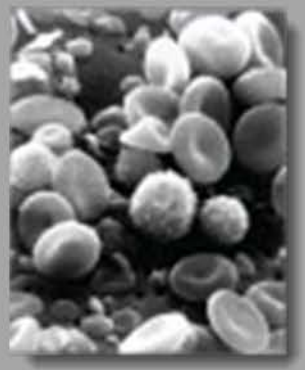


12th Annual Canadian Blood Services International Symposium

Plasma: Transfuse it, Fractionate it or Forget it?

Canadian Blood Services
it's in you to give

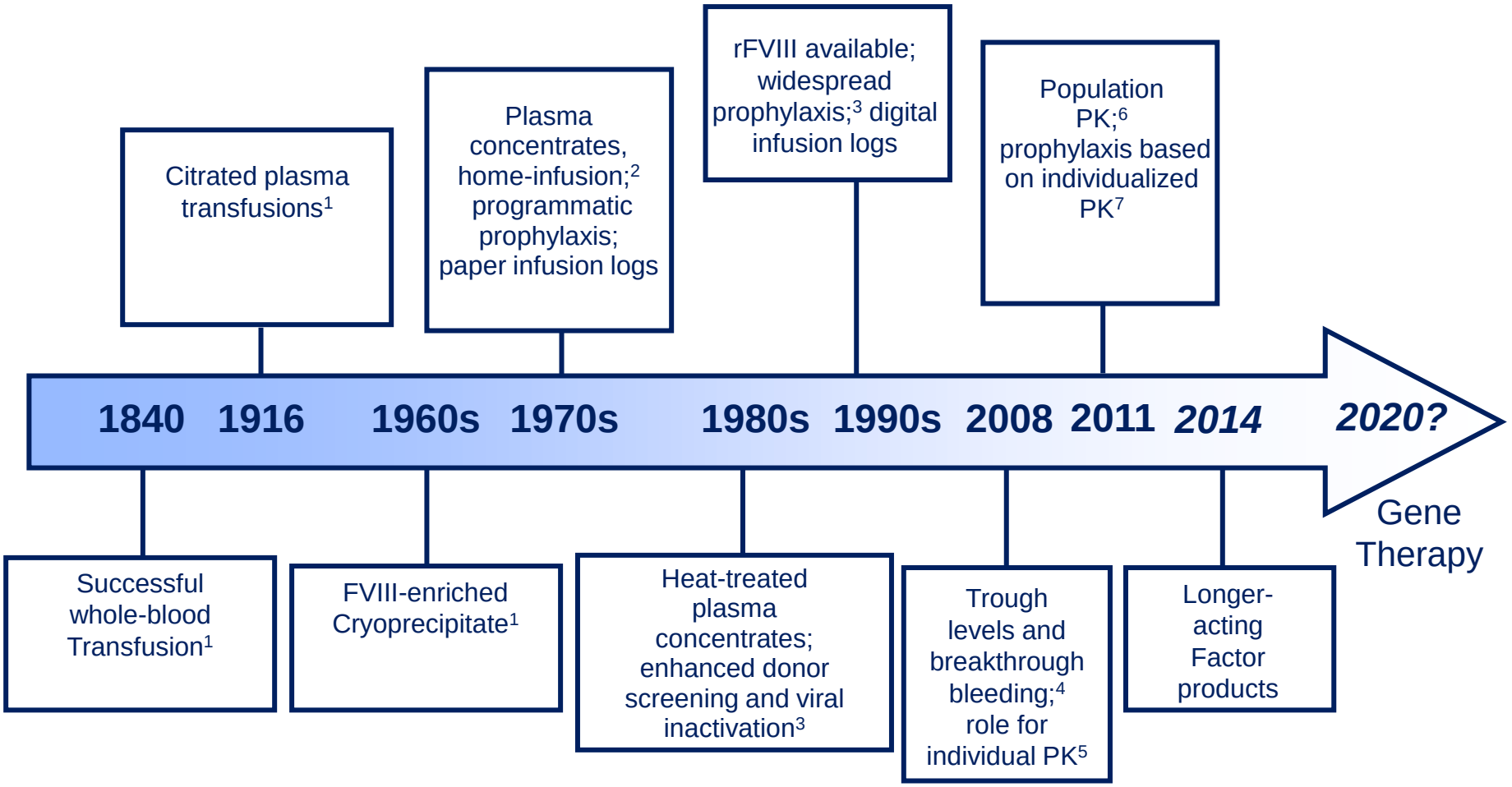
The Arrival of Longer Lasting Recombinant Products for Hemophilia

Steven Pipe, MD
University of Michigan
Ann Arbor, MI

Disclosures for: Steven Pipe

Conflict	Disclosure - if conflict of interest exists
Research Support	Pfizer
Director, Officer, Employee	ATHN
Shareholder	
Honoraria	Bayer
Advisory Committee	Blood Products Advisory Committee (FDA)
Consultant	Baxter, Novo Nordisk, CSL Behring, Pfizer
	Biogen Idec

Evolution of Hemophilia Care



1. ABB. Available at: http://www.aabb.org/resources/bct/Pages/highlights.aspx; 2. National Hemophilia Foundation. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=178&contentid=6. 3. Hemophilia-information.com. Available at: http://www.hemophilia-information.com/history-of-hemophilia.html; accessed May 17, 2013. 4. Collins et al. *J Thromb Haemost.* 2009;7(3):413-420. 5. Collins et al. *J Thromb Haemost.* 2010;8(2):269-275. 6. Bjorkman et al. *Blood.* 2012;119(2):612-618. 7. Valentino et al. *J Thromb Haemost.* 2012;10(3):359-367.

Contributors to increased life expectancy, reduced morbidity, and improved QoL in hemophilia

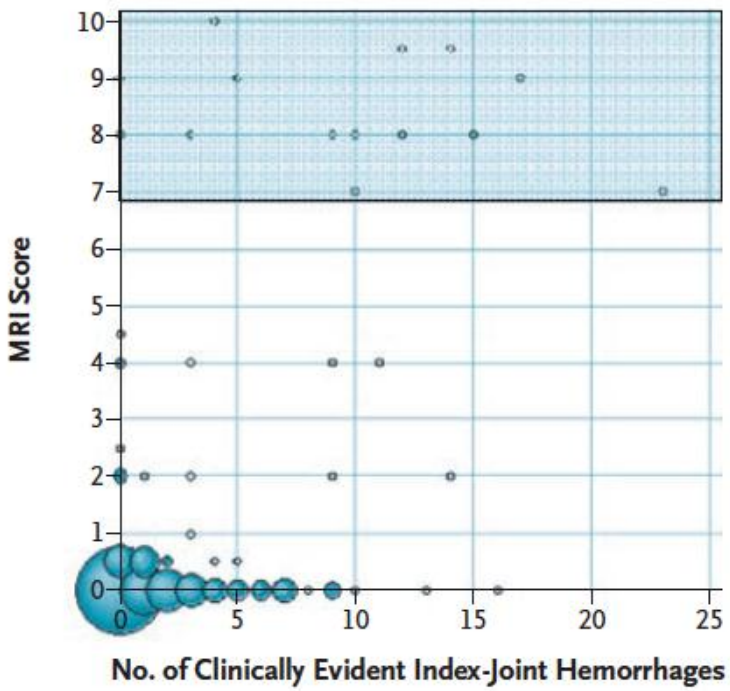
- **Availability of clotting factor concentrates**
  - Global factor use:patient outcome correlation (WFH Global Surveys)
  - Primary prophylaxis > Secondary prophylaxis > On demand
    - Annualized bleed/joint bleed rate (ABR/AJBR)
    - Joint scores
    - missed work/school academic performance
    - hospitalization days, surgeries
  - Prophylaxis with current therapies allows participation in activities previously impossible with hemophilia

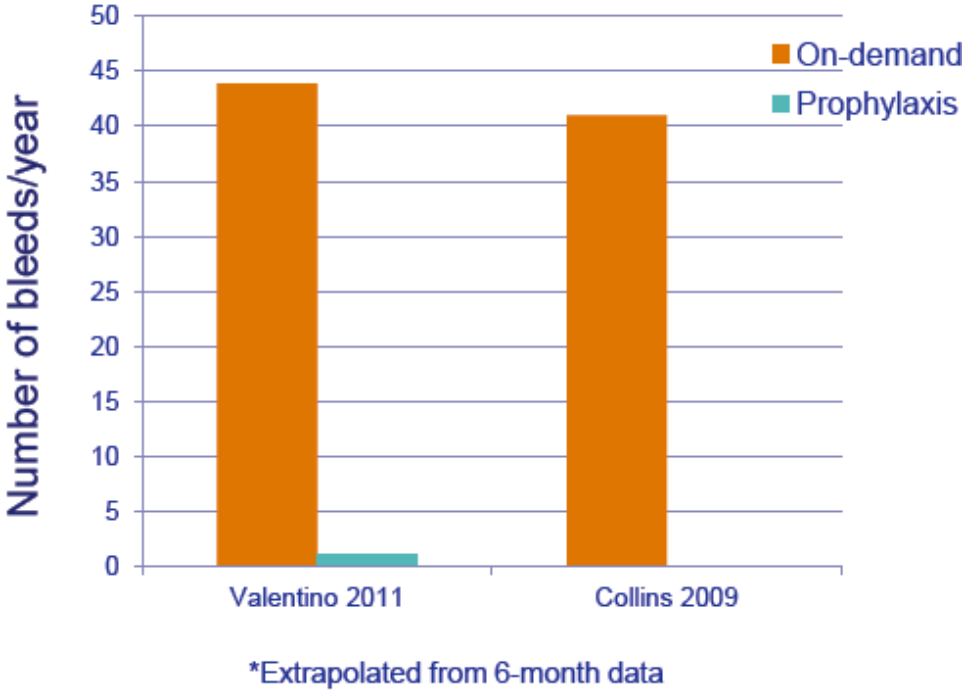
- **Comprehensive care**

  - HTC care shows positive impact in countries with both good access to replacement therapy (USA: Soucie, 2000) and limited access to replacement therapy (Thailand: Chuansumrit, 2004)

Outcomes

- Prophylaxis in children prevents joint bleeding, overall bleeding and joint disease.
- Prophylaxis in adults prevents joint bleeding and overall bleeding.





Manco-Johnson, NEJM 2007

Prophylaxis Regimens in Hemophilia

High-dose regimens (Sweden, Germany, UK, US, Italy)		
Hemophilia A Escalating dose regimens	25-40 IU/kg	Three times/week or every other day 500 IU once/week, rapidly increased to 2-3× times/week depending on IV access (Sweden) 50 IU/kg once/week→30 IU/kg twice/week→ 30 IU/kg every other day, according to bleeding frequency (Canada)
Hemophilia B	25-40 IU/kg	2-3×
Intermediate-dose regimens (The Netherlands)		
Hemophilia A	15-25 IU/kg	2-3× weekly
Hemophilia B	30-50 IU/kg	1-2× weekly

Coppola A et al. *J Blood Med.* 2010;1:183-195.

What has driven the prophylaxis regimens currently used?

- Pharmacokinetics/pharmacodynamics of the replacement therapy
- Accommodation of individual phenotypes
- Practical aspects of venous access
- Cost-effectiveness
- Informed from:
  - Retrospective and prospective cohort studies
  - RCTs
  - Short term surrogates – ABR, Joint scores, MRI
  - Long term outcomes

Each of these elements may potentially be impacted by new therapies

Aims of the Hemophilia Pipeline

- **Further improve patient outcomes**
  - Timing of prophylaxis initiation/escalation
  - Better bleeding control and joint function preservation
- **Reduce burden of administration**
  - Reduce dosing frequency
  - Reduce cost of therapy
  - Improve adherence
- **Individualize treatment regimens**
  - Adapt to individual pharmacokinetics
  - Active vs sedentary lifestyles
  - Variable clinical phenotypes

Hemophilia Clinical Trial Pipeline

BAX817 – rVIIa (Baxter)
Transgenic rhFVIIa (LFB)
OBI-1 – rpFVIII (Baxter)
CB813d – rVIIa analogue (Pfizer)
CSL689 – rVIIa:albumin fusion (CSL)
rVIIa:CTP (Prolor Biotech)

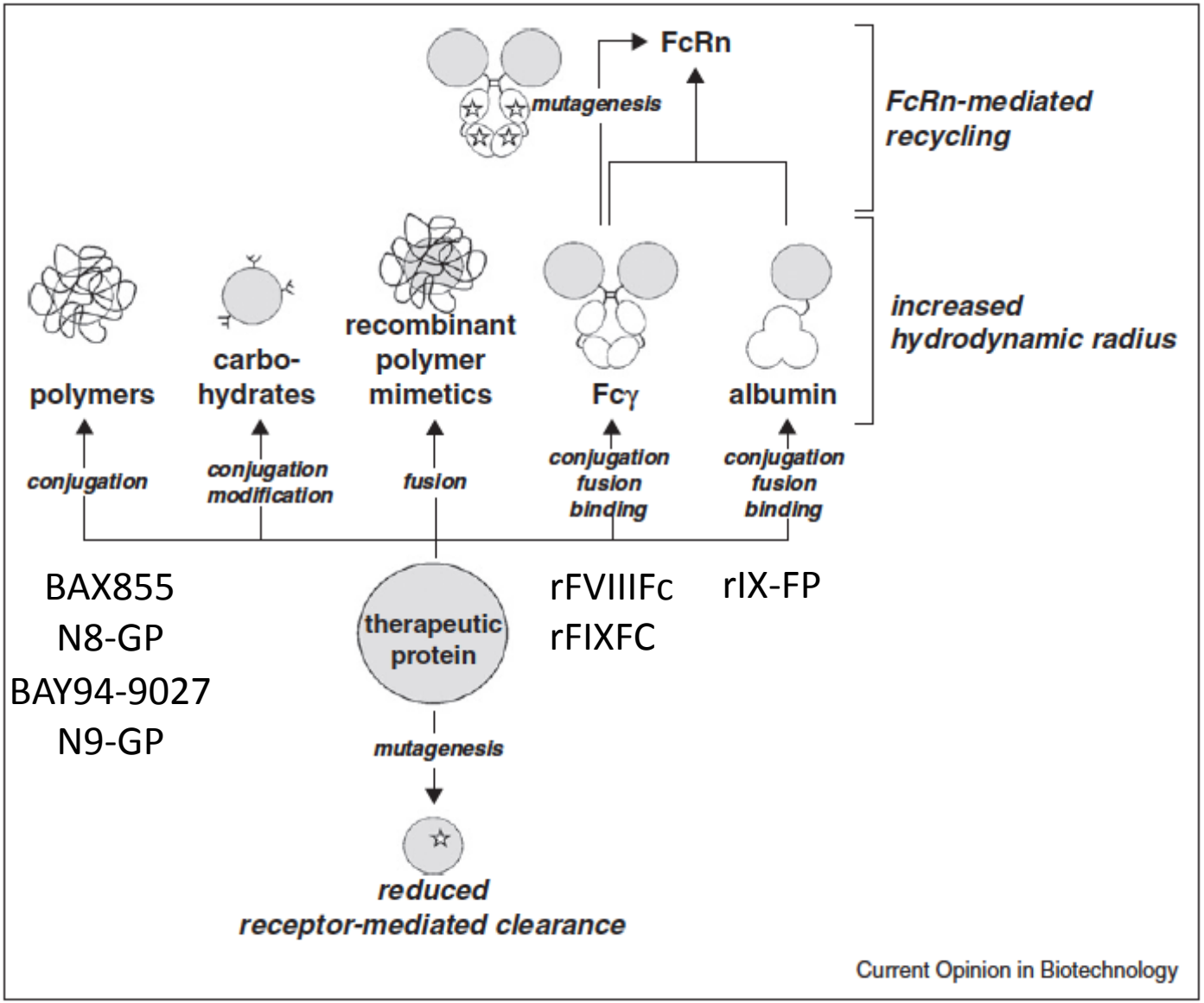
Octagenate – rFVIII (Octapharma)
Kogenate PF – rFVIII (Bayer)
N8 – rFVIII (Novo Nordisk)
GreenGene F – rFVIII (Green Cross)
rFVIII:Fc (Biogen Idec) *
BAY94-9027 – PEGylated rFVIII (Bayer)
N8-GP – PEGylated rFVIII (Novo Nordisk)
BAY855 – PEGylated rFVIII (Baxter)
CSL627 – SingleChain rFVIII (CSL)

IB1001 – rFIX (CanGene)
BAX326 – rFIX (Baxter)*
rFIX:Fc (Biogen Idec)*
N9-GP – PEGylated rFIX
CSL654 – rFIX:albumin fusion (CSL)

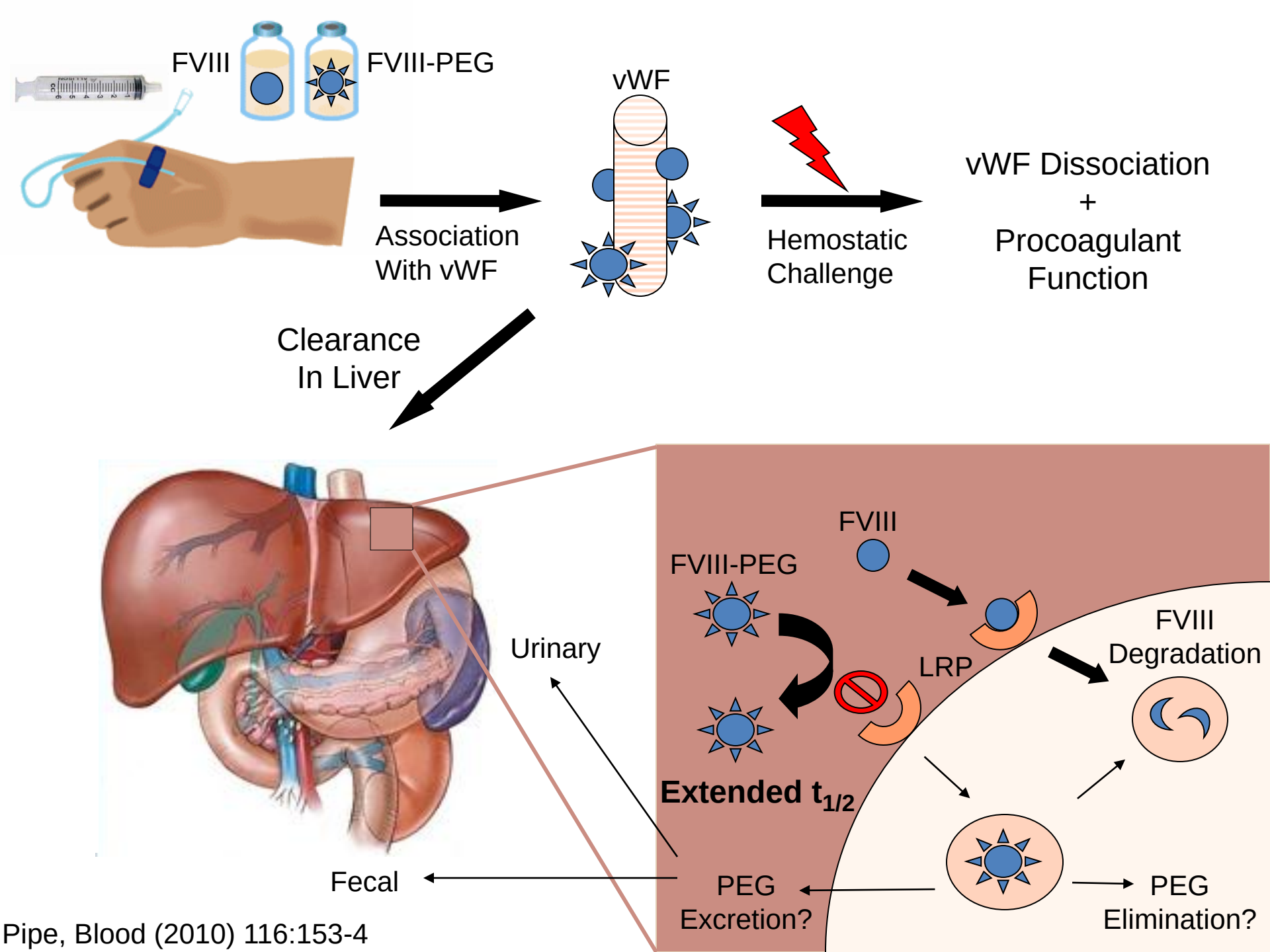
MC710 – pdFVIIa + pdFX (Kaketsuken)
ACE910 – SC bispecific Ab (Chugai)
siRNA vs Antithrombin (Alnylam)

New recombinants
Longer-acting
* Approved

Half-life Extension of Biologics



Kontermann (2011) 22:868-76



Pipe, Blood (2010) 116:153-4

BAX 855

- PEGylated from of rFVIII based on Advate manufacturing process
- 60% of PEG conjugated to B domain via lysine residues
- 2 moles PEG/FVIII, branched PEG with two 10-kDa arms
- No amino acid or N-glycan modifications
- Phase I[1]
  - 19 PTPs ≥18 y.o.
  - Half-life 1.5x longer than Advate, all patients achieved half-life extension
  - No inhibitors, no Ab to PEG, no allergic reactions

Baxter, press release: 1. Jan 7, 2013 2. Nov 13, 2013

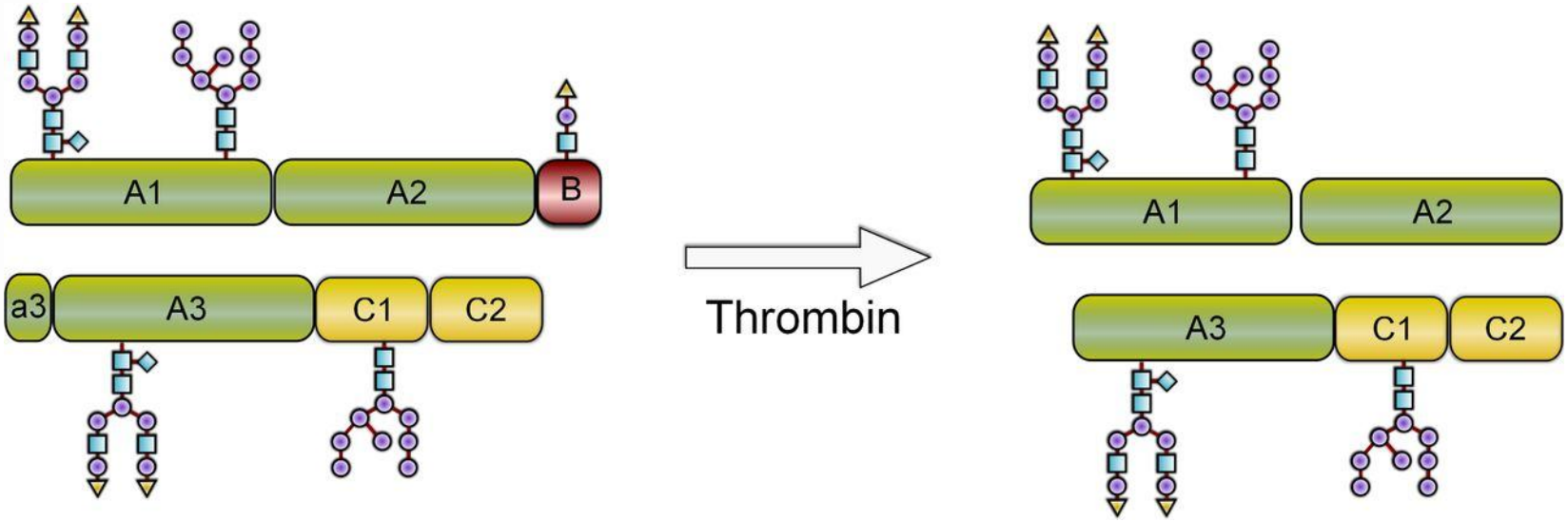
BAX 855

- Phase 3 Pivotal study
  - 138 PTP adolescents (≥12 y.o.) and adults
  - Twice weekly dosing (45 IU/kg) vs on-demand for 6 months
  - Half-life 1.4-1.5 x Advate
  - 95% reduction in media ABR (annualized bleed rate)
    - 1.9 vs 41.5
  - 96% of bleeds controlled with 1 or 2 infusions
  - No inhibitors, no treatment-related serious adverse events including no hypersensitivity
- Launched Phase 3 prospective, open-label, multicenter study in PTPs <12 y.o.

Baxter press release Aug 21, 2014

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

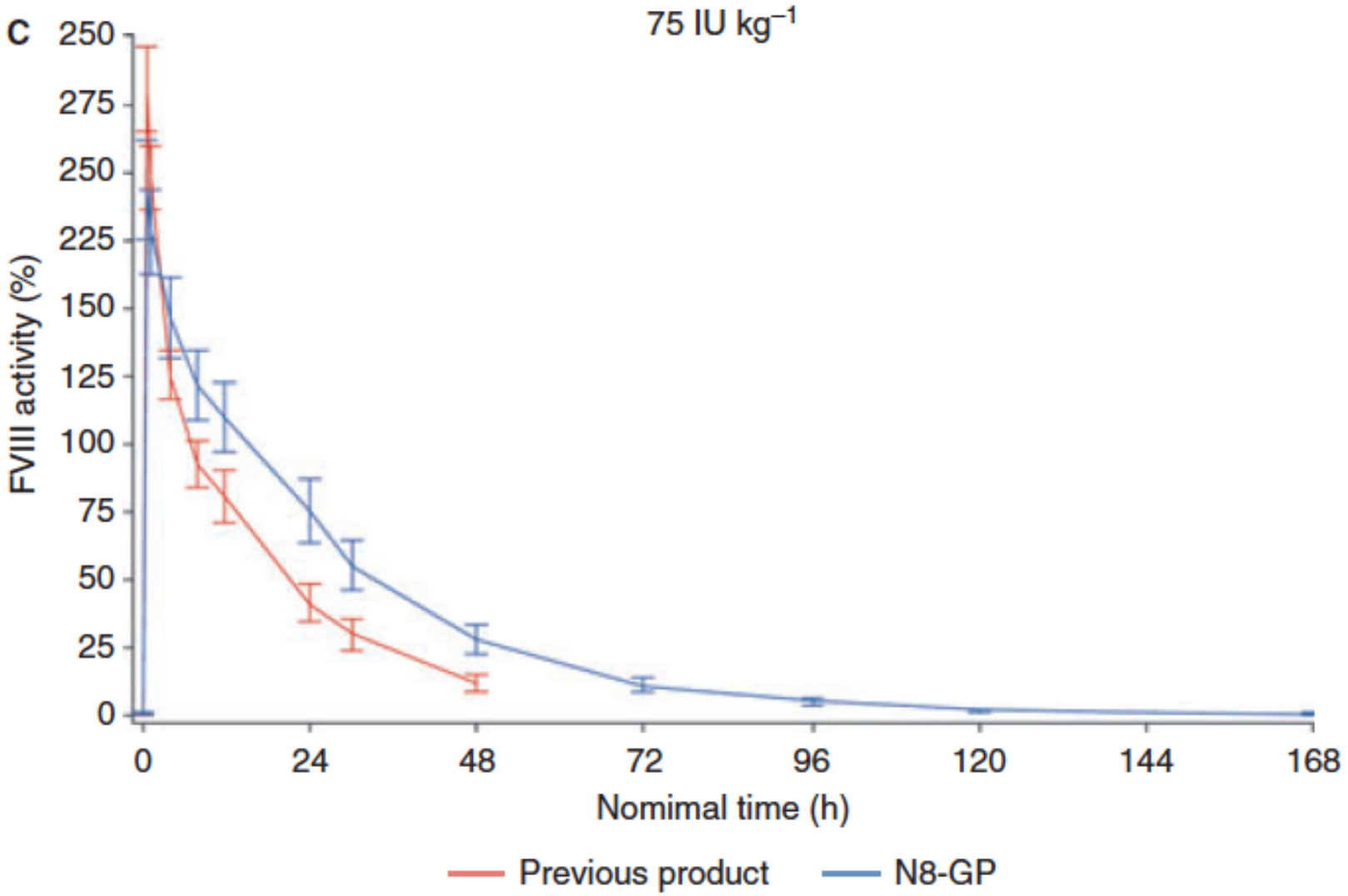
Schematic depiction of N8-GP before and after thrombin activation.



N8-GP corresponds to FVIII (turoctocog alfa) PEGylated with a 40-kDa PEG on the *O*-linked glycan in the 21-aa B-domain. After cleavage with thrombin, the activated molecule has the same primary structure as native FVIIIa.

Stennicke H R et al. Blood 2013;121:2108-2116

N8-GP Phase I Results



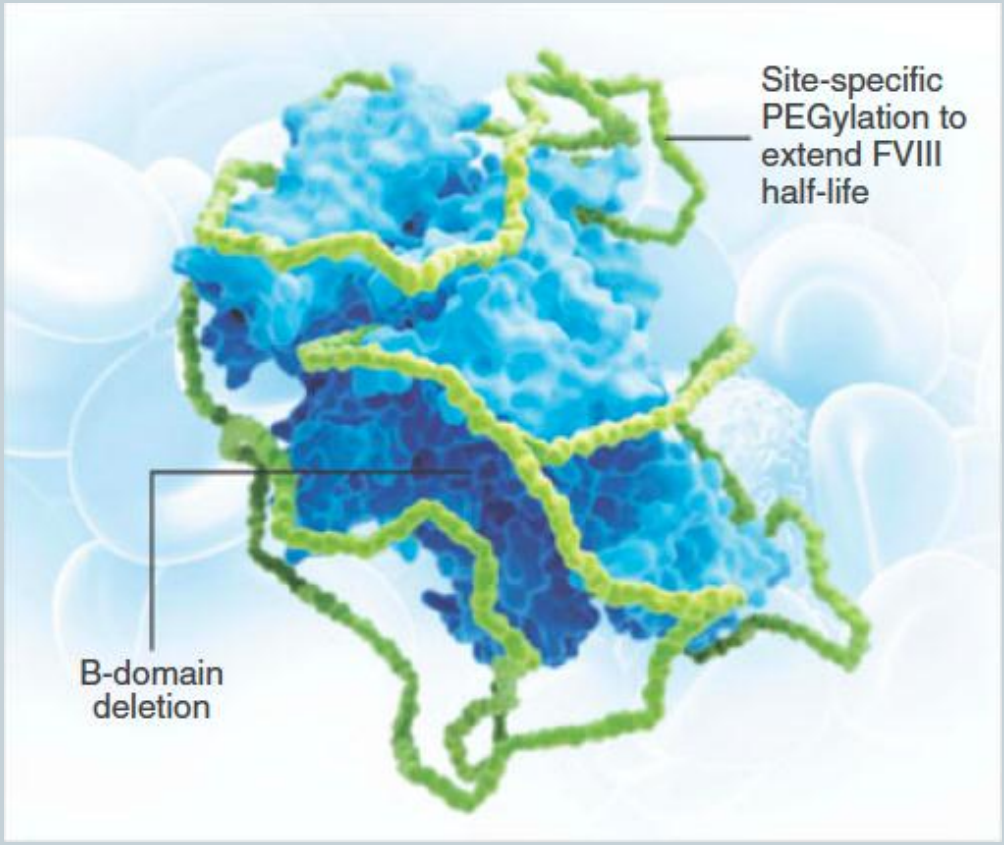
Tiede, J Thromb Hemost (2013) 11:670-8

N8-GP Phase 3 Trial

- 186 subjects ≥12 years
  - 175 subjects: prophylaxis regimen of 50 IU/kg q4days
  - 11 subjects: on demand
- Half-life 18.4 h, mean trough of 8%
- ABR 1.3 (median) on prophylaxis
- 1 patient developed a FVIII inhibitor yet responded well to prophylaxis throughout the study period

Novo Nordisk, press release, Mar 19, 2014

BAY 94-9027



- FVIII-BDD with selective light chain PEGylation via cysteine substitution
- 60 kDa branched PEG containing a maleimide linker

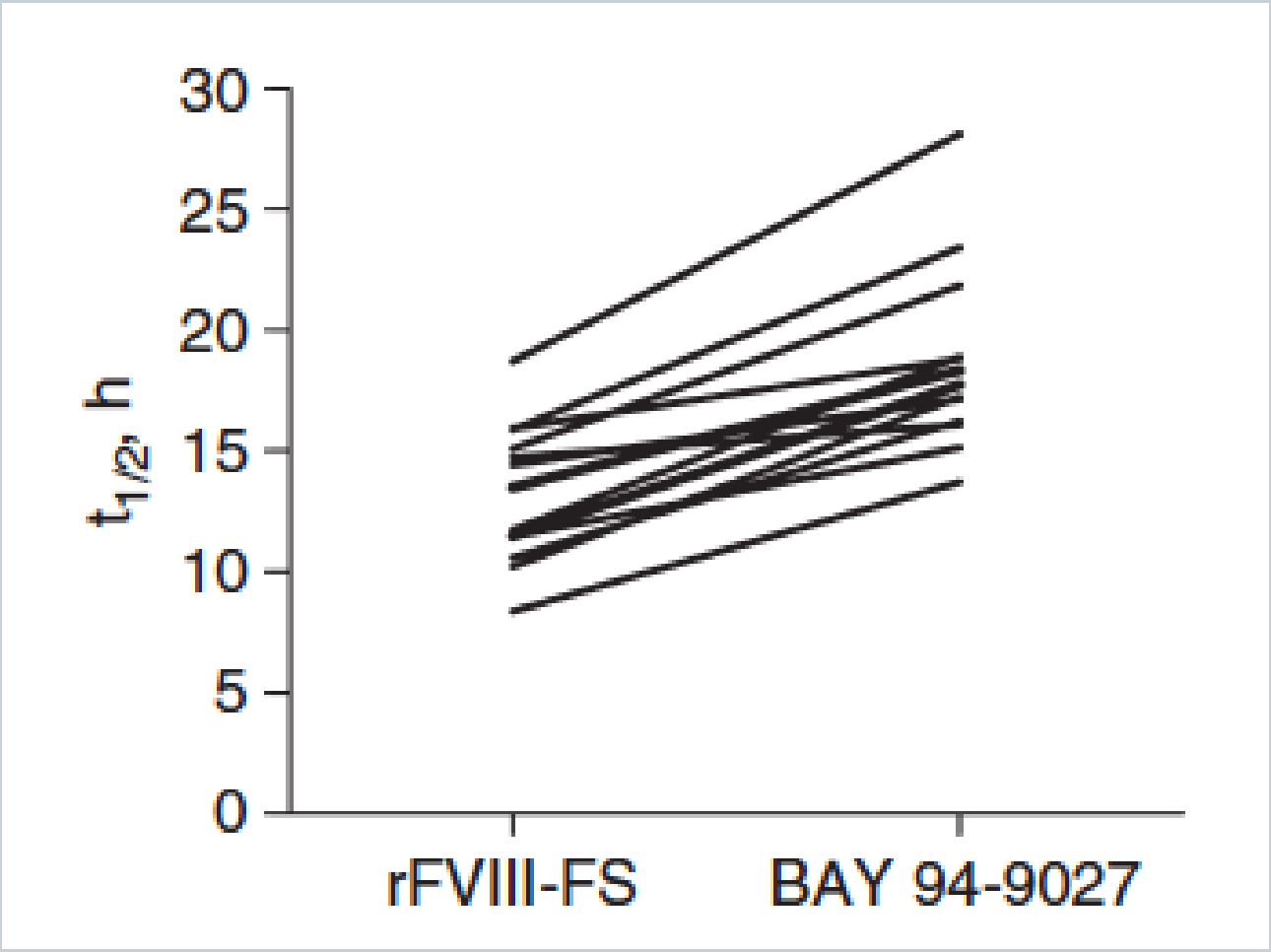
Coyle, JTH, 2014;12:488-96

Phase I Study of BAY94-9027

- 14 subjects with severe Hem A PTPs 21-58 y.o.
- 25 IU/kg 2x/wk and 60 IU/kg 1x/wk
- 19 h half-life vs 13 h for rFVIII-FS
- No treatment-related serious adverse events including no inhibitors or antibodies directed against PEG or BAY94-9207
- 1 serious AE, unrelated to treatment
  - Pelvic muscle bleed 5 days post-infusion
  - Notably, FVIII assay 4 days post-infusion was below quantitation limits

Coyle, JTH (2014)

Phase I Study of BAY94-9027



Coyle, JTH (2014)

Phase 3 Study of BAY94-9027

- 134 subjects (adol.-adult PTPs) with severe Hem A
- 3 prophylaxis arms
  - All 3 initiated on twice weekly dosing
  - After 10 wks, randomized to:
    - Q5d (n=43) or Q7d (n=43) regimen for 6 months
- 88% met bleed-control criteria over initial 10 wks
- All subjects on Q5d remained on this regimen
  - Median ABR 1.9
  - 44% of subjects experienced no bleeds
- 74% of patients on Q7d remained on this regimen
  - Median ABR of 3.9
  - 37% of subjects experienced no bleeds
- No inhibitors to factor VIII
- 2 drug-related hypersensitivity reactions were reported
  - 1 reported as serious but resolved without medical intervention

Press release Feb 18, 2014

rFVIIIFc

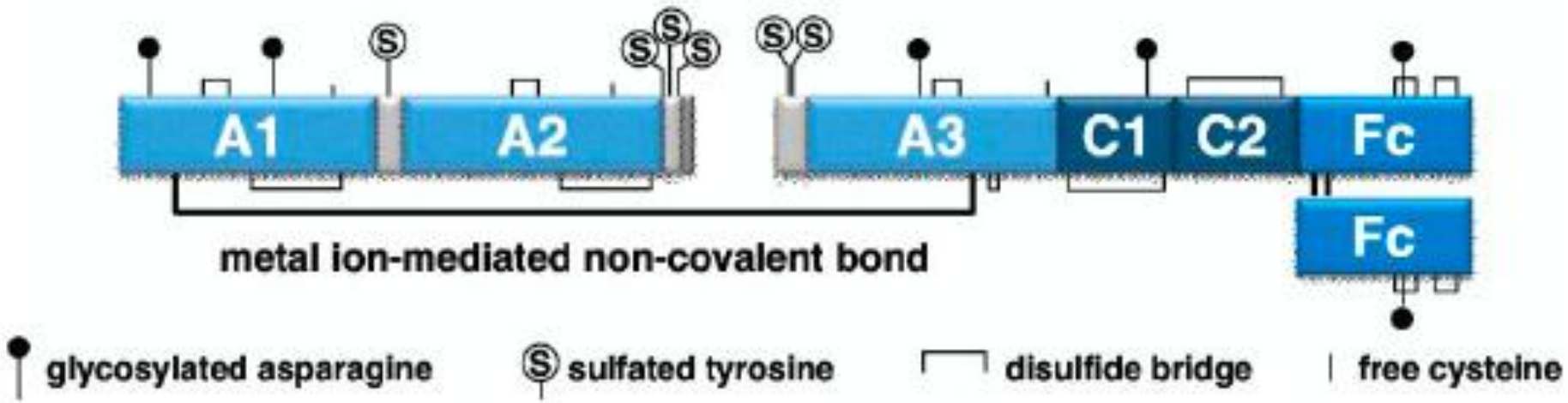
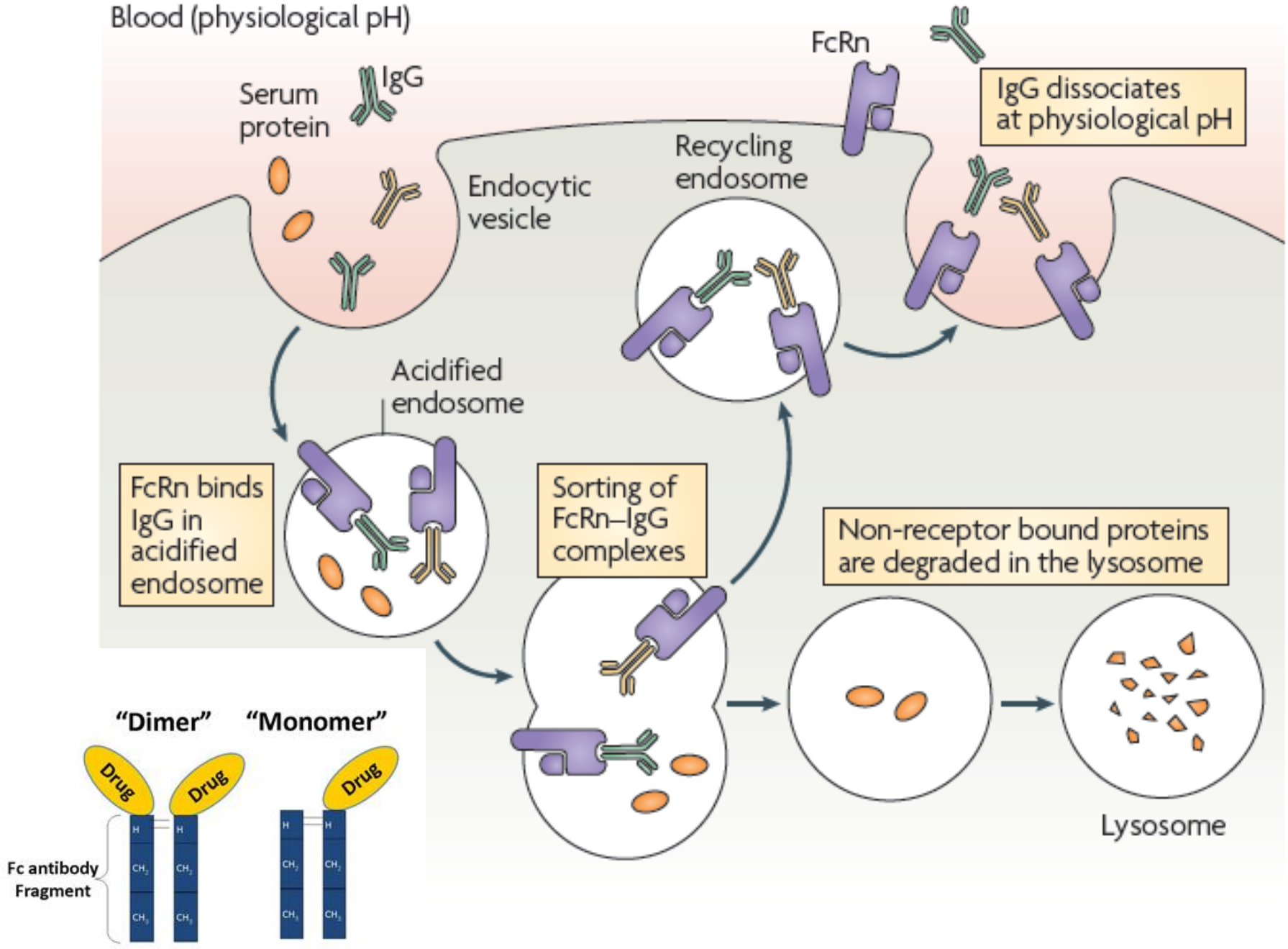


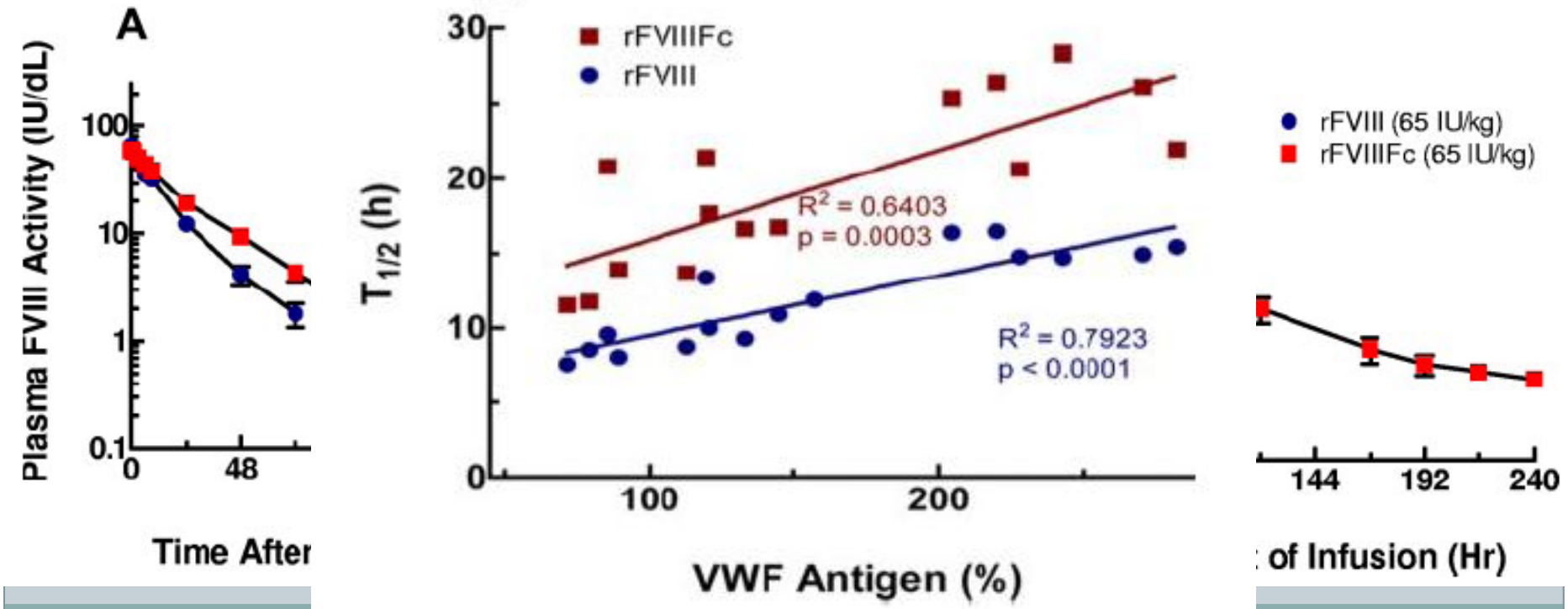
Figure 1. Schematic representation of rFVIIIFc monomer.

Dumont, BLOOD 2012


Blood (physiological pH)
Serum protein
IgG
Endocytic vesicle
FcRn
Recycling endosome
IgG dissociates at physiological pH
Acidified endosome
FcRn binds IgG in acidified endosome
Sorting of FcRn–IgG complexes
Non-receptor bound proteins are degraded in the lysosome
Lysosome
"Dimer"
"Monomer"
Drug
Drug
Drug
Fc antibody Fragment

Phase I trial of rFVIIIFc

- 16 adult men with severe hemophilia A
- No serious adverse events including no inhibitors
- 1.5 to 1.7-fold longer half-life compared to rFVIII



Powell et al., BLOOD (2012)

rFVIIIFc Phase 3 Trial Results

- 165 patients with severe hem A ≥12 y.o.
- 3 arms
  - Individualized prophylaxis (25-65 IU/kg, q3-5d)
    - Median dosing interval:
      - 3.5 days, 30% of patients on q5d last 3 months of the trial
      - 1.6 annualized bleed rate
  - Weekly prophylaxis (65 IU/kg)
    - 3.6 annualized bleed rate
  - On-demand
    - 98% of bleeds controlled with 1-2 infusions
    - 33.6 annualized bleed rate
- No inhibitors and no drug-related serious adverse events

Mahlangu, Blood (2014)

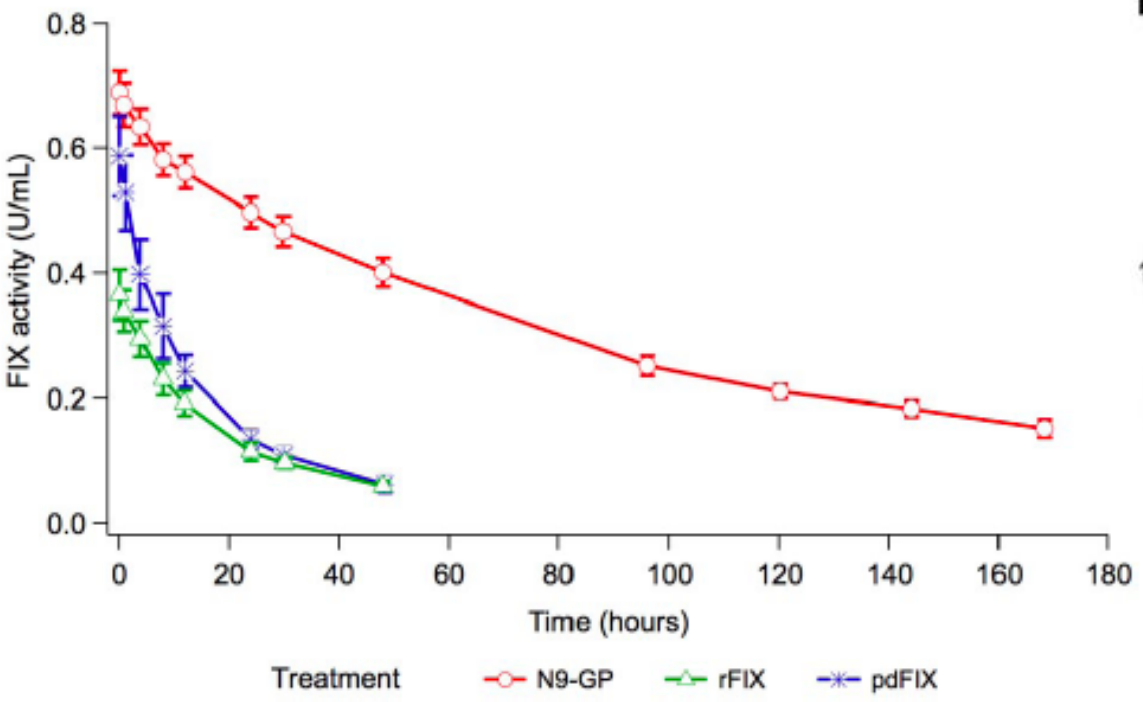
rFVIIIFc Phase 3 in Children

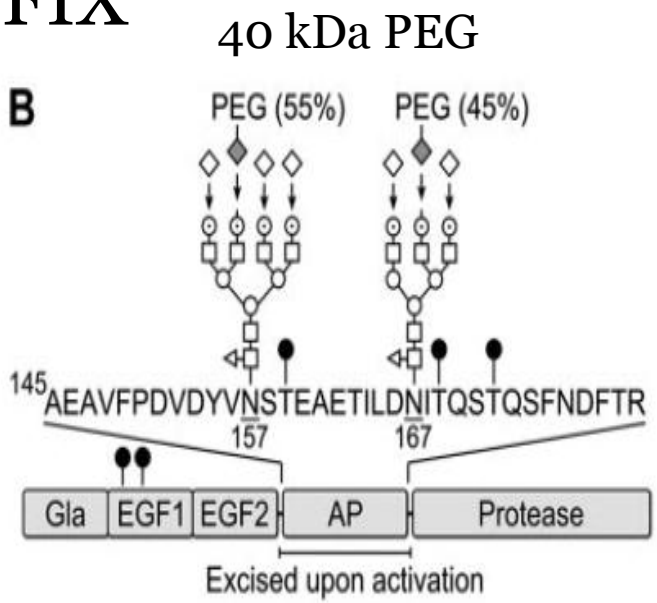
- 71 boys severe Hem A, ≥50 prior exposure days to FVIII
  - 33 age <6 years, 34 age 6-11 years completed the study
  - Avg 25 weeks on study, 61 subjects had >50 exposures
- Twice weekly dosing
  - 25 IU/kg Day 1, 50 IU/kg Day 4
  - Dose and interval adjusted per individual response
  - 90% of subjects on twice weekly dosing at end of study
- 1.5x extension of half-life
- Overall median ABR 2.0
  - Spontaneous bleeding ABR 0.0
  - 46% of subjects experienced no bleeds
  - 93% of bleeds controlled with 1-2 infusions
- No drug-related serious adverse events and no inhibitors

Biogen Idec Hemophilia, press release 4-10-14

Glycopegylated FIX: first human dose trial in Hem B

- 16 men with severe hem B
- Half-life of 93 h – 5x rFIX
- Better plasma recovery than rFIX





Ostergaard, Blood, 2011

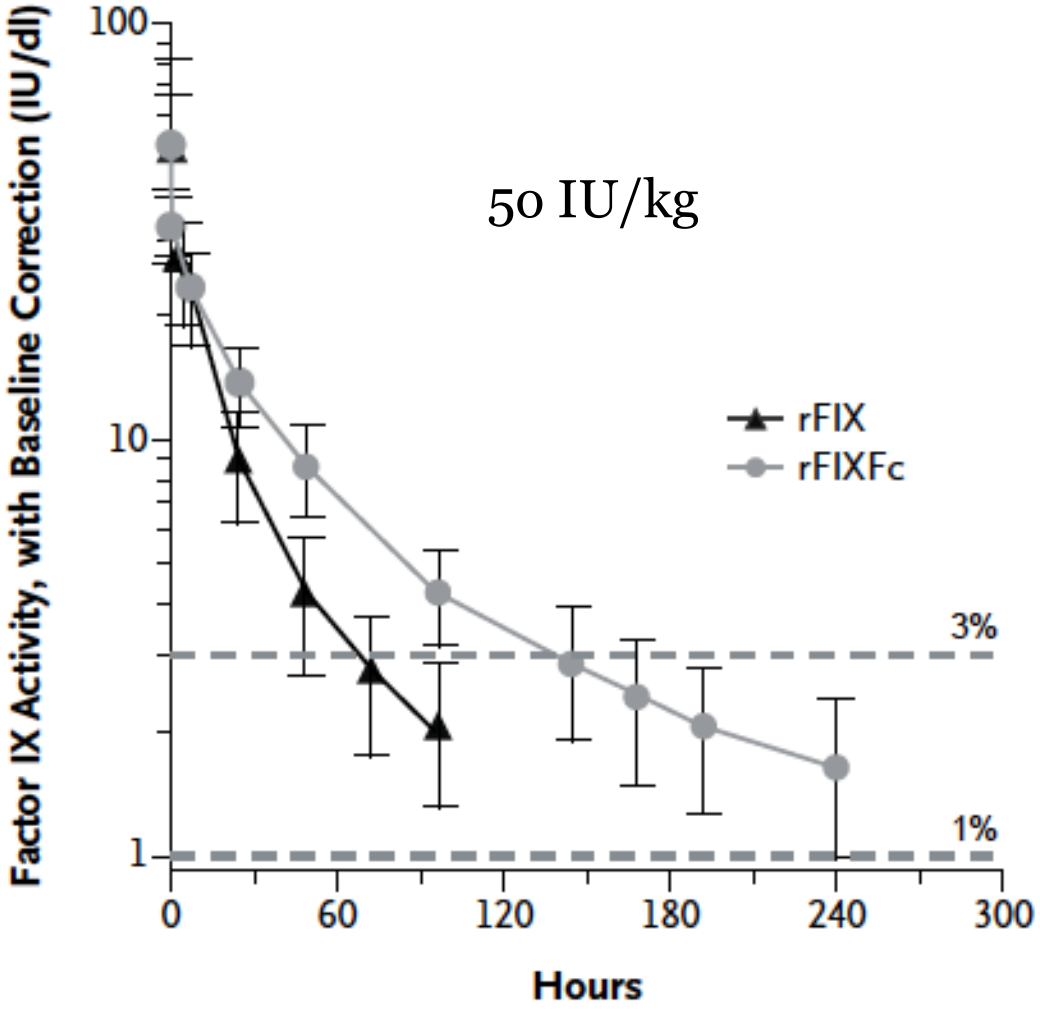
Negrier, Blood, 2011

Phase 3 Results with N9-GP

- 74 subjects
- 6 months on-demand
- 12 months prophylactic regimen
  - 40 IU/kg weekly
    - Median ABR 1.0
    - 99% of bleeds treated with a single infusion
    - Two-thirds reported complete resolution of target joints
  - 10 IU/kg weekly
    - Median ABR 2.9
  - Steady state $t_{1/2}$ of 110 h
  - No inhibitors

Novo Nordisk press release, May 17, 2013 and ISTH 2013

rFIXFc



50 IU/kg

Terminal half-life of 82.1 h

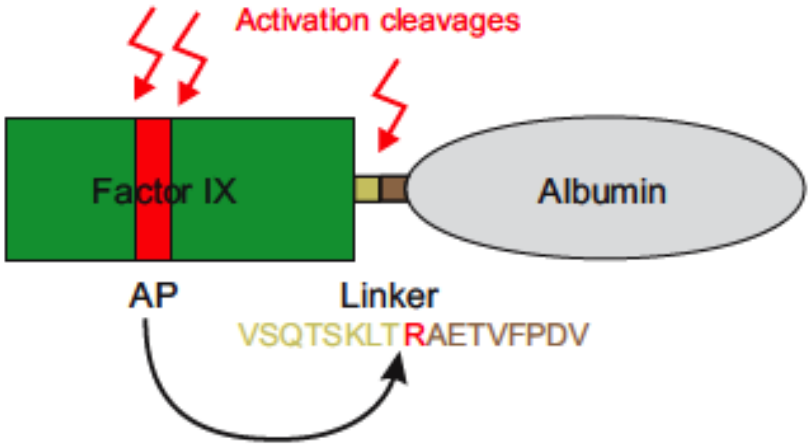
Powell, NEJM, 2013;369(24):2313-2323

rFIXFc Phase 3 Results

- Weekly treatment, starting dose 50 IU/kg:
  - 2.95 bleeding episodes per year
- Dosing 100 IU/kg at variable intervals:
  - 1.38 episodes per year
  - 53% of subjects had dosing intervals ≥14 d during last 3 months of the study
- Dosing only after bleeding episodes began:
  - 17.69 episodes per year
  - 90.4% controlled with a single injection
- No inhibitors

Powell, NEJM, 2013;369(24):2313-2323

rIX-FP



Terminal half-life 91.57 h

Santagostino, BLOOD (2012)

rIX-FP Phase I/II

- 17 subjects
  - 4 on-demand
  - 13 weekly prophylaxis
    - PK-directed dosing
    - ABR 1.255 (mean) and 1.134 (median)
    - 90% of bleeds treated with single infusion
- Following 25 IU/kg dose
  - Mean FIX activity of 3.75% and 2.67% above baseline at D7 and D14, respectively
  - Mean half-life of 95 h
- No inhibitors

Martinowitz, ISTH, 2013

What's Next?

- Novel biologics in pre-clinical testing
  - Bispecific antibody substitution for FVIII
  - Factor IX muteins as bypass therapy
  - Zymogen-like Factor Xa
  - Anti-TFPI antibody/peptides
- Non-protein therapies
  - Anti-TFPI
    - Natural – fucoidan
    - Synthetic – aptamers, small molecule inhibitors
  - Anti-protein C
  - Anti-antithrombin

} siRNA

Clinical Trial Regimens

- **Programmatic prophylaxis** (fixed dose and interval)
  - Once weekly for FIX
  - Twice weekly for FVIII
- **PK-driven** (dosed to target trough, fixed interval)
- **Phenotypic-driven** (variable dose and interval according to bleeding pattern and activity)
- **Convenience-driven** (higher dose, longer interval)

Untested Regimens

- **Cost-emphasis prophylaxis**
  - PK-driven, short interval, minimal (1%) trough target
- **Activity-focused prophylaxis**
  - Higher dose, Shorter interval, higher trough target
- **Target joint-focused prophylaxis**
  - Standard interval, higher trough target
- **Combination prophylaxis**
  - Eg. Longer-acting factor (IV) + siRNA-inhibited AT (SC)

    Longer-acting factor (IV) + anti-TFPI antibody (SC)

Outcomes with New Therapies

- Only ABR/AJBR to date in clinical trials
  - Still only a surrogate marker for joint outcomes
- Still needed:
  - Longer term joint scores
    - MRI, HJHS, functional
- Trough targets
  - Does 1% still mean 1%, for every agent, and with which assay?
- Economic impact
  - Will we be able to show these innovations have improved the cost-effectiveness of care?
    - Annualized cost of care
    - Improved clinical outcomes