
TF
FVIIa
TFPI
PS
Concizumab
KRK $\alpha_1$AT
PS
APC
FVIIIa
FIXa
FX
FVa
FXa
ALN-AT3
FII
FIIa
AT
Fibrinogen
Fibrin


A
factor VIIIa
factor X
A1
A2
A3
C2
C1
factor IXa
phosphatidylserine-exposed phospholipid membrane
factor Xa
B
emicizumab
factor X
factor IXa
factor Xa


Hemophilia A
FVIII
FVIIIa
Hemophilia B
FIX
FIXa
FX
FVIIa
FVII
Fitusiran
FXa
FVa
FV
Prothrombin
Thrombin
Fibrinogen
Fibrin


Synthetic
siRNA
Dicer
dsRNA
CLEAVAGE
RISC
STRAND SEPARATION
NATURAL
PROCESS
OF RNAi
TARGETED GENE
SILENCING
Target mRNA
COMPLEMENTARY PAIRING
CLEAVAGE
mRNA
DEGRADATION


TFPI
Factor Xa
Murine
Human


AAV5
capsid
Expression
cassette
Human wild type FIX
(codon optimized)
LP-1
(Liver-specific promoter)

# The End!

Sabırla dinlediğiniz için teşekkür ederim.