Long acting factors

Jamie Price
Haematologist
Princess Margaret Hospital

Technologies for half-life extension

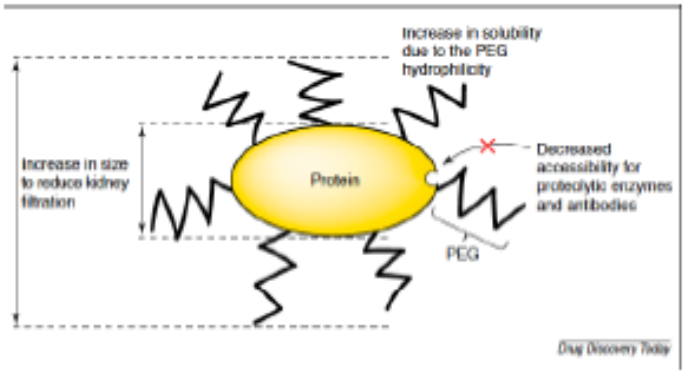
Microsphere/nanoparticle packaging
-Liposomes
-Polyethylene glycol

- Chemical modification
- – **Polyethylene glycol**
- – Hydroxyethyl starch
- – Polysialic acids
- Genetic modification
- – Mutation in the protein
- **Fusion with a protein with long half-life**
- **–Immunoglobulin fusion**
- **–Albumin fusion**

PEG-ylation to extend half-life

- Pegylation of proteins
  - Reduce renal clearance
  - Protect against enzyme digestion
  - Blocks interaction with clearance receptors (LRP)
  - E.g., PEG-IFN, PEG-G-CSF, PEG-aspariginase

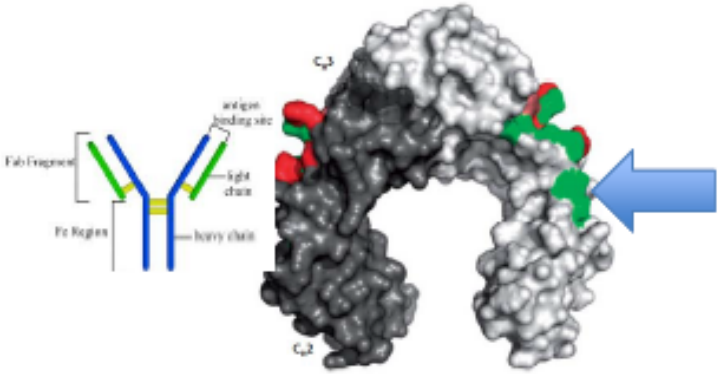
-Random PEG (multisite)
-Site-specific

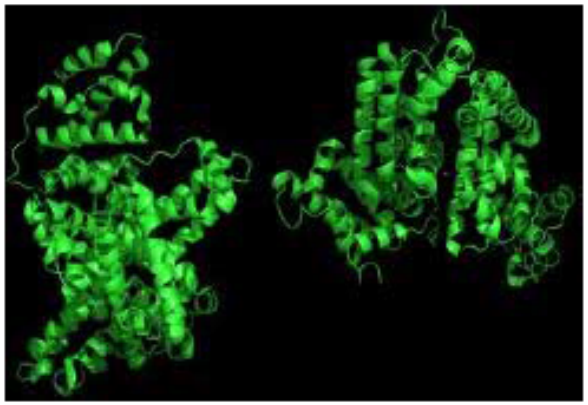


Fusion protein technology

Protein fused to another protein with natural longer half life in circulation

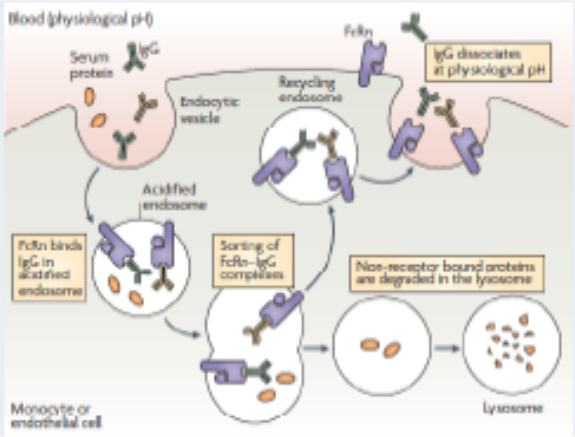
- Fragment crystalline (Fc) of IgG
- Albumin





Mutations of residues depicted in green can improve IgG binding to FcRn, thereby prolongs Fc coupled drugs

Fusion technology

Fc (of IgG_1)	Albumin
T1/2 ≈ 3 weeks	T1/2 ≈ 3 weeks
Neonatal Fc receptors on endothelial cells ↓ Internalise IgG & albumin binding to FcRn ↓ Protection from lysosomal degradation ↓ Recirculation to blood	
E.g., Romiplostim (TRA) & Etanercept	e.g., neugranin (Alb-G-CSF), Albiglutide (GLP-1-Alb)

Roopenian *Nature Reviews Immunology* 2007(7):715-25

Clinical studies with modified long-acting rFIX

Product (Manufacturer)	Technology	Cell line	t½, hr	t½ vs. rFIX	~ time to 1% trough after 50IU/kg
rFIX-Fc (Biogen-Idec) (Phase III)	Fc-Fusion protein (BDD-rFIXFc)	HEK	57-83	3x	10 d (2wks with 100IU/kg)
N9-GP (NovoNordisk)	Single site specific glycopegylation (40kDa PEG)	CHO	96-110	>5x	2-3 wks
RIX-FP (CSL-BEHRING)	Albumin fusion protein	CHO	89-96	>5x	2-3wks

Clinical studies with modified long-acting rFVIII

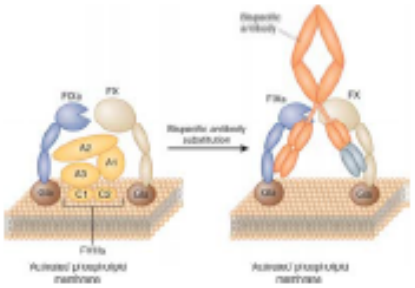
Product (Manufacturer)	Technology	Cell line	Half-life, hr	Half-life vs. rFVIII
rFVIII-Fc (Biogen-Idec)	Fc-Fusion protein (BDD-rFVIIIFc)	HEK	18.9	x1.5-1.7
N8-GP (NovoNordisk)	Single s… glycop… (40kDa… trunca…	CHO	…19	x1.6
BAY-94-9027 (Bayer)	Site sp… (60kDa… r…		…9	X1.4
BAX-855 (Baxter)	Controlled PEG (2x20kDa branched chain PEG) of full-length rFVIII	CHO	NA	X1.5

Similar pharmacokinetics

T1/2 (adults) ≈ 19h

1.4-1.7 fold longer than rFVIII

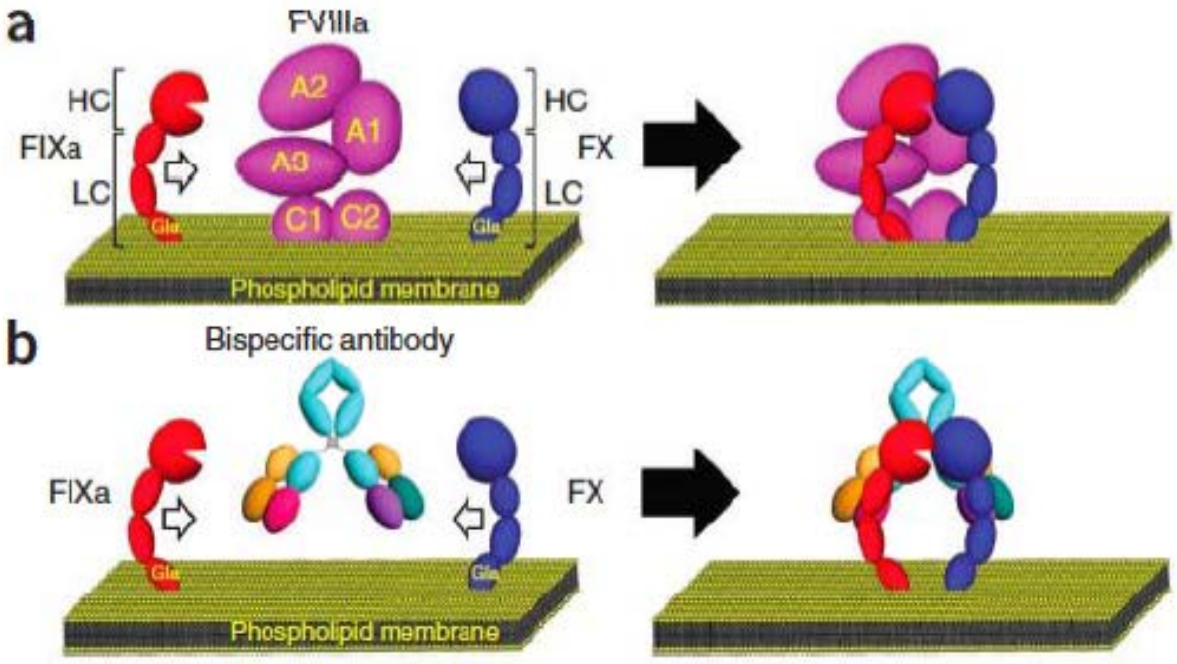
Anti-factor IXa/X bispecific antibody (ACE910) for haemophilia A



Novel approach

- Substituting FVIII function with antibody drug
  - Different antigenicity from FVIII; functions despite FVIII inhibitors
  - Longest-acting (t1/2 ~2wks vs 18.8h of long acting)
  - Subcutaneous administration (~100% bioavail)

ACE910



Kitazawa *Nature Medicine* **18**, 1570–1574 (2012)

Safety of ACE910 in volunteers

- No SAE
- One (of 48) developed anti-ACE910 antibodies (ADA)
  - After ADA development, ACE910 disappeared early from plasma
  - ADA positive patient showed NO abnormalities of coagulation (APTT, PT, FVIII, FIX, FX)

- hBS antibodies unlikely to cross react with FVIII (no similarities in sequences of variable regions of hBS23)

ASPIRE injection frequency (interim data cut)

A-LONG injection frequency (end of study)	Every 3d N = 28 (18.7%)	Twice weekly N=43 (28.7%)	Every 4d N=9 (6.0%)	Every 5d N=26 (17.3%)	Every 6d N=2 (1.3%)	Weekly N=33 (22%)
Every 3 days N = 35 (23.3%)	26	6	3	0	0	0
Twice weekly N = 33 (22.0%)	0	26	2	3	0	2
Every 4 days N = 4 (2.7%)	1	1	2	0	0	0
Every 5 days N=37 (24.7%)	0	1	2	22	2	10
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Once weekly[a] N = 19 (12.7%)	0	3	0	0	0	16

Change in injection interval
- Lengthened (n=28, 21.9%)
- No change (n=92, 71.9%)
- Shortened (n=8, 6.3%)

	Every 3d	Twice weekly	Every 4d	Every 5d	Every 6d	Weekly	Other N=2 (1.3%)	Episodic N=7 (4.7%)
Episodic treatment N=22 (14.7%)	1	6	0	1	0	5	2[b]	7

Pasi J et al. EAHAD (European Association for Haemophilia and Alliled Disorders) Helsinki Feb 2015

Table 4. Summary of annualised bleeding rate (ABR) during ASPIRE among subjects with an efficacy period[a]

Treatment group	n	ABR, median (IQR)		
		Overall	Spontaneous	Traumatic
Individualised prophylaxis	108	0.66 (0.00, 2.63)	0.00 (0.00, 1.23)	0.00 (0.00, 1.28)
Weekly prophylaxis	27	2.03 (0.60, 4.39)	0.76 (0.00, 2.66)	0.66 (0.00, 1.94)
Modified prophylaxis[b]	17	1.97 (0.96, 7.03)	0.96 (0.00, 5.51)	0.65 (0.00, 2.51)
Episodic	14	18.36 (10.45, 30.46)	13.27 (1.39, 16.60)	2.36 (0.00, 9.05)

[a]The efficacy period reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc according to the treatment regimens of the study, excluding major and minor surgical/rehabilitation periods.
[b]Two subjects in the modified prophylaxis group were treated episodically during A-LONG, and did not have a defined routine prophylaxis regimen during ASPIRE.

- No inhibitors
- No serious AEs attributed to rFVIIIFc

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Long-term Safety and Efficacy for rFVIIIFc in Children

- 61 (100%) of children who completed Kids A-LONG
  - Interim data (1-6-15)
  - Median duration: 51.1 wks
    - 37.7% ≥ 1 year
  - Median exposure days: 103.3
    - 57.4% ≥ 100 EDs

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ASPIRE injection frequency (interim data cut)

Kids A-LONG injection frequency (end of study)	Thrice weekly N = 1 (1.6%)	Every 3d N=5 (8.2%)	Twice weekly N=53 (86.9%)	Every 4d N=1 (1.6%)	Every 5d N=1 (1.6%)
Thrice weekly N = 1 (1.6%)	1	0	0	0	0
Every 3 days N = 4 (6.6%)	0	4	0	0	0
Twice weekly N =56 (91.8%)	0	1	53	1	1

Change in injection interval

- Lengthened (n=2, 3.3%)
- No change (n=58, 95.1%)
- Shortened (n=1, 1.6%)

Nolan B, et al. EAHAD 2015

Table 4. Summary of annualised bleeding rate (ABR) during ASPIRE among subjects with an efficacy period[a]

Treatment group	n	ABR, median (IQR)		
		Overall	Spontaneous	Traumatic
Individualised prophylaxis				
<6 years cohort	29	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
6 to <12 years cohort	30	1.54 (0.00, 3.41)	0.00 (0.00, 1.75)	0.00 (0.00, 1.82)
Modified prophylaxis				
<6 years cohort	1	6.55[b]	6.55	0.00
6 to <12 years cohort	1	0.00	0.00	0.00

[a]The efficacy period reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc according to the treatment regimens of the study, excluding major and minor surgical/rehabilitation periods.

[b]Subject was on-study for 0.31 years, and experienced 2 spontaneous joint bleeding episodes during that time.

- No inhibitors
- No serious AEs attributed to rFVIIIFc
- Avg total weekly consumption (median [IQR]):
  - <6 yo: 99.91 [88.62, 114.18]
  - 6 to <12 yo: 91.23 [81.02, 107.92]

Real-world Data with rFIXFc and rVIIIFc

- Retrospective analysis using a database composed of aggregate Specialty Pharmacy Provider (SPP) records (2012-Oct 2014)
- 118 hem B, median age 20 yr (2-63)
- 520 hem A, median age 18 yr (1-77)

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Figure 4. Early rFVIIIFc utilization

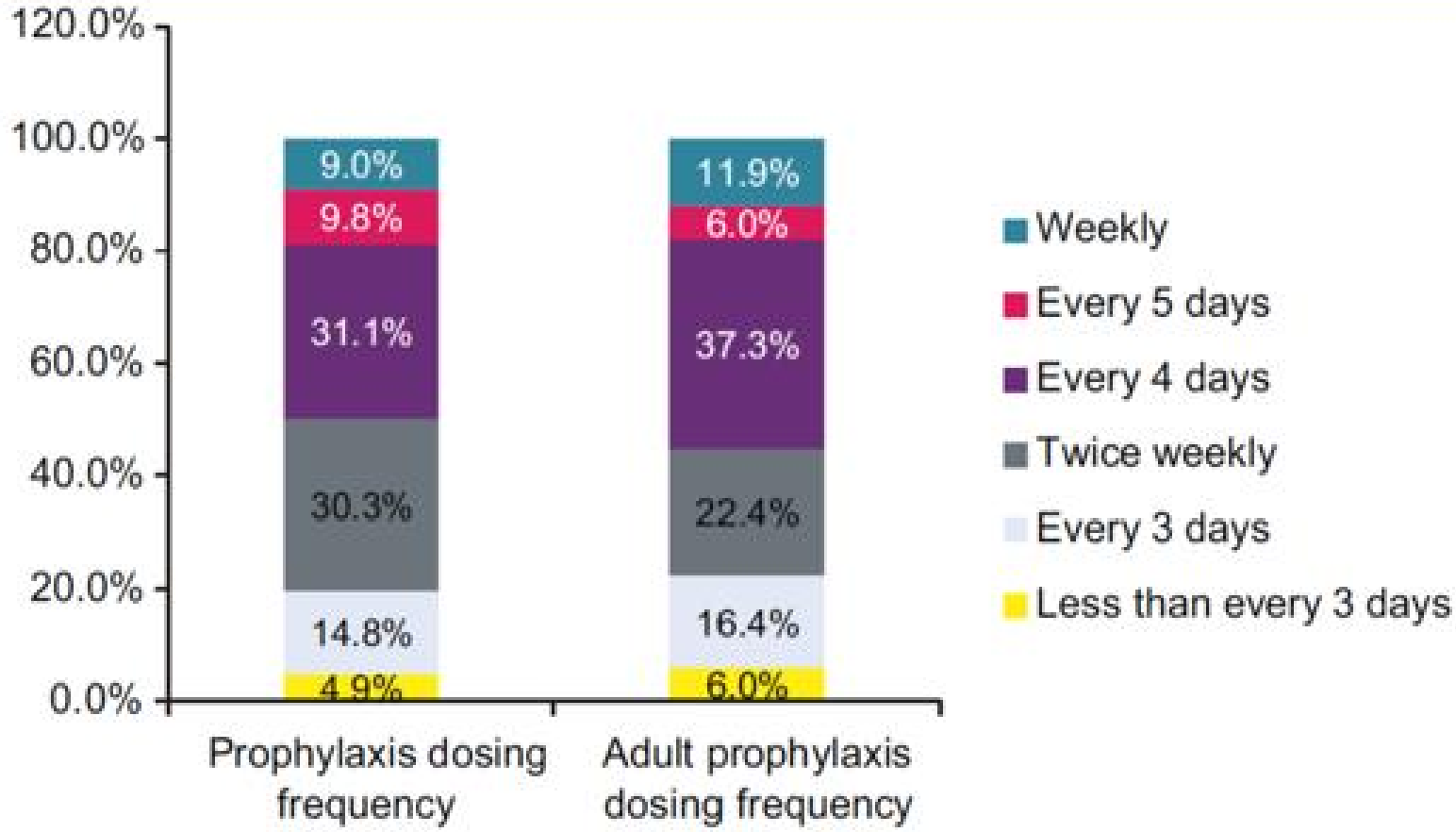

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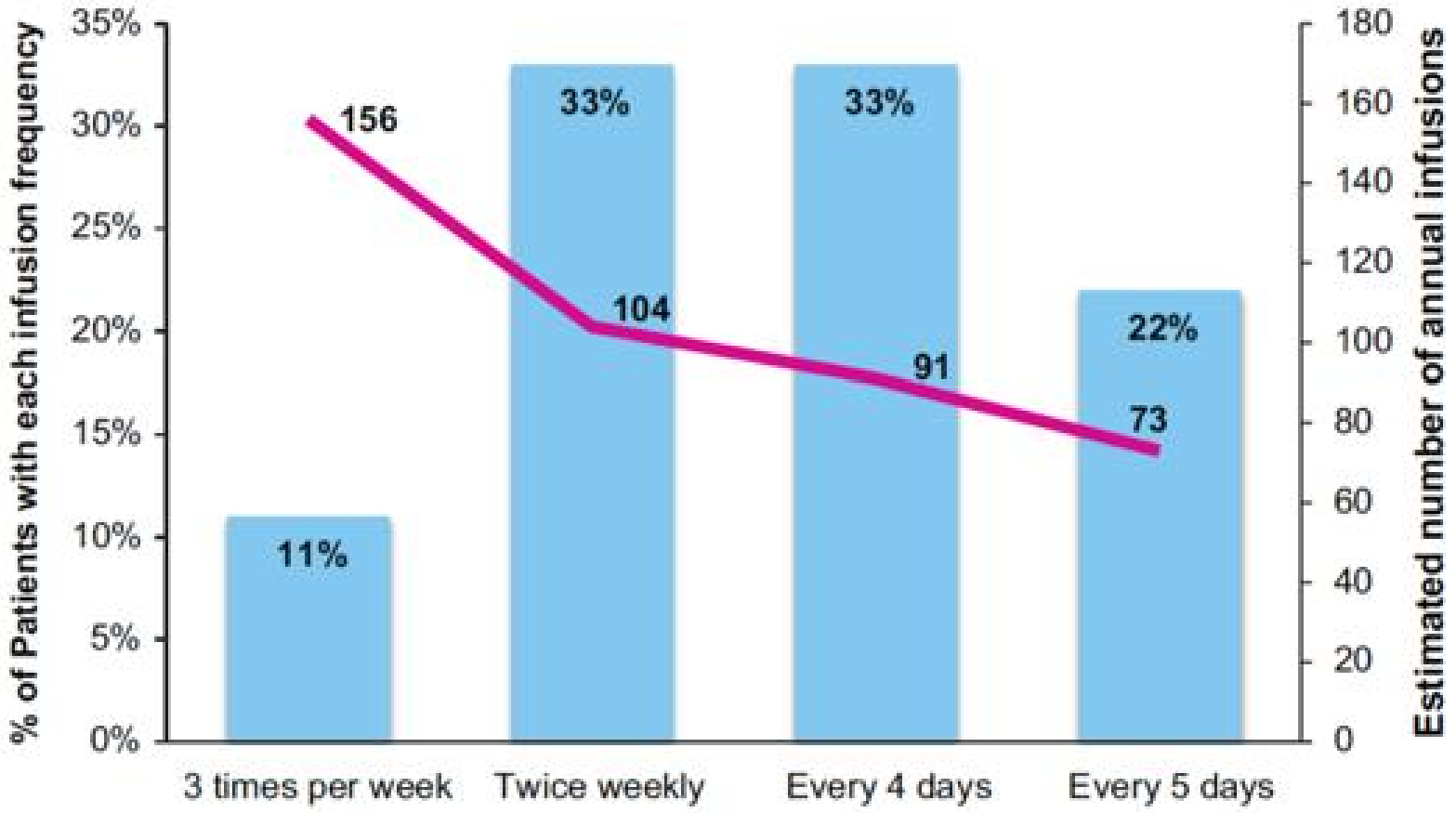
Figure 5. Infusion frequency of pateints switching to rFVIIIFc from rFVIII dosed TIW



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