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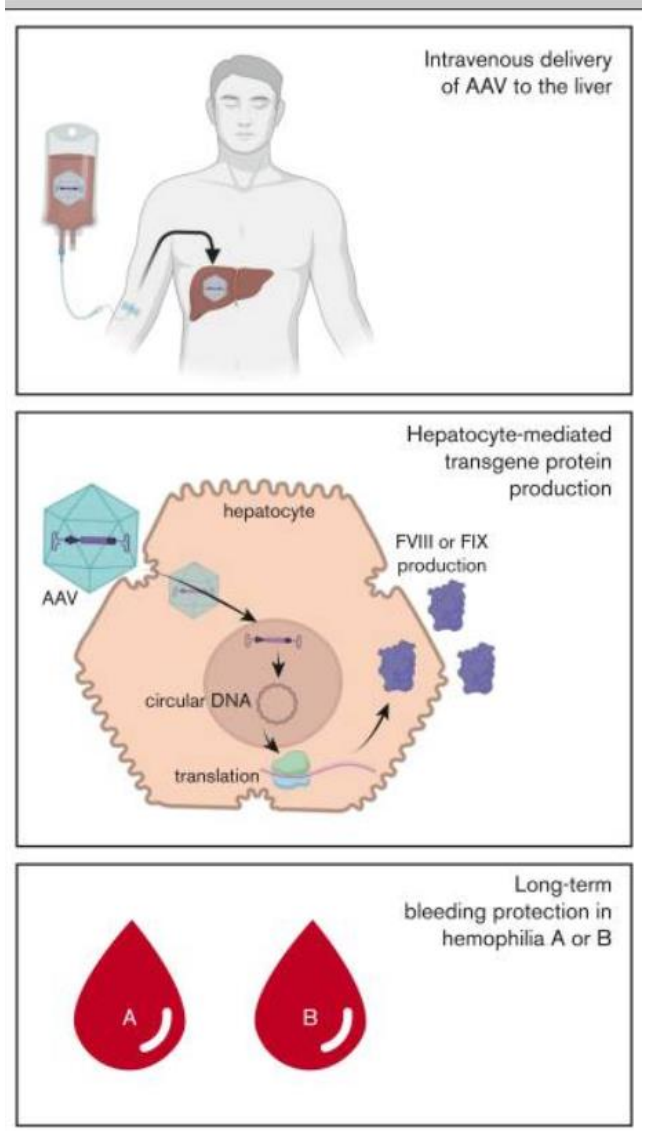
Gene Therapy and Laboratory Monitoring in Haemophilia

Anne Riddell
Health Services Laboratories
Haemophilia Centre,
Royal Free Hospital,
London, United Kingdom

Gene Therapy for Patients with Haemophilia

- Approximately 400 individuals with Haemophilia world-wide have participated in clinical gene therapy (GT) trails (December 2024)[1]
- Current Haemophilia GT products use adeno-associated virus (AAV) vectors that deliver functional genes (*F8* or *F9*) to liver hepatocytes[2].
- A single GT infusion, almost always results in endogenous production of factor (F) VIII or FIX protein
- Successful GT reduces bleeding in patients with Haemophilia, who should no longer require regular clotting factor replacement therapy



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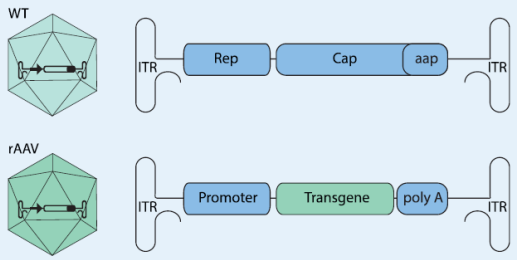
1. Miesbach W Batty P, Chowdary P et al. Adeno-associated virus-based gene therapy for hemophilia addressing the gaps. ResPractThrombHaemost.2025;9:e102673. 2. Lenting P J., Fong S. . Blood Adv. 2024 Dec 10;8(23):6081.

AAV Gene Therapy

WT AAV AND rAAV



Adeno-associated virus (AAV) is a parvovirus that is typically dependent on co-infection with other viruses for replication.[13] AAV has a single-stranded DNA genome of 4.8 kb with three major genes: *Rep* (Replication), *Cap* (Capsid), and *aap* (Assembly).[13]

- AAVs also contain inverted terminal repeats (ITRs), which are DNA sequences that are required for genome replication and packaging
- The *Rep* gene encodes four proteins for viral genome replication and packaging
- The *Cap* gene is responsible for producing the viral capsid protein that forms the outer shell
- The *aap* gene encodes the assembly-activating protein (AAP), which provides a scaffolding for capsid assembly

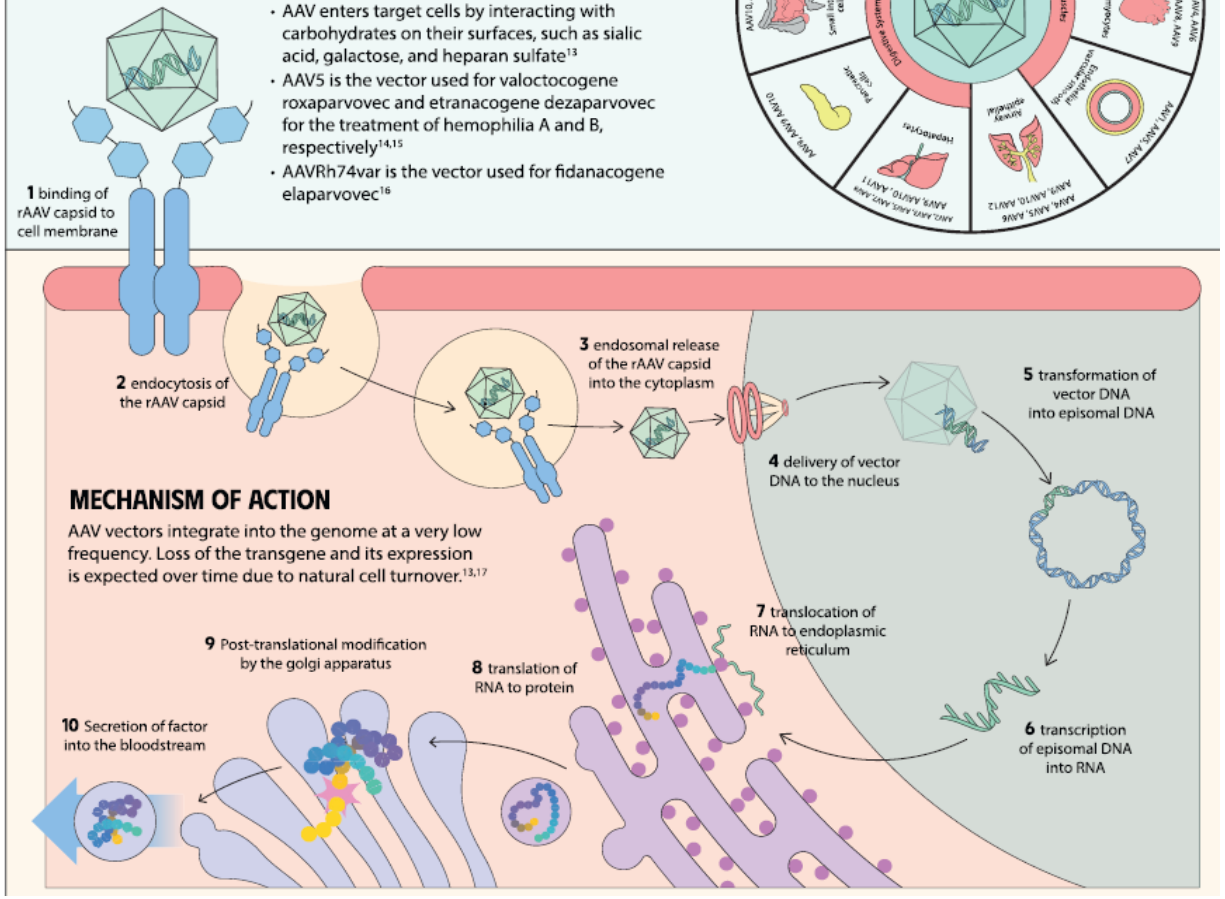
Recombinant AAV (rAAV) is a non-self-replicative vector without viral DNA that delivers transgenes into the cell nucleus, forming episomes (circular plasmids) encoded with therapeutic transgenes.[13]
ITRs play a crucial role in packaging the vector genome into the capsid and forming episomal DNA after transduction.[13]

AAV VECTORS

AAV vectors can accommodate any transgene under 5 kb (including the viral ITRs). When packaging cassettes exceed 5 kb, viral production yields are significantly reduced and/or transgenes are truncated during expression.[13]

- The sequences placed between the ITRs typically includes a mammalian promoter, gene of interest, and a terminator sequence[13]
- Tissue-specific promoters ensure that the transgene is mainly expressed in the cell type of interest[13]

- AAV enters target cells by interacting with carbohydrates on their surfaces, such as sialic acid, galactose, and heparan sulfate[13]
- AAV5 is the vector used for valoctocogene roxaparvovec and etranacogene dezaparvovec for the treatment of hemophilia A and B, respectively[14,15]
- AAVRh74var is the vector used for fidanacogene elaparvovec[16]



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Melissa F. Glasner, Steven Pipe, Wolfgang Miesbach.
Gene-based therapies for hemophilia. Res Pract Thromb Haemost 2025 Apr 25;9(4):102870

Availability of Gene Therapy for Patients with Haemophilia

- Adeno-associated viral vector (AAV) GT treatments have been approved by various regulatory bodies (in UK, Europe and USA):
  - Haemophilia A (HA)
    - ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) (BioMarin, USA)
  - Haemophilia B (HB)
    - HEMGENIX® (etranacogene dezaparvovec) (CSL Behring, Germany)
    - BEQVEZ™ (fidanacogene elaparvovec-dzkt) (Pfizer, USA) (European commission withdrew marketing authorisation in May 2025)
- Regular measurement of post GT FVIII and FIX levels is by using existing assays:
  - One stage APTT based clotting factor assay (OSA)
  - Chromogenic substrate assay (CSA)

What are the Laboratory Considerations for Post Gene Therapy Monitoring?

- Intensive monitoring of factor levels in first 6 months
- Are both OSA and CSA available
- Can low factor levels be measured accurately with OSA or CSAs?
- Do current assays under or over-estimate factor levels?
- Does the reported factor level correlate with the clinical picture?

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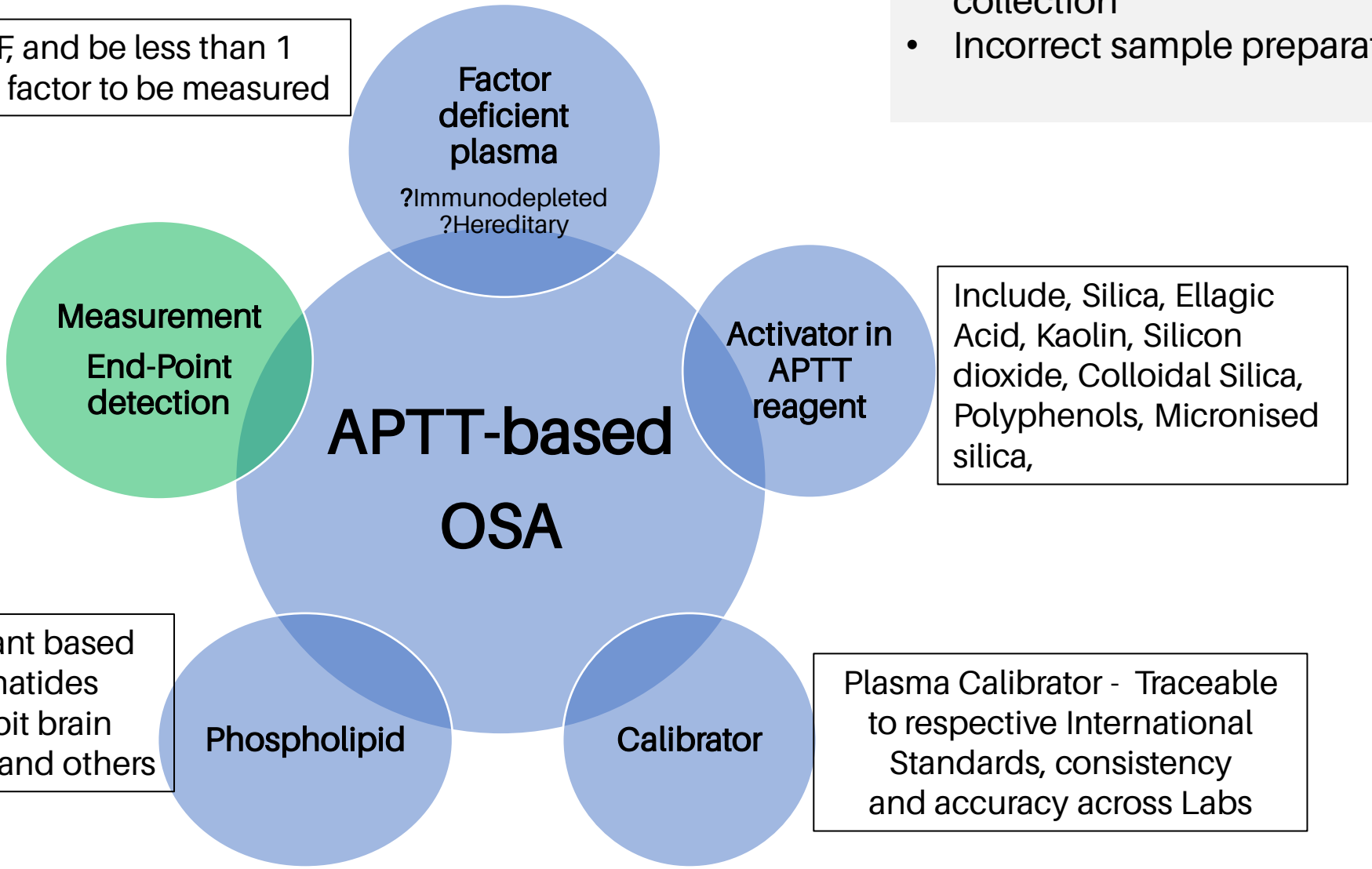
One Stage Assay (OSA)

Pre-analytical variables

- Sample activation during collection
- Incorrect sample preparation



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Adapted from Peyvandi F, Kenet G, Pekrul I et. al. J Thromb Haemost. 2020;18:1242–1255

OSA Summary

- FVIII OSA
  - Measures activation of FVIII and cofactor ability of FVIIIa
  - FVIII activated by endogenous thrombin (IIa) generated within the assay
- FIX OSA
  - Dependent on enzymatic activation of zymogen FIX to FIXa
- Modifications to FVIII or FIX
    - FC, albumin, pegylation to rFVIII and rFIX molecules or recently efanesoctocog alfa[1], can affect some OSA results
    - Dependent on type APTT reagent used (under or over estimation)[2]

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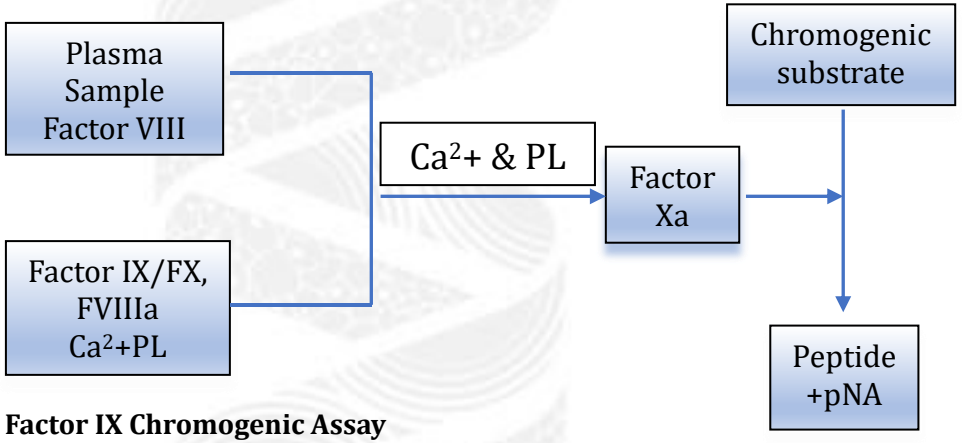
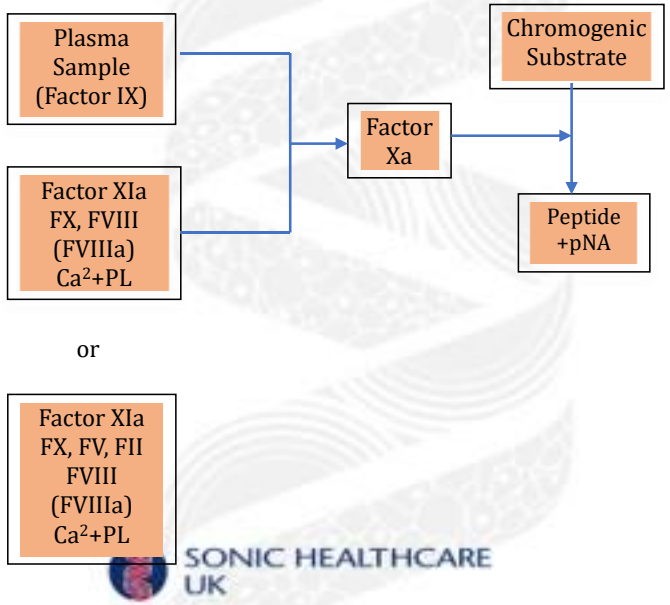
1. Steven Pipe, Ali Sadeghi-Khomami, Barbara A. Konkle, et.al., Haemophilia. 2024;30:214–223. 2. Gray E., Kitchen S., Bowyer A., Laboratory Measurement of factor replacement therapies in the treatment of congenital haemophilia A: A United Kingdom Haemophilia Centre Doctors Organisation guideline. Haemophilia 2020:26:6-16

Chromogenic Substrate Assays (CSA)

Factor VIII Chromogenic Assay



Factor IX Chromogenic Assay



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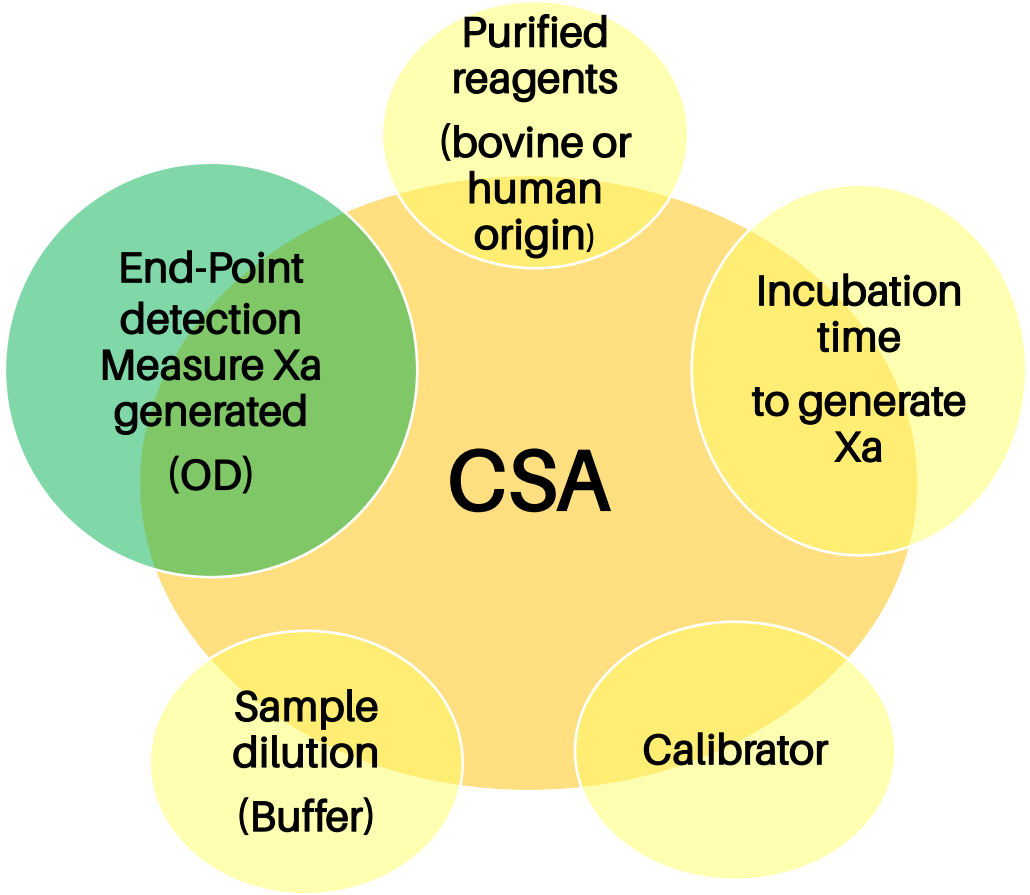
Lower inter & intra-laboratory variability



1. Adapted from Peyvandi F, Kenet G, Pekrul I et. al. J Thromb Haemost. 2020;18:1242–1255

CSA Summary

- FVIII
  - Measures cofactor ability of FVIIIa only
  - FVIII activated by addition of excess IIa (exogenous)

- FIX
  - FXIa activates FIX to FIXa
  - FIXa interacts with FVIIIa (activated by the exogenous IIa, or IIa formed by activation of exogenous prothrombinase complex) and FX on a phospholipid surface, converting FX to FXa

- Presence of modifications on FVIII
  - Known - addition of modifications e.g. efanesoctocog alfa, (CSA not recommended)[1]

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1. Steven Pipe, Ali Sadeghi-Khomami, Barbara A. Konkle, et.al., Haemophilia. 2024;30:214–223.

Which method (OSA or CSA) is a 'true' measurement of FVIII and FIX transgene clotting factors?

- Are post GT transgene FVIII and FIX the same as 'biological (native)' clotting factors?
- Should post GT clotting factors be expected to perform the same in our current assays as endogenous FVIII and FIX?

Biological (native) Clotting Factors	Post GT transgene Clotting Factors
• FVIII - Liver sinusoidal endothelial cells • Full-length FVIII	• FVIII - Liver hepatocytes • FVIII - B-domain missing (different modifications used in different GT products)
• FIX - Liver hepatocytes • Wildtype FIX	• FIX - Liver hepatocytes • FIX – original GT trials used wildtype coFIX, replaced with use of hyperactive FIX (FIX-Padua)
• Endogenous post translation modification	• Post transitional modifications, are they different?

What differences are seen when measuring FVIII and FIX levels post concentrate treatment?

Concentrates have a known potency assigned, traceable to an international concentrate standard

Measure episodic time points –post and fall-off clotting factor levels. Assays (OSA or CSA) use a calibrator traceable to a plasma international standard

Predicted recovery -dosage based on weight and target level

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1. Steven Pipe, Ali Sadeghi-Khomami, Barbara A. Konkle, et.al., Haemophilia. 2024;30:214–223.

What differences are seen when measuring FVIII and FIX levels post gene therapy treatment?

- No assigned potency to GT treatment
- No ‘true’ Internal Standard containing transgene derived FVIII or FIX available to be used as an assay calibrator/standard
- Not an episodic timepoint, measuring a ‘new’ baseline level of post gene therapy transgene clotting factor (can change over time)
- Not ‘predictable’ - post GT levels are likely patient specific and it is difficult to predict the final steady state transgene clotting factor level

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1. Steven Pipe, Ali Sadeghi-Khomami, Barbara A. Konkle, et.al., Haemophilia. 2024;30:214–223.

What is currently know when monitoring post GT FVIII clotting factors?

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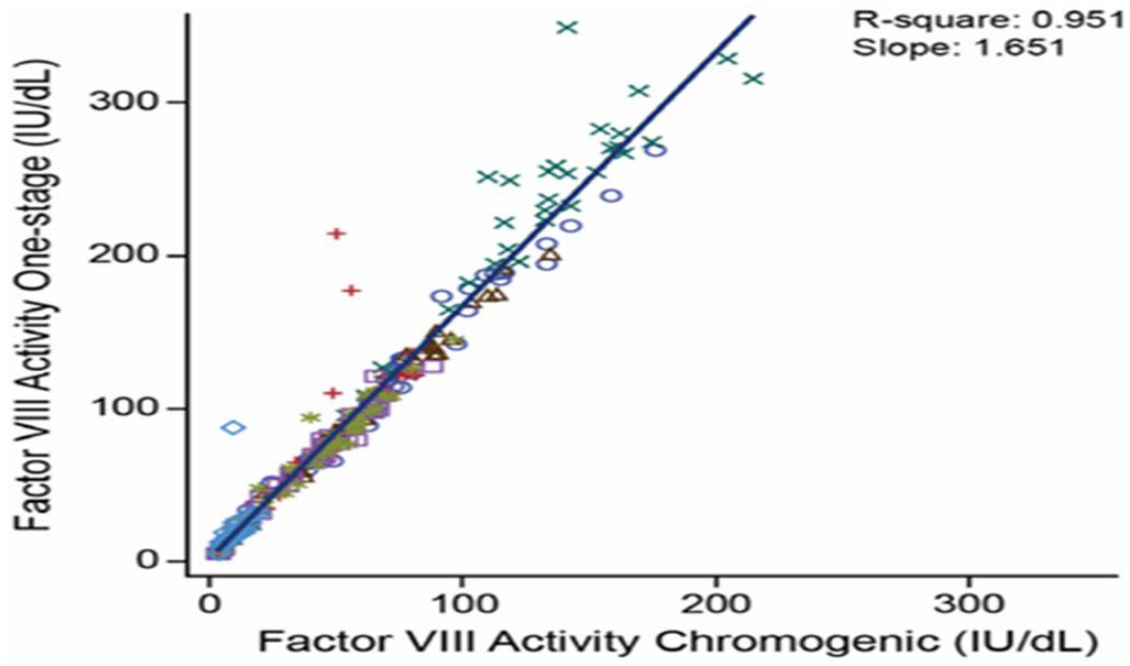
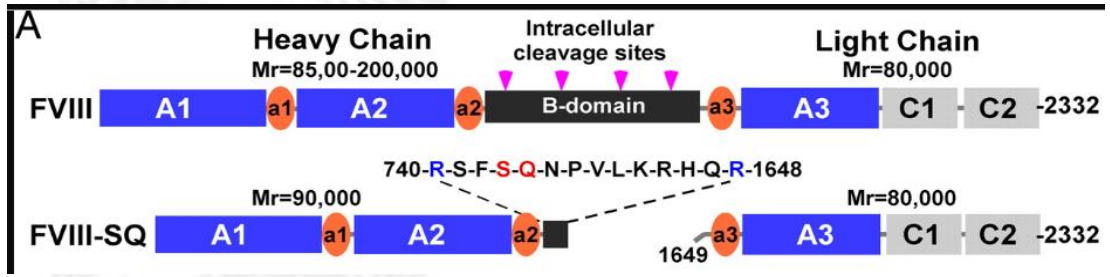
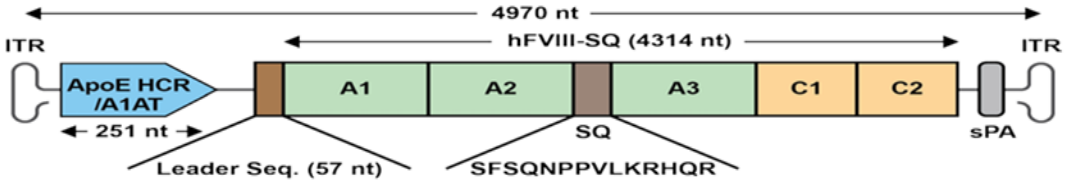
Factor VIII Gene Therapy - Phase 1 study (ROCTAVIAN™)







Valoctocogene roxaparvovec AAV5-hFVIII-SQ[1] infusion (generates a FVIII-B domain less GT transgene factor)

FVIII levels were – OSA was ~1.65 times higher than CSA result. Discrepancy was seen in preclinical studies and is not human specific.

Seven-year follow-up study[2] - Median OSA/CSA ratio ~1.9

FVIII Assay (APTT= Actin FSL), CSA used Coatest SP assay (Chromogenix)

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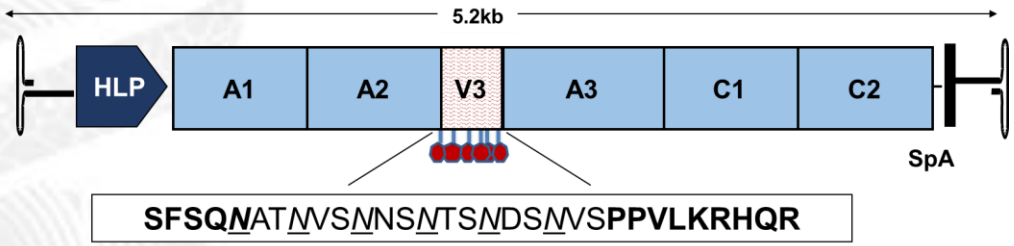
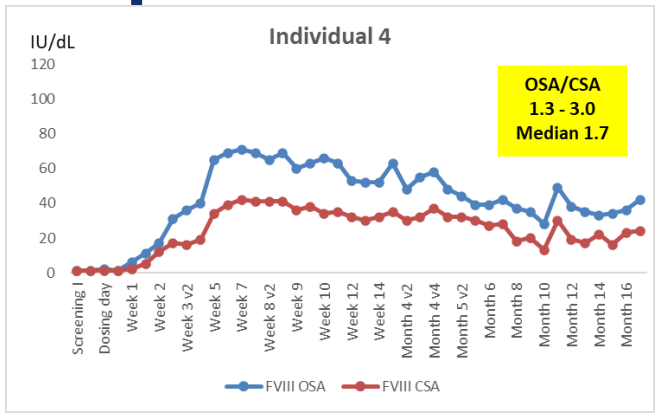
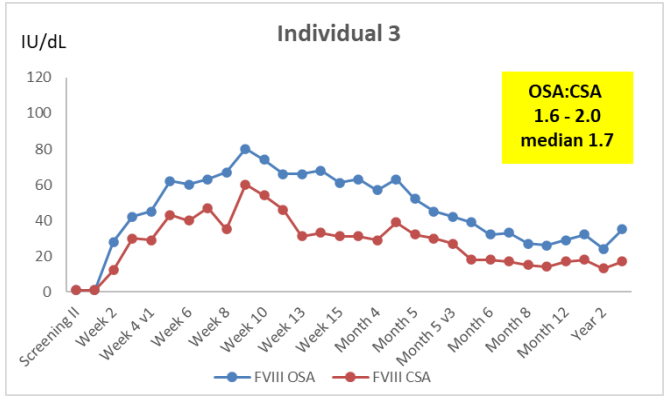
1. Rangarajan S, Walsh L, Lester W et al. N Engl J Med, 2017 Dec 28;377(26):2519-2530. 2. Symington E, Rangarajan S, Lester W et.el., Haemophilia. 2024;30:1138–1147. 3. Figure by Cao W June 2008, Proceedings of the National Academy of Sciences, 105(21):7416-21

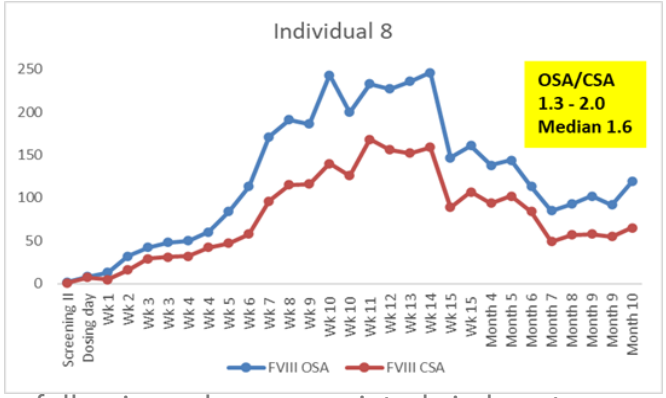
Factor VIII Gene Therapy for severe HA - GO-8 phase I/II Study[1]



- AAV-HLP-hFVIII-V3 (generates a FVIII-B domain less GT transgene factor), produced 3-fold higher FVIII expression in pre-clinical studies
- FVIII measured by OSA (SynthASil) and a CSA (BIOPHEN FVIII) - example results of 3/12 patients enrolled up to year 2 (OSA higher than CSA level)
- Stable expression of factor VIII up to 5 years (2023). Nine of 12 participants have remained off FVIII prophylaxis[1]







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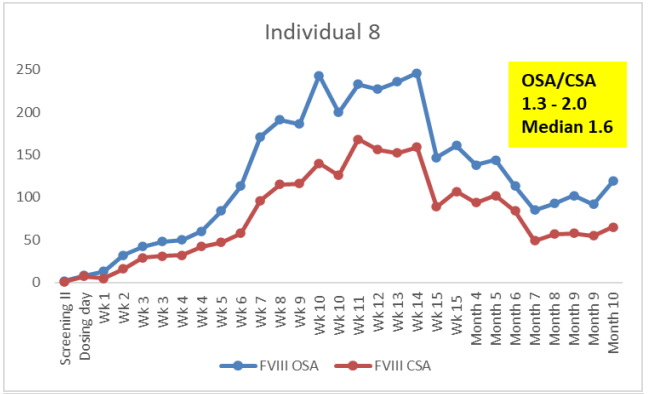
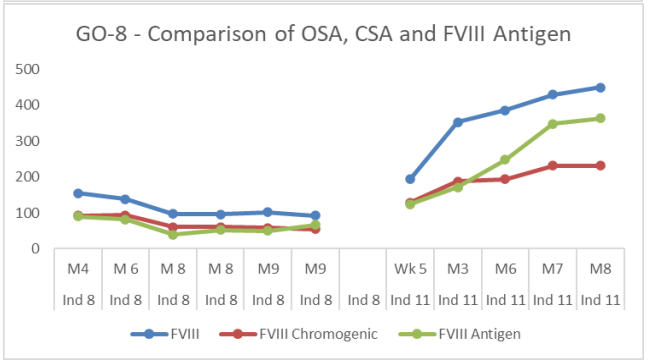
1. Chowdary P, Reiss U., Tuddenham E.G.D. et al ASH 2023 - Go8: Stable expression of factor VIII over 5 years following adeno-associated viral vector-mediated gene transfer in participants with severe haemophilia using a novel human factor VIII variant.

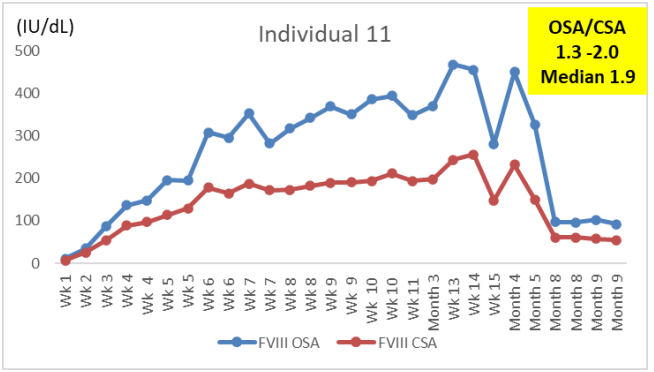
Internal Study Comparing FVIII OSA, CSA and Antigen levels in patient samples (n=2) post GT (AAV-HLP-hFVIII-V3) (GO-8)

- Observed FVIII CSA levels appeared to correlate with FVIII Antigen levels in Individual 8, but not in Individual 11 at very high levels (>200 IU/dL)

- Assays used: OSA (SynthASil APTT), CSA (BIOPHEN® FVIII), FVIII antigen (Asserachrom® FVIII Ag ELISA)







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Observations

- Higher OSA compared to CSA
- Highest OSA compared to CSA FVIII levels were when patients were on prophylactic steroids
- FVIII OSA:CSA ratios
  - Consistent across our patient group (median ranged ~1.6 – 1.9)
  - Similar to OSA/CSA differences reported in Phase 1/II Roctavian™ study (median = 1.65)

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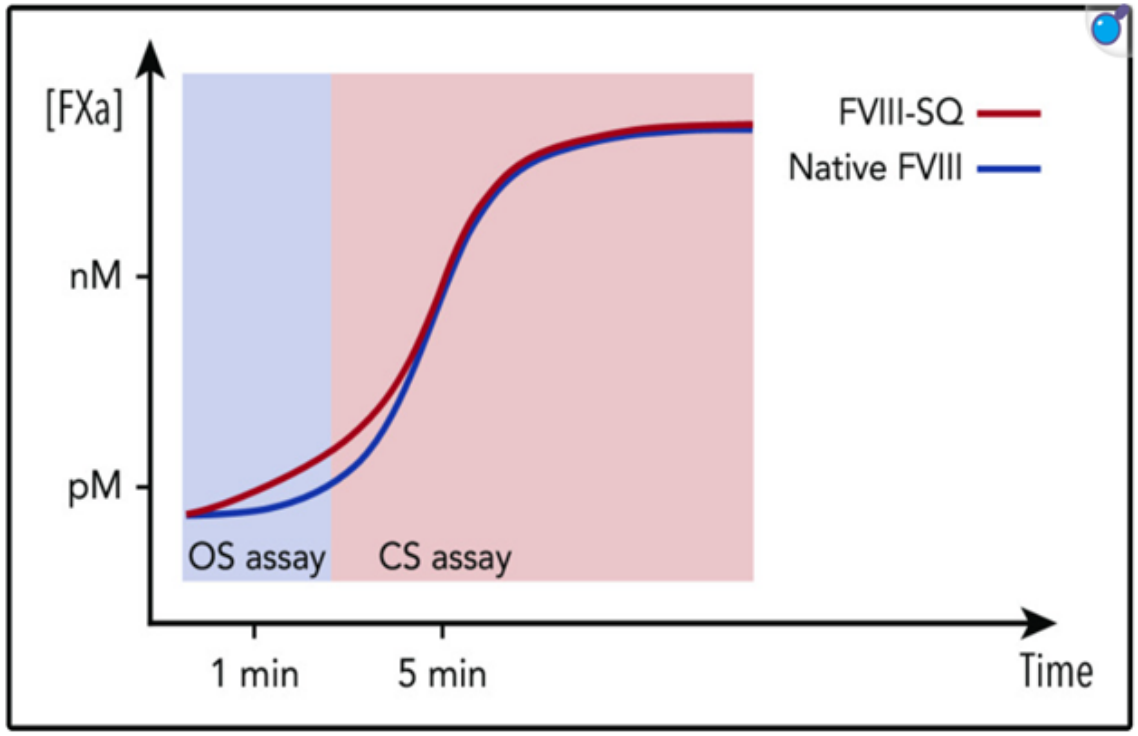
What aspects of post FVIII GT FVIII OSA/CSA discrepancies have been investigated?

- Underlying mechanism not known, reproducible and occurs across all studies[1]
- ?Secondary to expression in hepatocytes and/or codon optimization *F8* DNA impacting functional properties[1]
- Transgene-derived FVIII (BMN 270-SQ) activity produces an initial burst in FXa and thrombin in OSA that is not observed with the CSA[2]
- Does this explain higher FVIII OSA values observed in GT patients?



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1. Samuelson-Jones B.J., Small J., George L. Roctavian Gene Therapy for Haemophilia A. Blood Advances 2024: 8: 19 5179 – 5189.
2. Rosen S., Tiefenbacher S, Robinson M et al. Activity of transgene-produced B-domain–deleted factor VIII in human plasma following AAV5 gene therapy. Blood. 2020;136(22):2524–2534

Summary – Monitoring FVIII-GT levels

- Discordant results in same sample by OSA and CSA

- Consistent across all reported trials
- OSA higher compared to CSA
- OSA:CSA median ratios are similar across reported studies

- Recommendations:
  - Use type of assay for monitoring as per SMPC
  - Recent UKHCDO Gene Therapy Taskforce guidelines – FVIII CSA1
  - Unclear which assay tracks with bleeding phenotype post FVIII GT?

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1. Chowdary P., Duran B., Batty P., et al. UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults. Haemophilia; 2024;1–13

What is currently known about monitoring post GT FIX clotting factors?

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FIX Gene Therapy

- First GT trials used AAV vectors that produced codon optimised or native wildtype FIX (E.g. UCL sponsored – AAV8 AGT4HB trial[1]) (Follow-up period now12 years)
- Licensed FIX GT products (HEMGENIX and BEQVEZ) use (AAV5 or AAV AAVRh74 respectively) FIX Padua (R338L) produces a hyper-functional FIX
- GT FIX Padua has a high specific activity - Antigen: Activity ratio = 1:8
- Comparable to case report of wt FIX Padua - Antigen:Activity 1:5-10X[2]
- 2018, factor activity assay data for a FIX gene therapy candidate PF-06838435 (SPK-9001)(BEQVEZ) containing a high specific activity FIX-Padua variant (p.R338L)presented at ASH[3]

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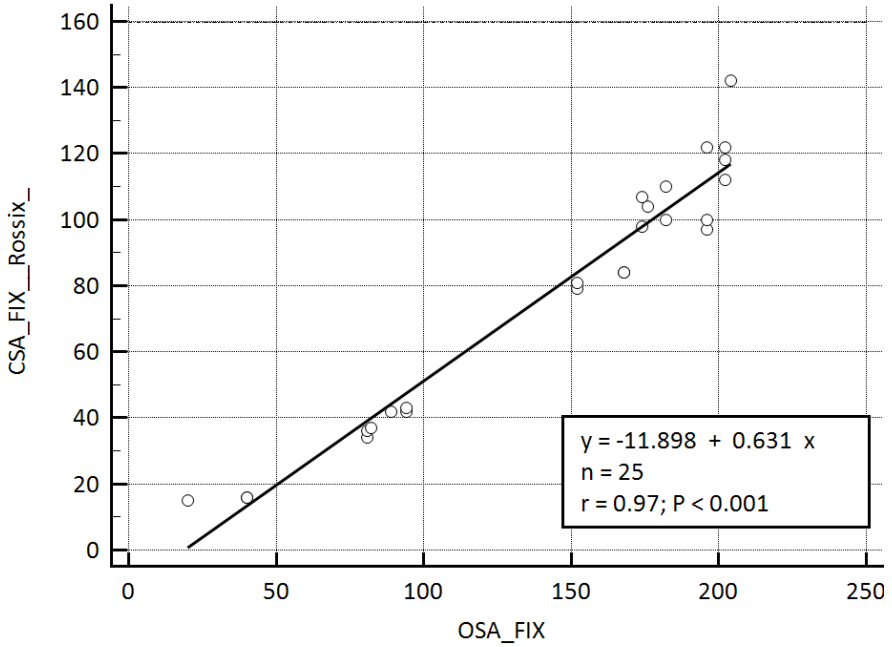
1. Nathwani A.C., Reiss, U.M., Tuddenham E.G.T. Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B N Engl J Med 2014;371:1994-2004. 2. Simioni P., Tormene D. Tognin G. et. al., X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua) 2009 N Engl J Med 2009;361:1671-1675. 3. Robinson M, George LA, Samuelson-Jones BJ, et al. Activity of a FIX-Padua transgene product in commonly used FIX: C one-stage and chromogenic assay systems following PF-06838435 (SPK-9001) gene delivery. Blood. 2018;132:2198.

Phase 1 / 2 B-AMAZE (FLT180a) Study in Haemophilia B

- AAV3 vector with gain-of-function FIX (FIXR388L) sequence
- 10 participants recruited
- Post FIX levels measured by OSA (SynthASil)
- FIX levels ranged from 7 – 280 IU/dL over the trial period[2]
- 2018 started to use CSA and a discrepancy between OSA and CSA (CSA lower than OSA)[1]
- Analysis of left-over local lab (RFH) samples (n=25) with a CSA (Rossix) and OSA
- ↓CSA vs OSA (CSA:OSA 0.4 – 0.8)



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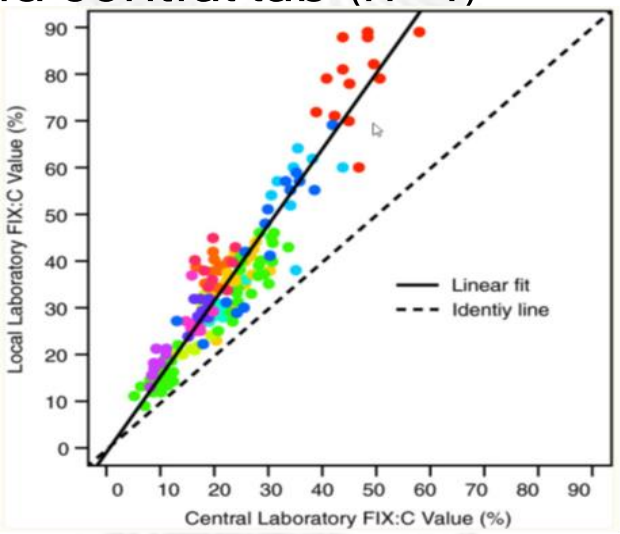
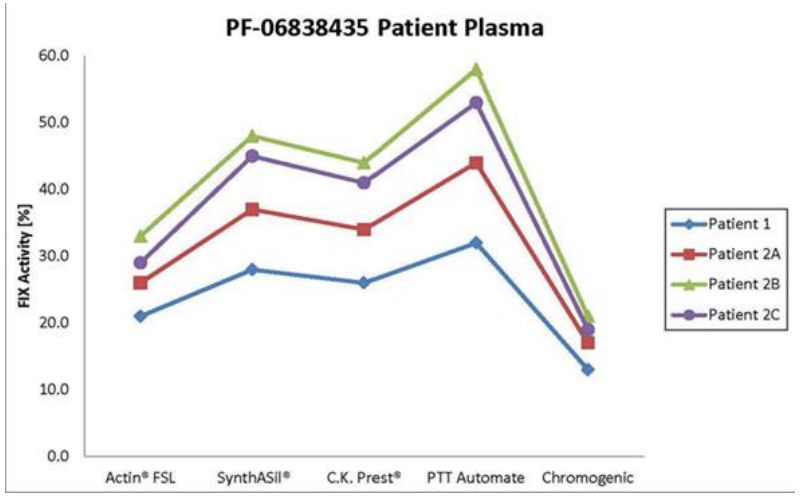
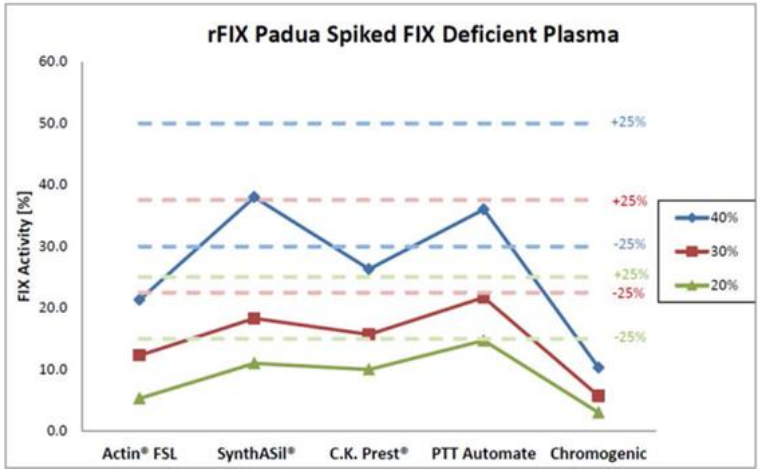
1. Chowdary P, Shapiro S., Boyce S., et. Al FLT180a . Next Generation AAV Vector for Haemophilia B - Long Term, Follow- up and In-depth Analysis of Transgenic FIX Using One- stage, Chromogenic and Global Assays. J Thromb Haemst 2019: 3 (S1).
2. Chowdary P, Shapiro S, Makris, et al. Phase 1-2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia BN Engl J Med. 2022 Jul 21;387(3):237-24

What have others shown when measuring FIX-388L?

- During Phase 1/2 trial for BEQVEZ[1] OSA FIX differences between Central Lab vs Local Lab were seen[1]
- Compared pooled congenital FIX-deficient plasma spiked with purified rFIX Padua (BEQVEZ) or rHFIX (BENEFIX) from ~20% to ~40%, study subject samples (n=5) at local (n=4) and central lab (n=1)







- FIX OSA (Actin FSL) had lower results other FIX OSAs. FIX levels by CSA were lowest, OSA selection may be an important consideration when measuring FIX-Padua activity.

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1. Robinson MM, George LA, Carr ME, et al. Factor IX assay discrepancies in the setting of liver gene therapy using a hyperfunctional variant factor IX-Padua. J Thromb Haemost 2021;19:1212-1218.

Second BEQVEZ FIX-Padua Field Study

- Compared FIX-R338L (fidanacogene elaparvovec (BEQVEZ) participant plasma samples) to wild-type FIX in normal control plasma samples

- Samples tested in a Central Lab and 18 local labs in 13 countries
  - OSA (N=10 APTT reagents) and CSA (N=2 types)

- FIX-R338L activity ↑silica–based FIX OSA versus ellagic acid–based OSA and CSAs

- Results support previous findings that a range of FIX activities may be determined for a given sample depending on the specific assay and/or reagents used[1]

1. Pittman D., Carrieri C., Soares H., Field Study and Correlative Studies of Factor IX Variant FIX-R338L in Participants Treated with Fidanacogene Elaparvovec 2024 Thromb Haemost.Jun 11;124(10):912–921

What did FLT180a investigators do to investigate FIX OSA/CSA differences?

- Field Study - rFIX-R388L (rFLT180a) spiked into FIX def. plasma at (5, 20, 50, 100 and 150 IU/dL) (surrogate samples - mimic patient levels)
- Two control samples - (plasma SSC/ISTH Std (Lot 4) & WHO 5th concentrate Std included
- Samples (n=7) sent to 38 laboratories in 11 countries (3 separate deliveries)[1]

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1. Foley JH, Shehu E, Riddell A, et al. Differences in wild-type- and R338L-tenase complex formation are at the root of R338L-factor IX assay discrepancies. Blood Adv 2023;7:458-467.

FLT180a Field Study Results

- 33 clinical samples from 5 patients in FLT180a trial also measured by FIX OSA (SynthASil) and CSA (Rossix) in the central lab
- Inter-laboratory variability similar for R388L-FIX samples and pdFIX Controls
- 1.8-fold variation across OSA assays, 3-fold range variation between OSA and CSA
- OSA group differences seen:
  - Linked to activating reagent/phospholipids
  - Activating reagent and/or reaction time, impacts FXIa generation
- CSA differences appear to be a function of how FVIIIa is generated[1&2]

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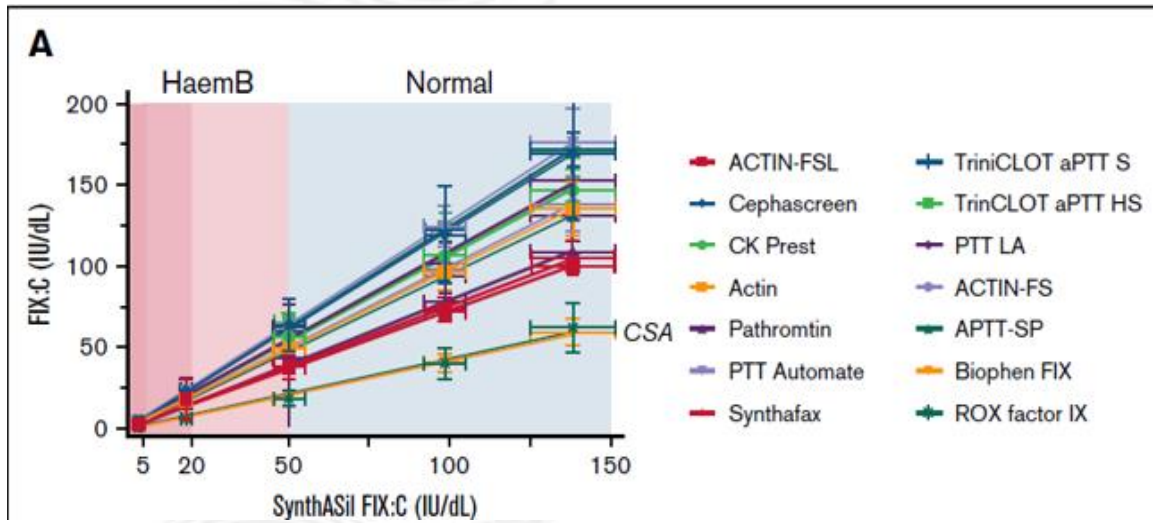
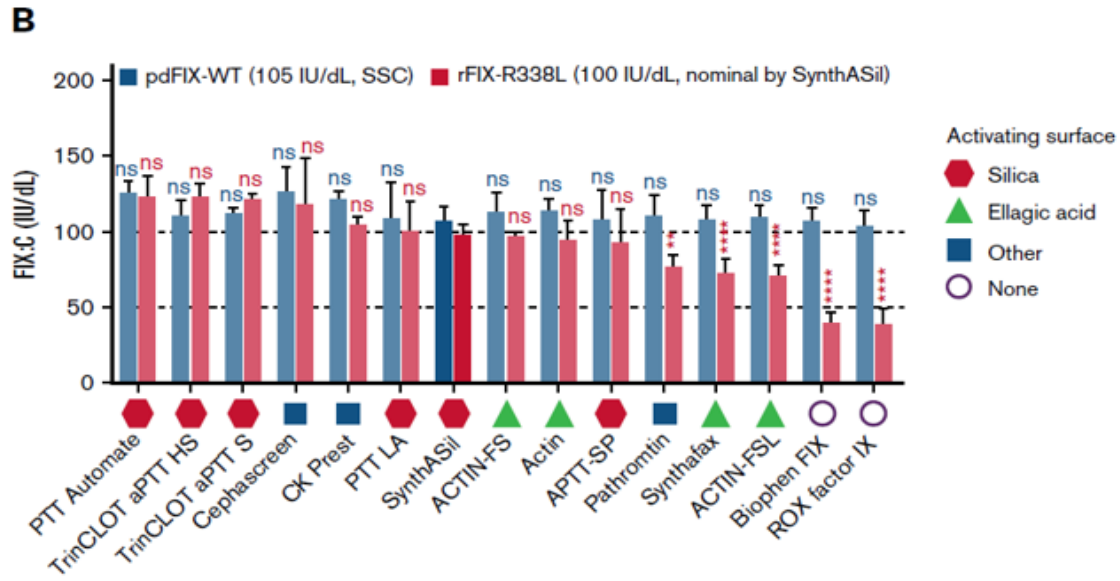
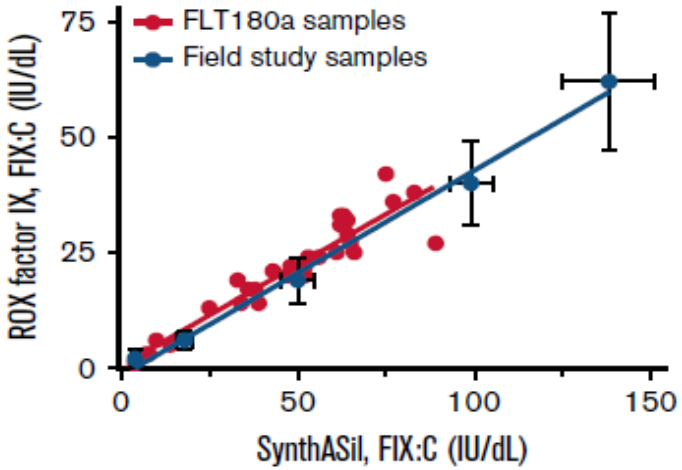
1. Foley JH, Shehu E, Riddell A, et al. Differences in wild-type- and R338L-tenase complex formation are at the root of R338L-factor IX assay discrepancies. Blood Adv 2023;7:458-467. 2. Samelson-Jones B, Camire R, Arruda V. Hyperactivity of FIX Padua (R388L depends on FVIIIa co-factor activity. JCI 2019:4; (14) 1-14

FLT180a Field Study Results cont







Values from FLT180a patient samples compared with the activity of rR338L-FIX spiked into FIX def. plasma by HemosIL SynthASil OSA FIX method

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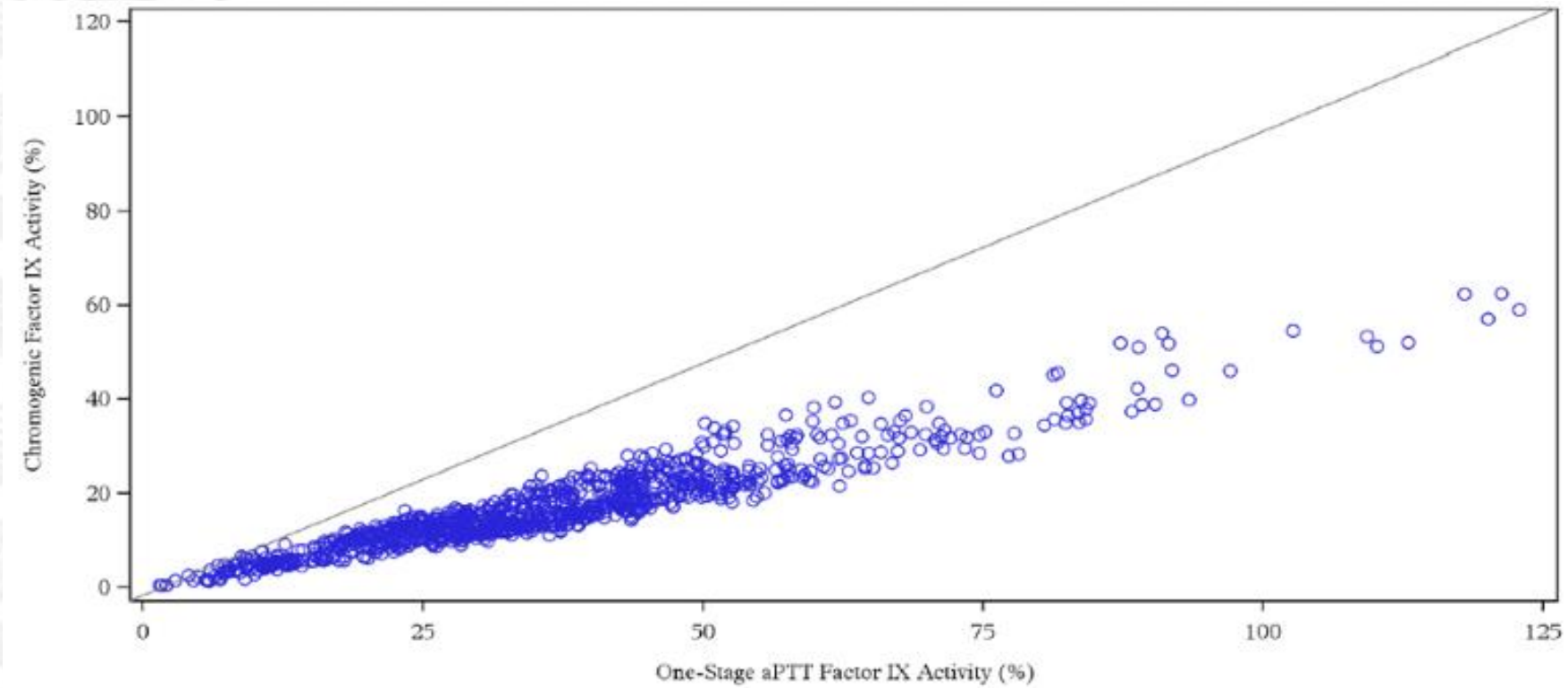
FIX Gene Therapy Trial – HOPE B



- AMT061 - licensed as HEMGENIX – HOPE B[1]

- Lower CSA compared to OSA results (0.41 to 0.55)

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1. Steven W. Pipe, M.D., Frank W.G. Leebeek, M.D., Ph.D., Michael Rech Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B N Engl J Med 2023;388:706-718

Summary - Monitoring FIX-GT levels

- Discordant OSA and CSA results obtained
  - Consistent across all reported trial results

- OSA levels higher (up to 2.5Xs) than CSA levels
  - CSA:OSA median ratios are similar across current reported studies

- Recommendations:
  - Use type of assay for monitoring as per SMPC
  - UKHCDO GT Taskforce guidelines – recommend against FIX CSA[1]

- Currently it is unclear which assay (OSA or CSA) tracks with bleeding phenotype post FIX GT?

SONIC HEALTHCARE UK

1. Chowdary P., Duran B., Batty P., et al. UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults. Haemophilia; 2024;1–13

Latest FVIII Gene Therapy Studies

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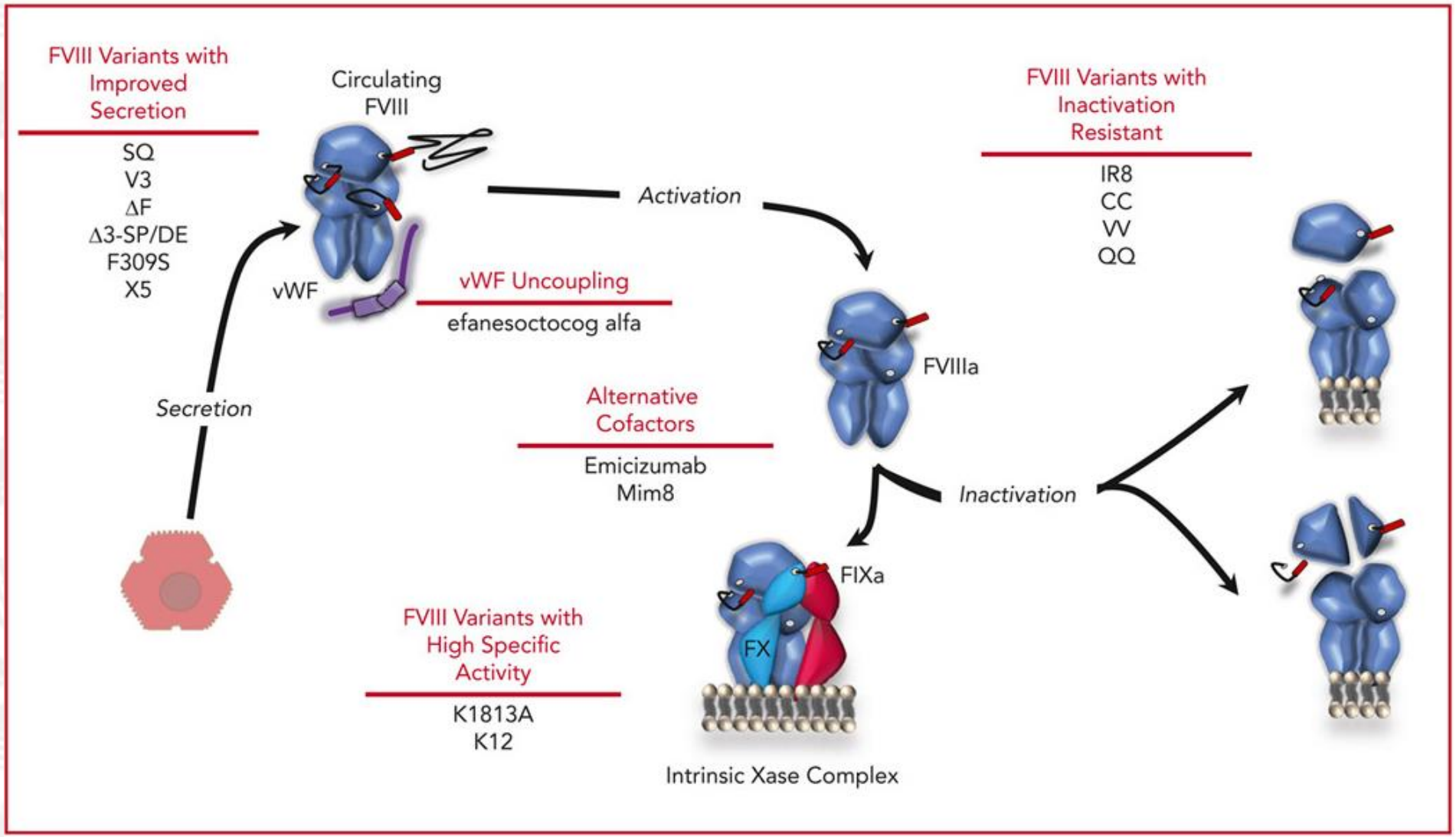
FVIII Gene Therapy (Factor VIII Variants : Improved Secretion)



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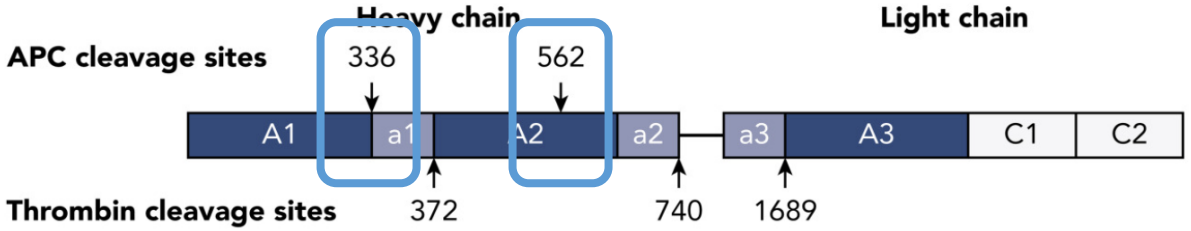
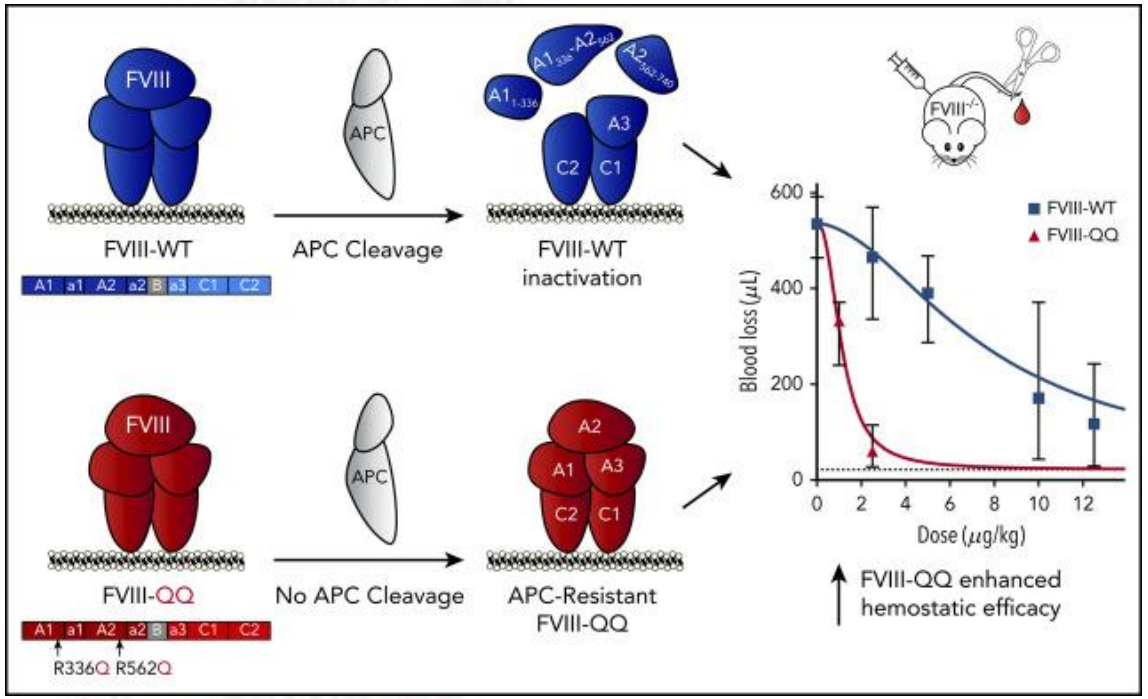
Slide from Dr Paul Batty, RFH Haemophilia and Thrombosis Centre, London, UK

Factor VIII Variants : Inactivation Resistance

Sternberg et al 2024 Nature Comms



FVIII-QQ: Arg336Gln + Arg562Gln



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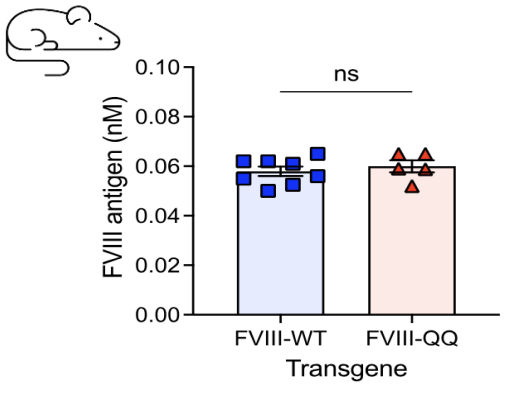
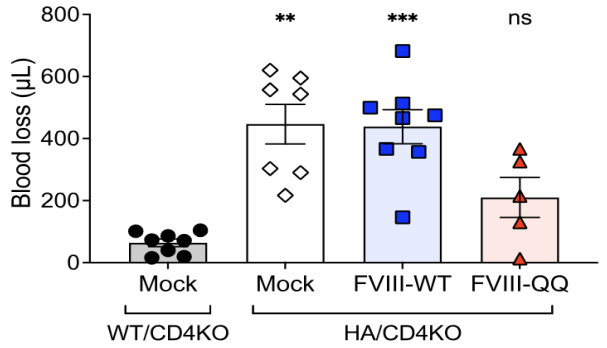
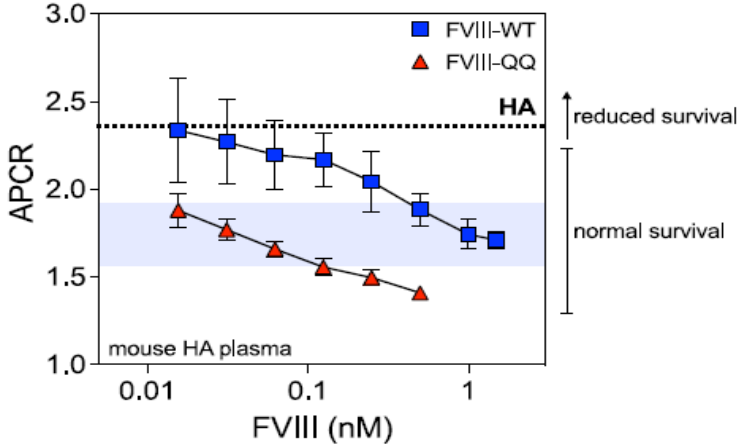
Slide from Dr Paul Batty, RFH Haemophilia and Thrombosis Centre, London, UK

Improvement in Bleeding Phenotype





Enhanced Procoagulant Function of FVIII-QQ



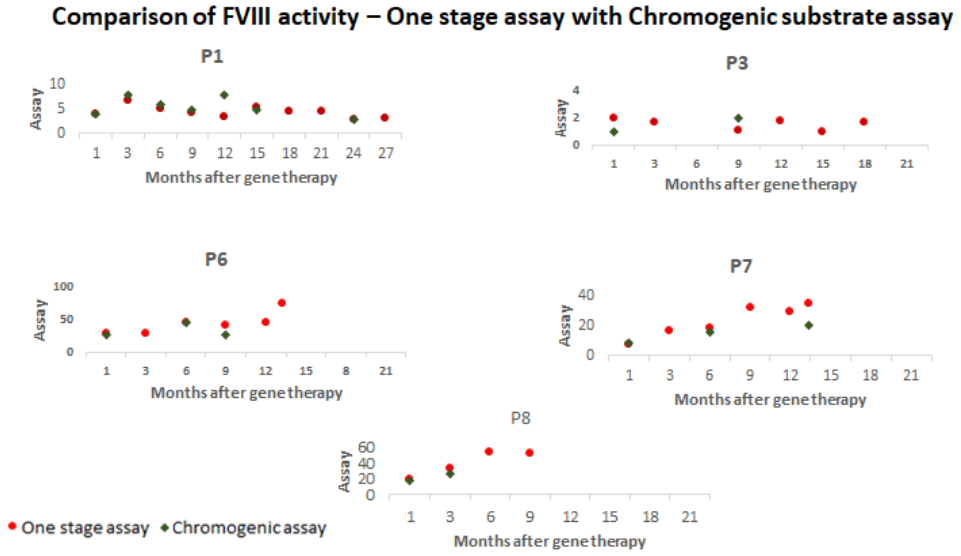
Express an enhanced function FVIII variant to normalize hemostasis at low plasma FVIII concentration permitting expression durability in this model

Lentiviral Gene Therapy with CD34+ Hematopoietic Cells for HA

Phase I Study - patients (N=5) underwent myeloablative conditioning, followed by transplantation of autologous hematopoietic stem cell (HCS) transduced with the (CD68-ET3-LV vector) (LV=Lentivirus) containing a new F8 transgene - (ET3) with a myeloid-directed CD68 promoter

- Median FVIII activity levels, by OSA, after day 28 - 5.2 IU/dL (range, 3.0 to 8.7) and by last follow-up visit 1.7 IU/dL (range, 1.0 to 4.0)

- Authors noted concordance between the FVIII OSA and the CSA values



OSA and CSA results
(Brand of reagents used not stated

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A. Srivastava, A. Abraham, F. Aboobacker, G. Singh, T et al. N Engl J Med 392;5 nejm.org January 30, 2025

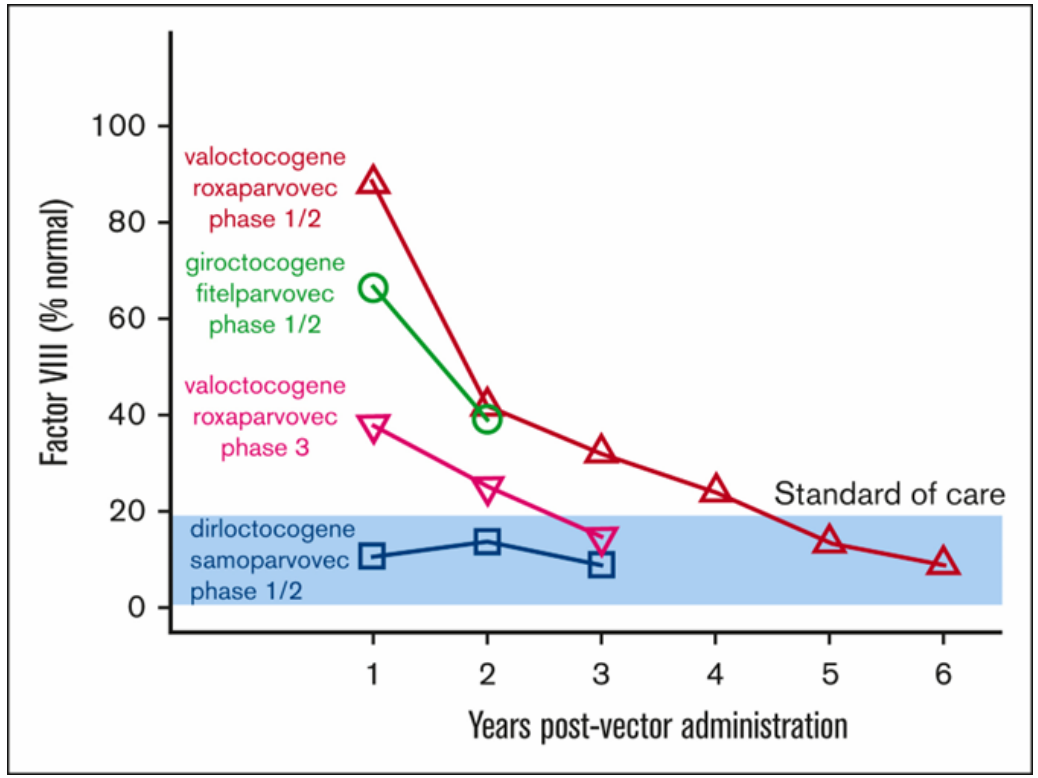
Practicalities of Long-Term Laboratory Monitoring

- Able to maintain stability of OSA and CSA over many years
- Choosing the ‘correct’ or recommended assay and ‘stay’ with it
- If assay changes occur - use GT samples in a verification study
- The Laboratory assays should be:
  - Reproducible and accurate
  - Standardised and Quality controlled
  - Good Sensitivity – how low do we need to measure accurately (know LLOQ)

SONIC HEALTHCARE UK

1. Chowdary P., Duran B., Batty P., et al. UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults. Haemophilia; 2024;1–13

Factor VIII Gene Therapy



Average FVIII levels over time after AAV gene therapy.

Median FVIII levels as determined by either OSA or estimated OSA by multiplying the available CSA values by 1.6, except for giroctocogene fitelparvovec for which only mean values reported.

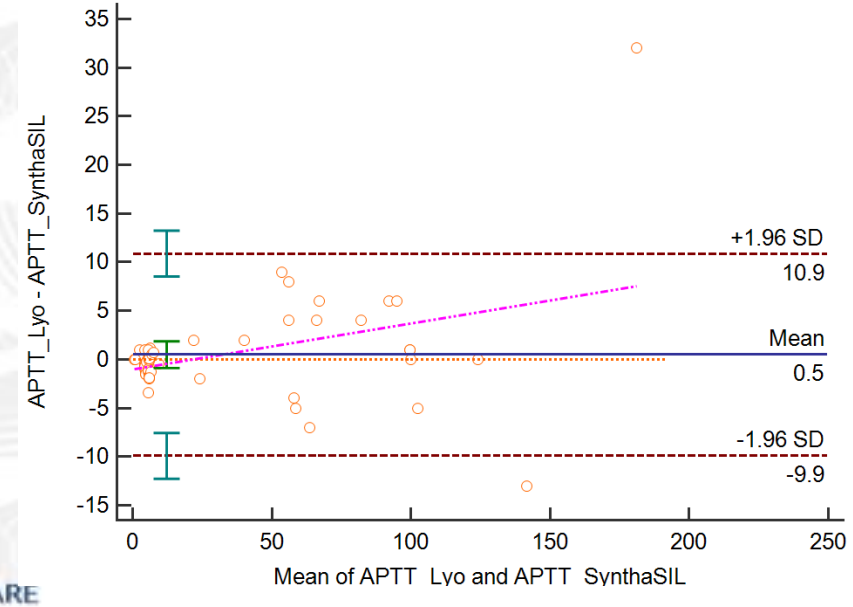
The blue rectangle indicates prophylactic FVIII or FVIII-equivalency achieved by current standards of care.

1. Benjamin J. Samelson-Jones, Juliana C. Small, Lindsey A. George, Roctavian gene therapy for hemophilia A, Blood Adv, 2024

What happens if a change of reagent type is required in your FIX Assay?

We changed APTT reagent 2 years in to monitoring patients who received full-length WT FIX AAV5-AGT4HB trial

Compared HemosIL OSA Lyo (Werfen) to HemosIL SynthASIl FIX OSA FIX levels patient samples (normal, post concentrate treatments and samples containing post FIX AGT4HB GT



	Normal Level (~100 IU/dL) APTT-Lyo/APTT-SynthaSIL	Abnormal Level (~25IU/dL) APTT-Lyo/APTT-SynthaSIL
Intra Assay CV%	5.9/4.6	7.0/3.7
Inter Assay CV%	2.9/5.5	5.0/6.7

Conclusion:
No significant difference in results following APTT reagent change including no effect on post GT FIX measurements seen

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Guidance

- Guidelines:
  - UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults[1]
    - 'No conclusive evidence for which OSA or CSA best reflects the in vivo FVIII activity, most GT programmes now exclusively report FVIII:C using CSA'
    - 'FIX CSA has limited laboratory and clinical applicability and should not be used for the routine monitoring of FIX transgene expression'
    - 'Known variability between APTT reagents in the OSA field studies of the Padua FIX molecule'
    - Careful selection of assays and reagents
  - Qualification Criteria of Gene Therapy for Haemophilia—Opinion of the EAHAD Gene Therapy Working Group[2]
    - Recommend factor assay results be available within 6 hours

SONIC HEALTHCARE UK

1. Chowdary P., Duran B., Batty P., et al. Haemophilia; 2024;1–13
2. Miesbach W., Boban A., Chowdary P., Coppins M., et.al. Haemophilia. 2025 Jul 17;31(5):966–972

Guidance

- SmPC has sections on the Laboratory measurement or post GT FVIII or FIX clotting factor levels including information on assays used on the phase 1-3 studies:
  - https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix
  - https://www.ema.europa.eu/en/documents/product-information/roctavian-epar-product-information_en.pdf

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1. Chowdary P., Duran B., Batty P., et al. Haemophilia; 2024;1–13
2. Miesbach W., Boban A., Chowdary P., Coppins M., et.al. Haemophilia. 2025 Jul 17;31(5):966–972

Summary

- Clinical Team inform the Laboratory when sending samples for post monitoring levels:
  - What product (concentrate or GT product or both) so, the right assay can be selected
  - Communication between clinical and lab teams is essential
- Field studies using real post GT patients or 'spiked' GT factor samples enables comparison to a known sample with transgene clotting factors, and helps to inform correct assay choice
- Laboratories should:
  - Run verified, timely, accurate, & appropriate assays
  - Keep consistency of assays for monitoring post GT factor levels (ideally use same OSA or CSA throughout)
  - Likely **long-term monitoring required (Years) will be required**, changes in reagents/analysers/assays do occur:
    - Verify changes using post GT samples
    - Participate in EQA schemes

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