



**21<sup>ST</sup> AUSTRALIAN CONFERENCE** ON HAEMOPHILIA, VWD AND  
RARE BLEEDING DISORDERS  
*WORKING TOGETHER - IMPROVING OUTCOMES*

# **Australian Experience and Challenges with New and Emerging Haemophilia Therapies**

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# Topics

## New and Emerging Therapies

- Australian Experience
- Challenges and Opportunities Ahead



# Whole Team Approach

**Musculoskeletal Experts**

- Rheumatologist
- Orthopaedic surgeons

**Physiotherapists**

**Laboratory Scientists**

**Patient Support Organisation and Advocacy Groups**

**Haemophilia Foundation**

**Research**

**Government Funders**

**Nurses**

**Hospitals**

**Dentists**

**Doctors**

**Social Workers**

**General Practitioners**

**Patients and their Families**

**HIV Specialists**

**Chronic Pain Specialist**

**Telehealth**

**Psychologist**

**O&G team**

**Outreach to Rural areas**

**Liver Specialists**

**Geriatricians**

**Cardiologist**

# Evolution of Haemophilia Therapies

## 1950s-1960s

Blood, Plasma  
Cryoprecipitate

## 1960s-1970s

Plasma-derived  
clotting factor  
concentrates

- On-demand therapy
- **Wide spread viral contamination : Hepatitis, HIV**

## 1980s-1990s

Recombinant  
clotting factor  
concentrates

- Improved pathogen safety
- Home prophylaxis
- Haemophilia Treatment Centres

**BURDEN of  
treatment with  
factor  
concentrates**

## 2000s-2010s

Extended half-life  
(EHL)  
clotting factor  
concentrates

- Fewer injections
- **Improved QOL** / adherence to prophylaxis

## 2010s and beyond

Novel Therapies  
“Steady State”

- Non-factor replacement (NFT)
  - Antibodies
  - Re-balancing :siRNA
- Gene therapy

**BEYOND factor  
concentrates**

# What we have now: 2023

Recombinant products available to all patients (recombinant products since 2004)

## Factor VIII

1. Advate (Takeda) – recombinant standard Half Life FVIII
2. Xyntha (Pfizer) – recombinant standard Half Life FVIII
3. Adynovate (Takeda) – Extended Half Life FVIII
4. Eloctate (Sanofi) – Extended Half Life FVIII

## Non-Factor replacement

1. Hemlibra (Haemophilia A)

## VWF containing FVIII concentrates

1. Biostate (CSL) – plasma derived. Contains Both FVIII and VWF

## Factor IX

1. BeneFIX (Pfizer) – recombinant FIX
2. Alprolix (Sanofi) – EHL FIX

## Bypassing agents:

1. rVIIa Novoseven (NovoNordisk)
2. FEIBA (Takeda)



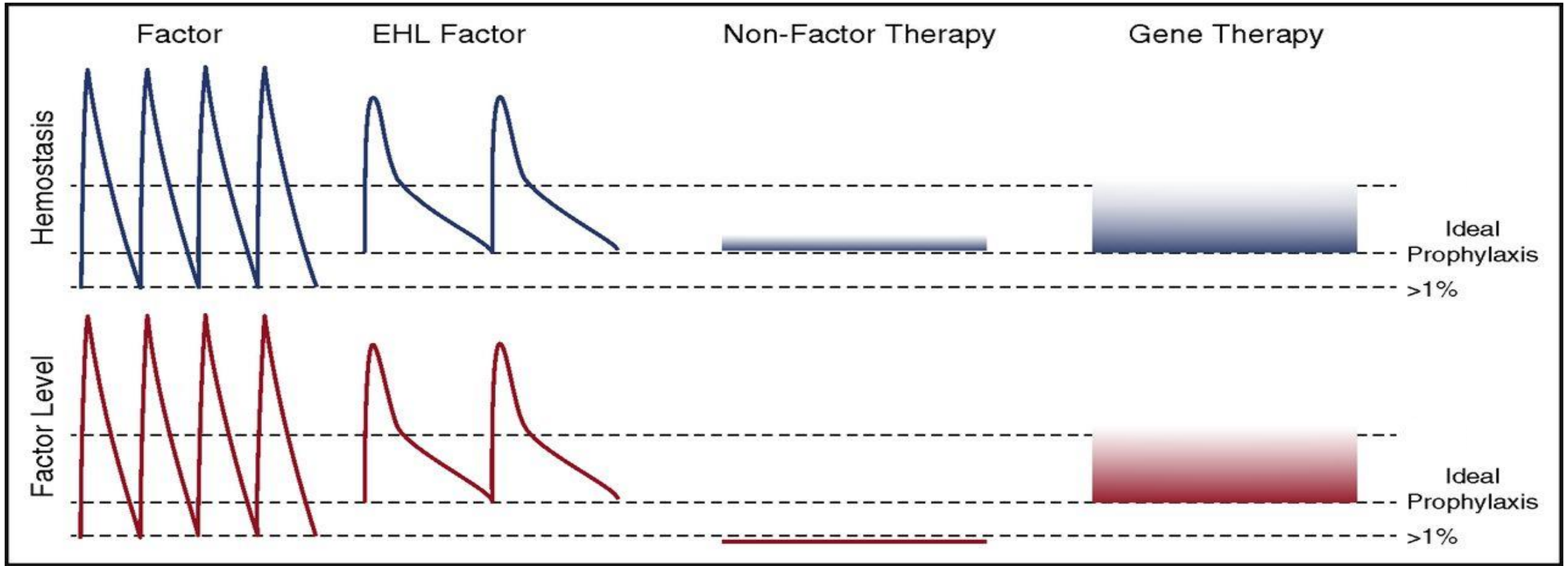
Tender Outcomes - Imported Plasma and Recombinant Products – Patients with Bleeding Disorders



**Clinical Trials of Newer Therapies**



# Newer therapies for Haemophilia



Valder R. Arruda, Bhavya S. Doshi, Benjamin J. Samelson-Jones, Novel approaches to hemophilia therapy: successes and challenges, Blood, 2017

PEG  
Fc receptor  
Single chain  
Albumin

**BIVV001**  
(Efanesoctogoc Alfa)

Antibodies and Re-Balancing therapies:

- Antibodies: **Emicizumab**
- Anti-TFPIs : **Concizumab**
- siRNA (ATIII): **Fitusiran**
- **Serpin PC**
- **Protein S**

**Gene Therapy**

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

# **Australian Sites have participated in 64 Clinical Trials\***

(not including some of the investigator initiated studies)

- Includes previous (completed) and active trials
- Some are interventional with newer therapies
- Some are non-interventional : joint health; bleeding patterns

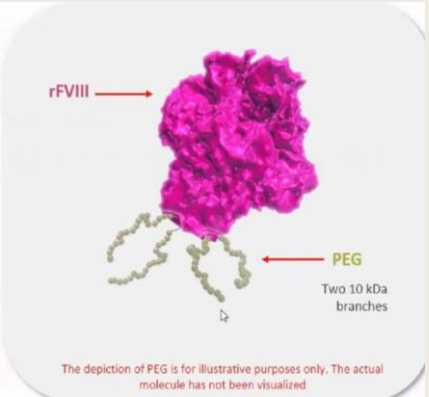
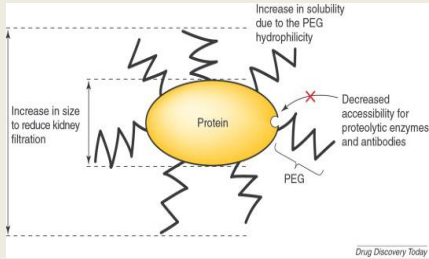
\* <https://clinicaltrials.gov/>

# Technologies for Factor VIII and IX Half-Life Extension



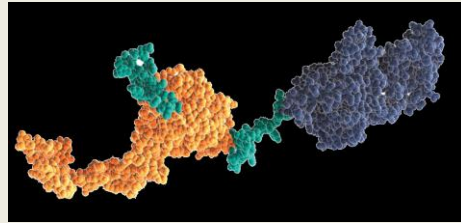
Increase Circulation Time of FVIII/FIX - Fewer Injections

## PEGylation

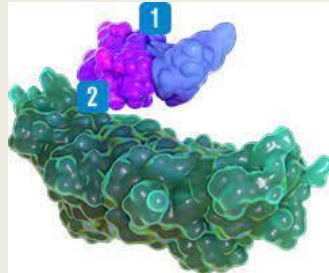


## Fusion Proteins

- Albumin

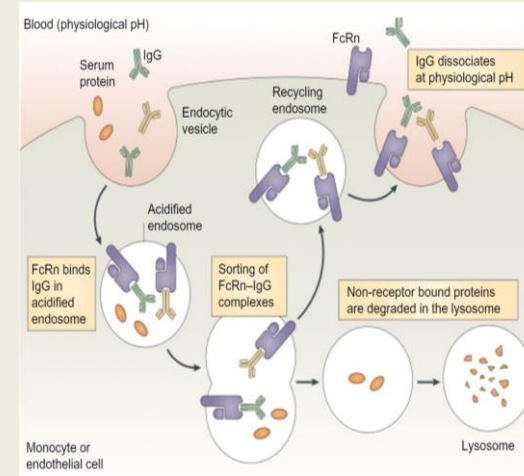


## Single Chain (FVIII)



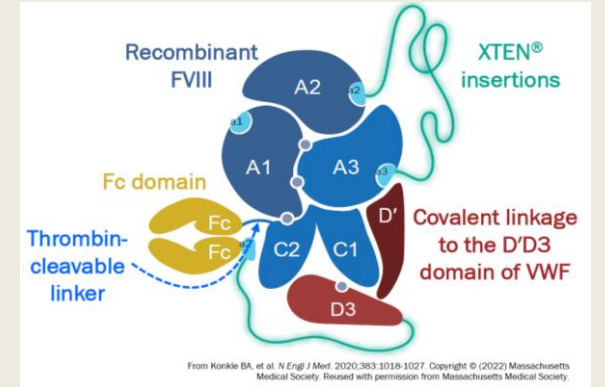
## Fusion Proteins

- IgG<sub>1</sub>-Fc receptor



## Fusion Proteins

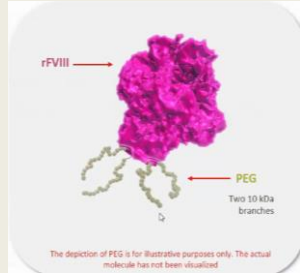
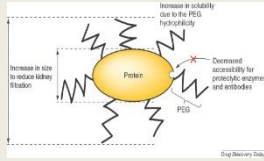
- IgG<sub>1</sub>-Fc receptor/XTEN (Trial)



1. Veronese and Pasut (2005) Drug Discovery Today, Vol 10, 21: 1451-1458. 2. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. 2007;7(9):715-725. 3. Chhabra ES, et al. Blood. 2020;135(17):1484-1496. 4. Konkle BA, et al. N Engl J Med. 2020;383(11):1018-1027.



# PEGylation



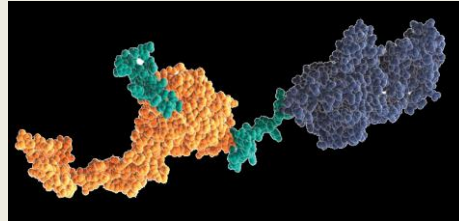
**Adynovate (BAX855) : VIC, SA, WA**

*Espertoc (N8-GP) : NSW, VIC, QLD*

*Refixia (N9-GP): QLD, VIC*

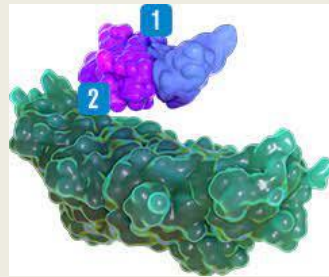
# Fusion Proteins

- **Albumin**



*Idelvion (Albumin fusion): NSW, VIC*

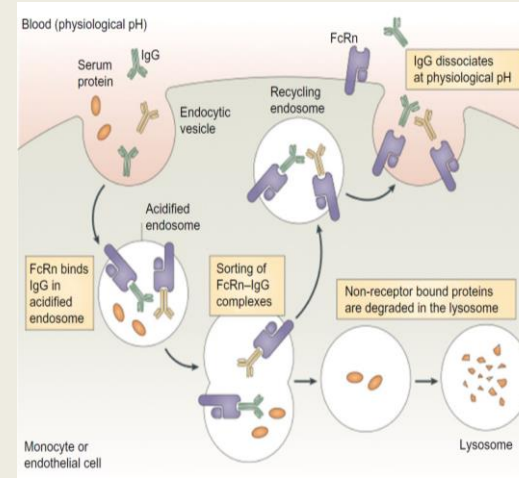
# Single Chain (FVIII)



*Afstyla; WA, VIC*

# Fusion Proteins

- **IgG<sub>1</sub>-Fc receptor**

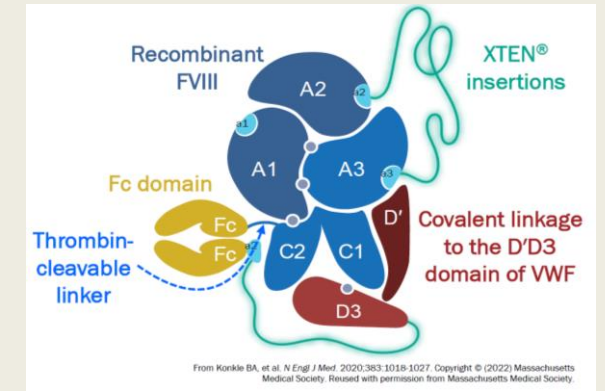


**Eloctate Trials : QLD, VIC, WA, NSW**

**Alprolix Trials: NSW, VIC, WA, SA**

# Fusion Proteins

- **IgG<sub>1</sub>-Fc receptor/XTEN (Trial)**

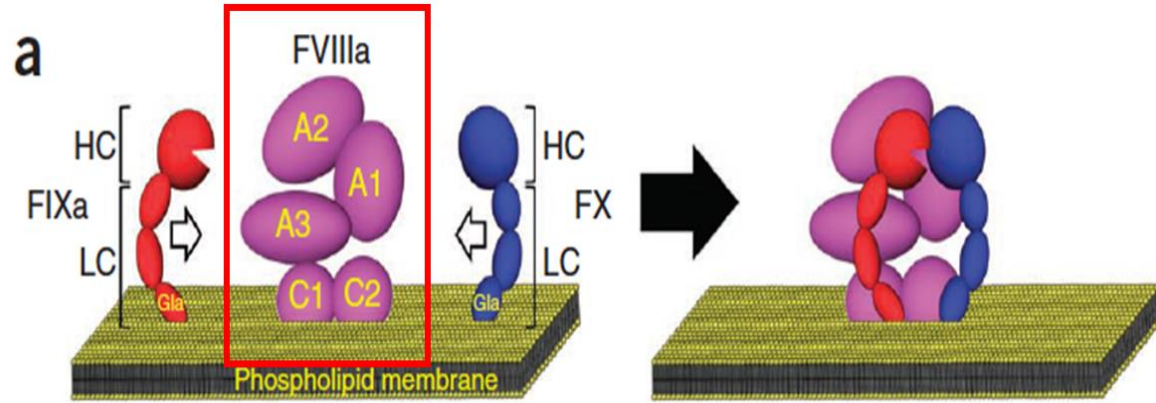


*Altuvio (BIVV001) : NSW, QLD, WA*

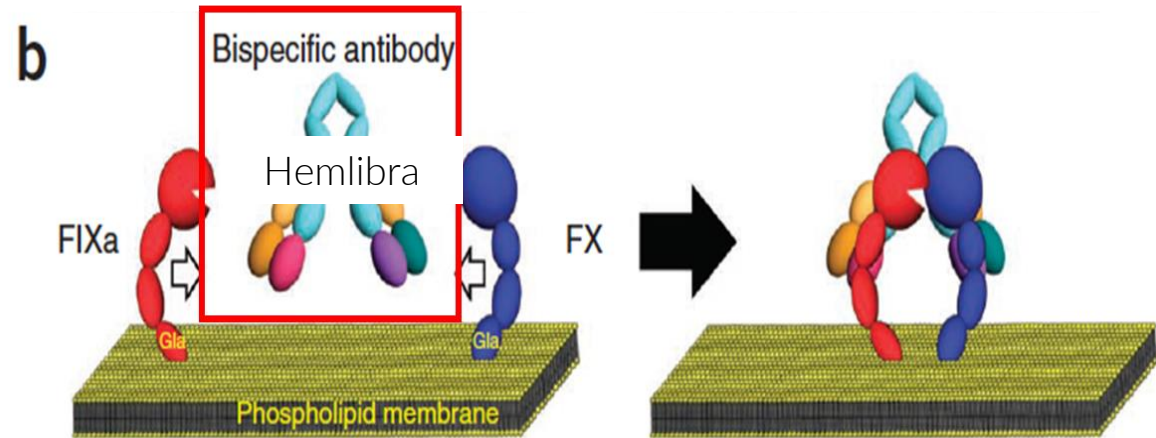
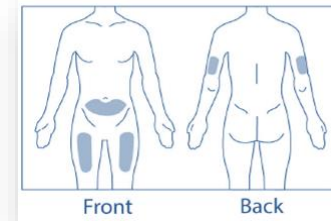
*Red : what is currently funded for use in Australia ; Blue : Australian sites participate in the pivotal trials for these products, but they are not currently funded*

# Non-Factor Replacement Therapies

## Monoclonal Antibodies : Hemlibra (Emicizumab)



- Restores the function of missing FVIII
- Haemophilia A patient **WITH** and Without inhibitors
- **Steady state level**



### Pivotal Studies for Emicizumab in Australia

**HAVEN 1: NSW, VIC**

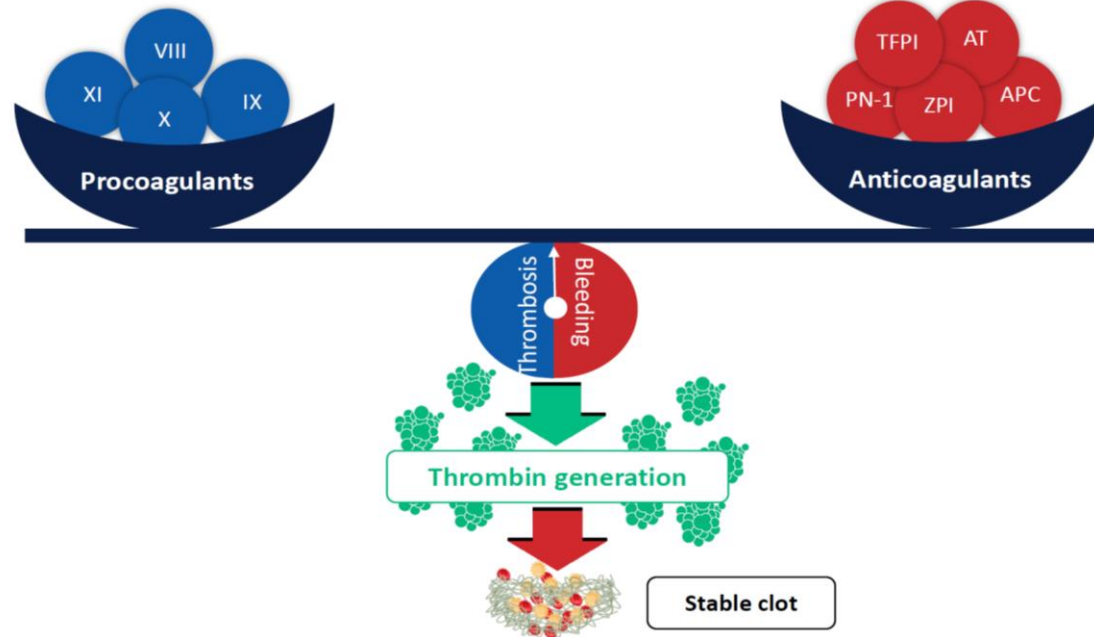
**HAVEN 3: VIC, SA, WA**

**HAVEN 4: SA, QLD**

**HAVEN 7: NSW, VIC**

**STASEY: WA, NSW, VIC**

# Non-Factor Replacement Therapies Re-Balancing Therapies (Trial)



## Clinical Trial Sites in Australia

Anti-TFPIs : Concizumab, Marstacimab

Concizumab : VIC, WA

Marstacimab : VIC, NSW

siRNA (ATIII): Fitusiran

NSW, VIC, WA

Serpin PC (APC):

NSW, VIC

Protein S:

QLD

# Gene Therapies :

**EMA approval : Roctavian (Haem A) – June 2022**

**FDA approval Hemgenix (Haem B) - Nov 2022**

**(Most still undergoing clinical trial)**

Hemophilia A Clinical Gene Therapy Trials (September 2020)

Gene Therapy – Product Name		Clinical Trial Stage	Sponsor
1. BMN-270	AAV5	Phase 3	Biomarin
2. SB-525	rAAV2/6	Phase 3	Pfizer (Sangamo)
3. SPK-8011	AAV-Spark200	Phase 3	Roche (Spark)
4. BAY-19429	AAVhu37FVIII	Phase 1/2	Bayer
5. Spark-8016	AAV-Spark200	Phase 1/2	Spark
6. Spark-8016 (inhib)	AAV-Spark200	Phase 1/2	Spark
7. Go-8	AAV2/8 – FVIII-V3	Phase 1	UCL-St. Jude
8. ET3	HSC – lentivirus	Phase 1	Expression Therapeutics
9. YUVA-GT-F801	HSC/MSK – lentivirus	Phase 1	SGIMI
10. Pleightlet (MUT6)	Autologous CD34 – lentivirus	Phase 1	Med College Wisconsin

Hemophilia B Clinical Gene Therapy Trials (September 2020)

Gene Therapy – Product Name		Clinical Trial Stage	Sponsor
1. AMT-061	FIX Padua – AAV5	Phase 3	CSL Behring/UniQure
2. SPK-9001	FIX Padua – AAV-Spark100	Phase 3	Pfizer (Spark)
3. FLT180a	FIX Padua – AAVS3	Phase 1/2	Freeline
4. AMT060	WT FIX – AAV5	Phase 1/2	UniQure
5. SB-FIX	AAV6 – ZFN targeted	Phase 1/2	Sangamo
6. YUVA-GT-F901	FIX-Lentivector	Phase 1	Shenzhen Geno-Immune Medical Institute (SGIMI)

## Clinical Trial Sites in Australia

**NSW, VIC, SA, WA, QLD**



# Why Participate in Clinical Trials of Newer Therapies?



*More than just a lab rat...*

*Taking the whole team on the clinical trial journey with you ... they will continue the journey with you*

Experience with Newer Therapies : Patients and Clinicians

- Better informed : How best to use them
- Access to newer therapies for patients
- Experience gained in clinical trials allows us to build on real world experiences and helps us to make informed decisions, for example Gene Therapy Road Map by AHCDO

**Better placed to face the opportunities and challenges ahead**





# Challenges and Opportunities with the Newer Therapies

## Shifting Paradigms :

- Peaks/Troughs... Steady State.... (*Cure*)
- No longer a blood product / missing factor
  - Funding
- Bleeding and Clotting – how to balance treatment and safety
  - Emicizumab : death, thrombosis, TMAs
  - TFPIs : thrombotic event
  - Fitusiran : death ; thrombosis
- Patient Identity
  - Haemophilia as part of who they are vs Not wanting to think of haemophilia
- Changing Roles for HTC ... How best to meet patient needs?
- Novel treatments for Women, VWD, Rare Bleeding Disorders



# HTC .. Meeting the Changing Needs of Patients

## Changing Roles of the Multi-Disciplinary Team

### Hemophilia comprehensive care centre (HCCC)

- Provide 24-hour service with experienced staff
- Provide inhibitor care and immune tolerance services
- Provide safe and effective CFCs and other hemostasis products
- Provide community liaison, including school and home visits
- Offer laboratory services with 24-hour assay cover
- Provide access to hospital-based nursing staff, physical therapy services, social workers, dental services, obstetric and gynecological services, and psychosocial support
- Provide HIV and hepatitis C care
- Provide access to a genetics laboratory and genetic counselling
- Provide home treatment
- Keep reliable records
- Undertake medical education
- Initiate and participate in research

### Haemophilia Treatment Centre

- IV competency
  - patients now need to go to HTC / ED as unable to IV inject factor
  - ? Burden on health care system
  - Delay in early treatment of bleed
  - Independence ( travel)
- How to stay relevant and engaged with patients
  - Advice on treatment choice
  - Advocacy
  - Peer support ; meeting place for patients
- Laboratory
  - Measuring levels ( assay variability for different products)
  - Assays for new treatment : eg Emicizumab assays
  - Global assays for rebalancing therapies

# *How do we capacity build our Haemophilia Treatment Centre...Journey Together*

## **Up-skilling the Haemophilia Treatment Centre Multidisciplinary Team**

- Haemophilia Nurses
  - Not all haemophilia nurses are clinical trial nurses
- Psychology Support : psychologist; social workers
- Liver Specialist : new roles
- Involving other specialist : cardiologist, geriatricians....
- Gene Therapy:
  - Regulatory bodies
  - Pharmacist and laboratory facilities: cellular products
  - Supporting smaller HTC (“spokes”) in monitoring and supporting patients who have received gene therapy



## Summary

- Haemophilia treatment has changed dramatically, especially in the last 10 years; rare disease with a lot of innovation
- With innovation : new challenges, new paradigms and new questions
- “Beyond ABR...Beyond Zero bleeds.” What are new outcome measures are relevant and needed. How can we do better ?
- How do we continue to innovate and provide good equitable care
- Bringing everyone on the journey... **as we work together... to improve outcomes together ... for a better future**