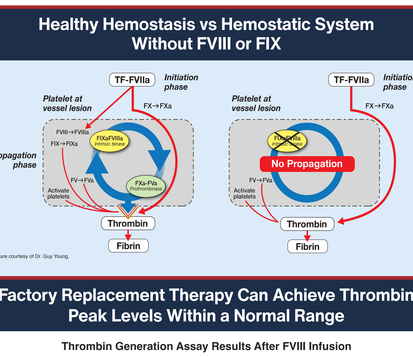
Hemostasis in Hemophilia

Mechanisms of Disease and Rationale for New Therapies

Hemophilia, Physiologic Coagulation, and Hemostasis

Hemophilia A and hemophilia B are the result of deficiencies in FVIII or FIX, respectively. These deficiencies prevent propagation of the coagulation cascade, ultimately resulting in a failure to develop meaningful amounts of thrombin and fibrin and a related inability to clot.



Healthy Hemostasis vs Hemostatic System Without FVIII or FIX

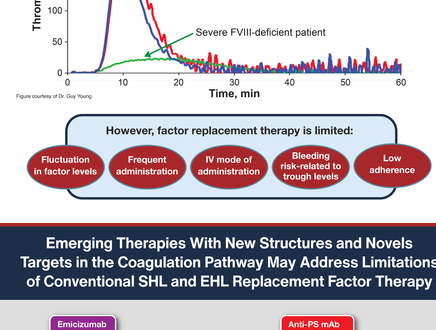


Figure courtesy of Dr. Guy Young.

Factory Replacement Therapy Can Achieve Thrombin Peak Levels Within a Normal Range

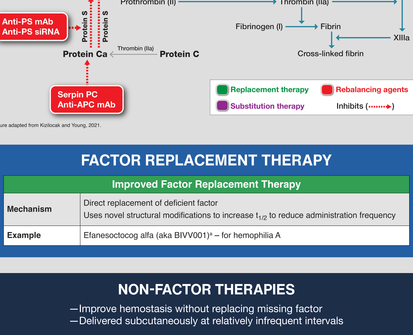


Figure courtesy of Dr. Guy Young.

However, factor replacement therapy is limited:

- Fluctuation in factor levels
- Frequent administration
- IV mode of administration
- Bleeding risk related to trough levels
- Low adherence

Emerging Therapies With New Structures and Novels Targets in the Coagulation Pathway May Address Limitations of Conventional SHL and EHL Replacement Factor Therapy

Figure adapted from Kizlocak and Young, 2021.

FACTOR REPLACEMENT THERAPY

Improved Factor Replacement Therapy	
Mechanism	Direct replacement of deficient factor Uses novel structural modifications to increase $t_{1/2}$ to reduce administration frequency
Example	Efanesoctocog alfa (aka BIVV001)[a] – for hemophilia A

NON-FACTOR THERAPIES

—Improve hemostasis without replacing missing factor
—Delivered subcutaneously at relatively infrequent intervals

Substitution Therapies	
Mechanism	Act as an FVIII mimetic, serving to facilitate the interaction between FX and FIXa convert FX to FXa
Select Examples	Emicuzmab and Mim8[a] • Bispecific antibodies that simultaneously bind FX and FIXa

Rebalancing Agents	
Mechanism	Inhibit coagulation inhibitors to restore the balance of procoagulation and anticoagulation
Select Examples	Fitusiran[a] • Antithrombin inhibitor for hemophilia A and hemophilia B Concizumab[a] and marstacimab[a] • TFPI inhibitors for hemophilia A and hemophilia B

[a]Entity is investigational as of 10/21/2022.

Conclusions

Factor replacement therapy targets the pathological coagulation deficiency in hemophilia A and B, but is limited by administration challenges and relatively short half-lives

Novel factor replacement therapies with structural features that improve half-life may address limitations of available SHL and EHL therapies

Non-factor therapies, including rebalancing agents and substitution therapies, target other components of the coagulation pathway in attempts to restore hemostasis

Gene therapies are also in phase 3 trials

References

Callaghan MU, et al. *Blood*. 2021;137:2231-2242.
Dargaud Y, et al. *Thromb Res*. 2012;130:929-934
Kizilocak H, Young G. *Expert Opin Emerg Drugs*. 2021;26:337-350.
Konkle BA, et al. *N Engl J Med*. 2020;383:1018-1027
Ostergaard H, et al. *Blood*. 2011;138:1258-1268
Pasi KJ, et al. *Haemophilia*. 2020;26(suppl 4):154.
Shima M, et al. *N Engl J Med*. 2016;374:2044-2053.
Thornberg CD, et al. *Hemophilia*. 2012;18:568-574.

Abbreviations

APC: activated PC
AT: antithrombin
EHL: extended half-life
FII: factor II
FIX/FIXa: factor IX/activated FIX
FVIII/FVIIIa: factor VIII/activated FVIII
FVIIa: activated factor VII
FX/FXa: factor X/activated FX
FV/FVa: factor V/activated FV
IV: intravenous
mAb: monoclonal antibody
PC: protein C
PS: protein S
SHL: standard half-life
siRNA: small-interfering RNA
$t_{1/2}$: half-life
TF-FVIIa: tissue factor-factor FVIIa complex
TFPI: tissue factor pathway inhibitor