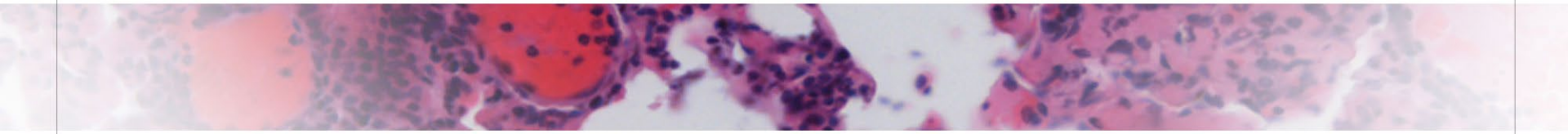
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Development of an *Ex Vivo* Precision Gene Engineered B Cell Medicine that Produces Active and Sustained Levels of FIX for the Treatment of Hemophilia B

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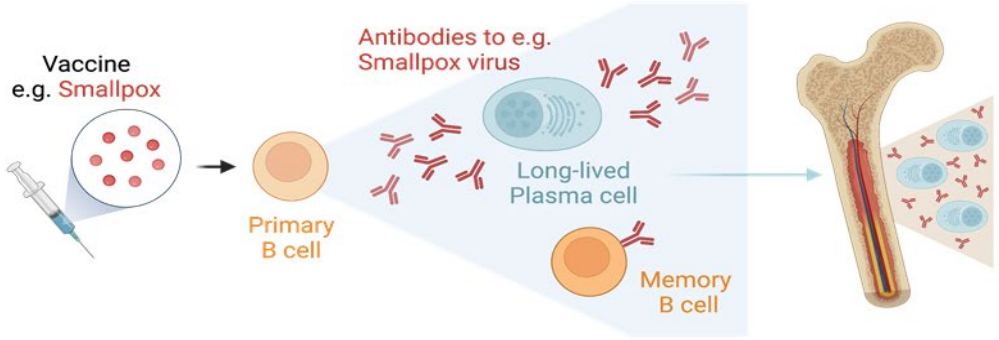
Be Biopharma, Cambridge, MA, USA

Disclosure Slide

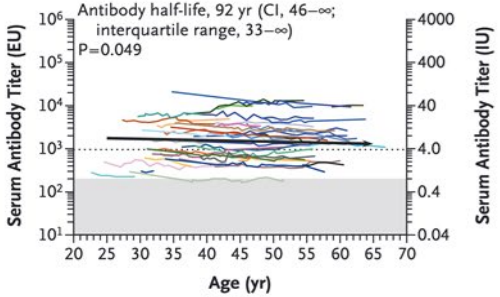
- All authors are employees of and have equity in Be Biopharma

B Cell Biology: Natural Sustained Protein Production and Bone Marrow Engraftment Without Conditioning

B Cell Biology



Longitudinal analysis of serum antibody titers in 45 subjects[1]



Constant protein production: 1000s of molecules/cell/sec[2]

Longevity: native human plasma cells can persist for decades[3]

Inherently stealthy: naturally evade the immune system

1. Amanna, Carlson, and Slifka (2007) *NEJM, 2.* Hibi and Dosch (1986) *Eur J Immunol*; Eyer *et al* (2017) *Nat Biotech, 3.* Landsverk *et al* (2017) *J Exp Med*

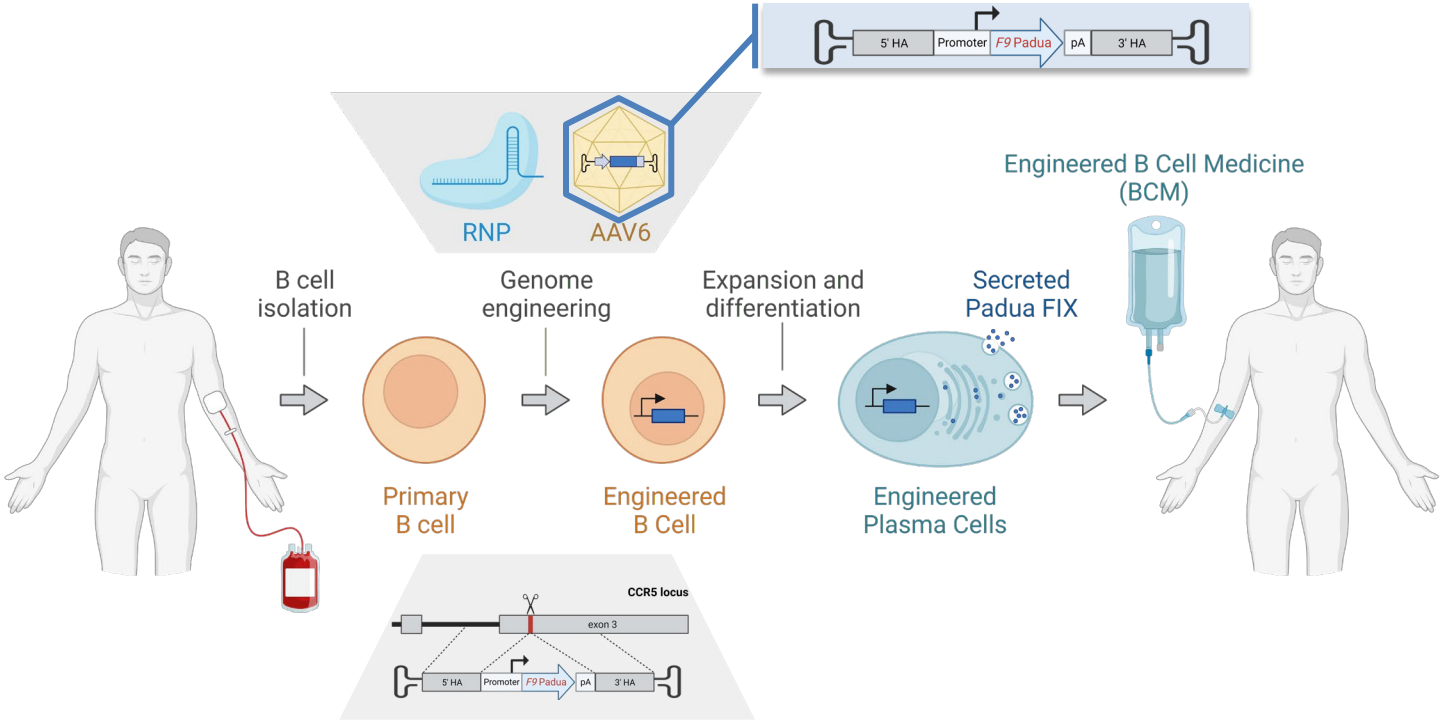
Current Challenges in Developing Treatments for Hemophilia B

Nicholas
Growing up with Hemophilia B
(Picture courtesy of the CDC)*

Criteria for Desired FIX Replacement

1. Constant FIX therapy window **2. Single dose IV infusion**	• Eliminates nadir • Eliminates further joint damage/ pain • Eliminates adherence issues • Decreases patient burden	**Not satisfied by rFIX replacement**
3. Can treat children **4. Titratable & redosable**	• Eliminates bleeds in childhood • Prevents irreversible joint damage/pain • Enables patient-specific FIX mgmt.	**Not possible with AAV Gene Therapy**

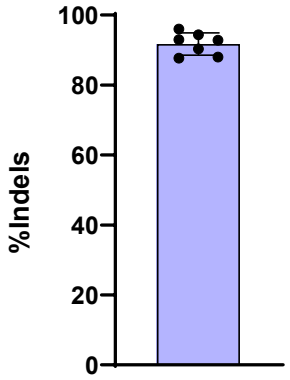
BE-101 is a B Cell Medicine Precision Engineered to Serve as FIX Protein Factory in the Body Upon Infusion Without Pre-Conditioning



Figures created with BioRender.com

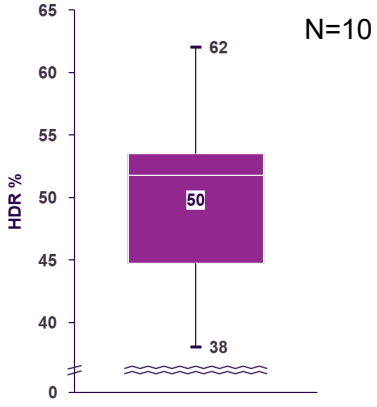
Optimized Gene Editing and *Ex Vivo* Culture Methods Reproducibly Generate >50% Precision *F9* Padua Gene Engineered Plasma Cells

>90% gene editing efficiency



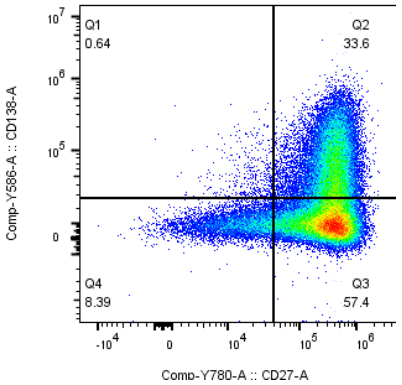
CCR5 Locus Cutting Efficiency

Up to 60% *F9 Padua* transgene insertion



F9 Insertion Efficiency

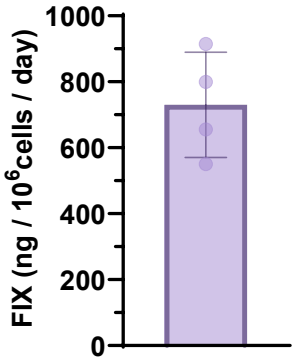
Well-differentiated plasma cells (CD38+ >97%)



CD38+/CD27+/CD138+ Phenotype

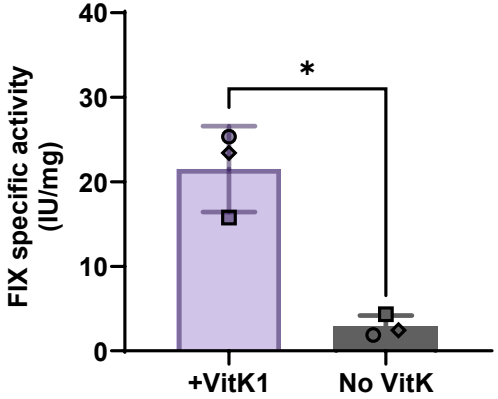
Demonstrating Vitamin K-Dependent Biological Activity *In Vitro* of Precision Gene Engineered B Cell Derived Factor IX

Prolific protein production



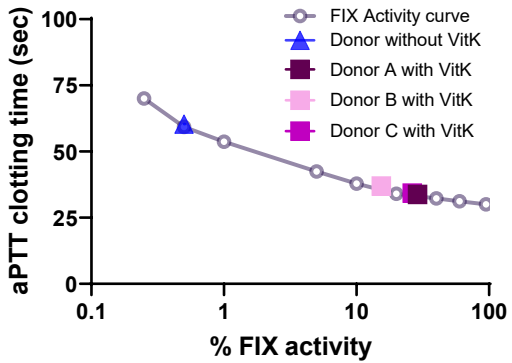
Padua FIX Protein Secretion from BCM

Vitamin K dependent γ–carboxylation in GLA domain



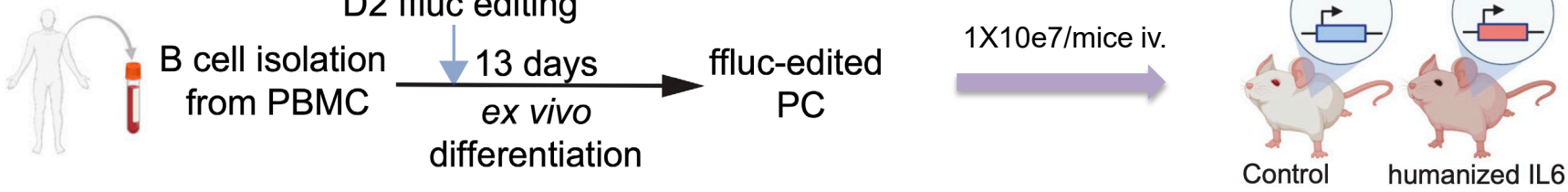
BCM Derived Padua FIX Activity in Chromogenic Assay

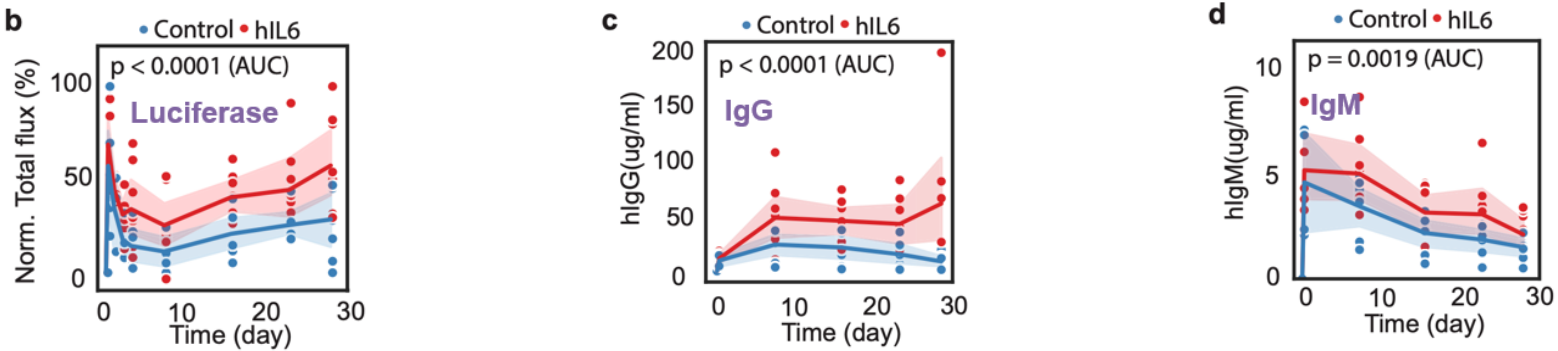
Decreasing clotting time in aPTT assay



BCM Derived Padua FIX Activity in aPTT Assay

Use of hIL6 Transgenic Mice Enhance Engraftment of Human Plasma Cells



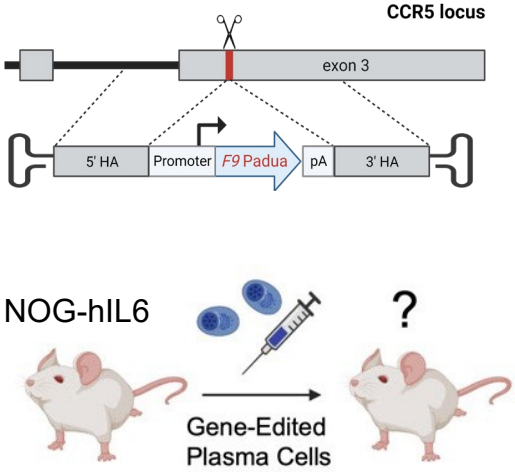


control; n = 7 animals from two independent experiments
hIL-6-B-NDG knock-in hIL-6; n = 8 animals from two independent experiments

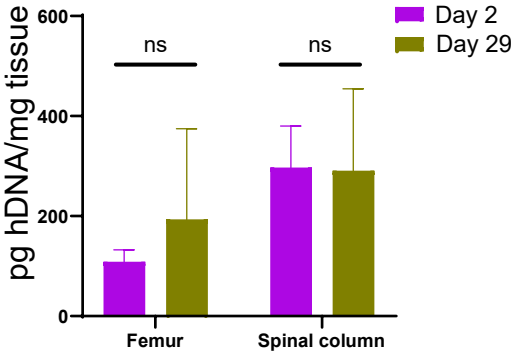
Adapted from, Cheng et al., Nature Comm, doi.org/10.1038/s41467-022-33787-8

Rapid Bone Marrow Trafficking and Stable Engraftment of BE-101 after a Single IV Administration to NOG-hIL6 Mice

FIX Engineering Strategy

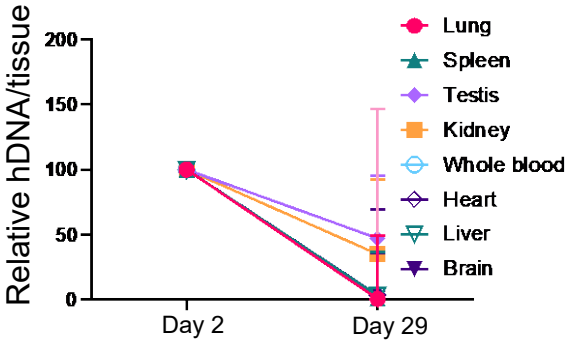


Engraftment and persistence in bone marrow tissues over time



n = 3 mice per time point (from Donor D) Mann-Whitney U test

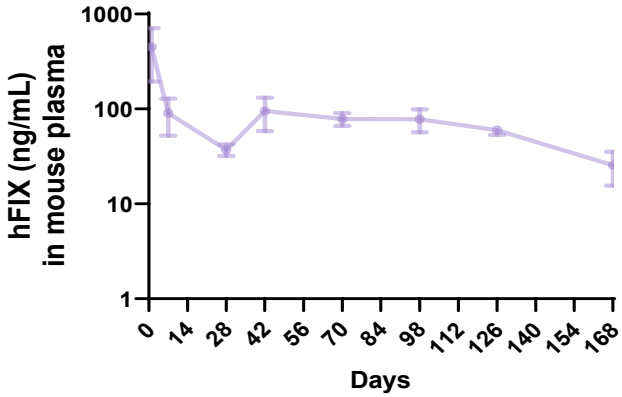
Decreased in all other tissues examined



n = 3 mice per time point (from Donor D)

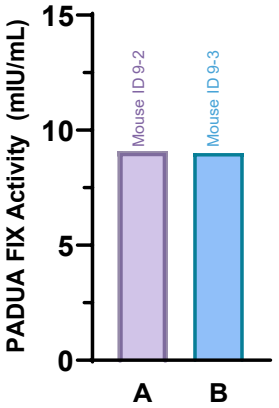
Long-term Secretion of Engineered B Cell Derived Factor IX for >168 Days after a Single IV Administration to NOG-hIL6 Mice

Sustained hFIX plasma level



n = 3 mice per time point (from Donor E)

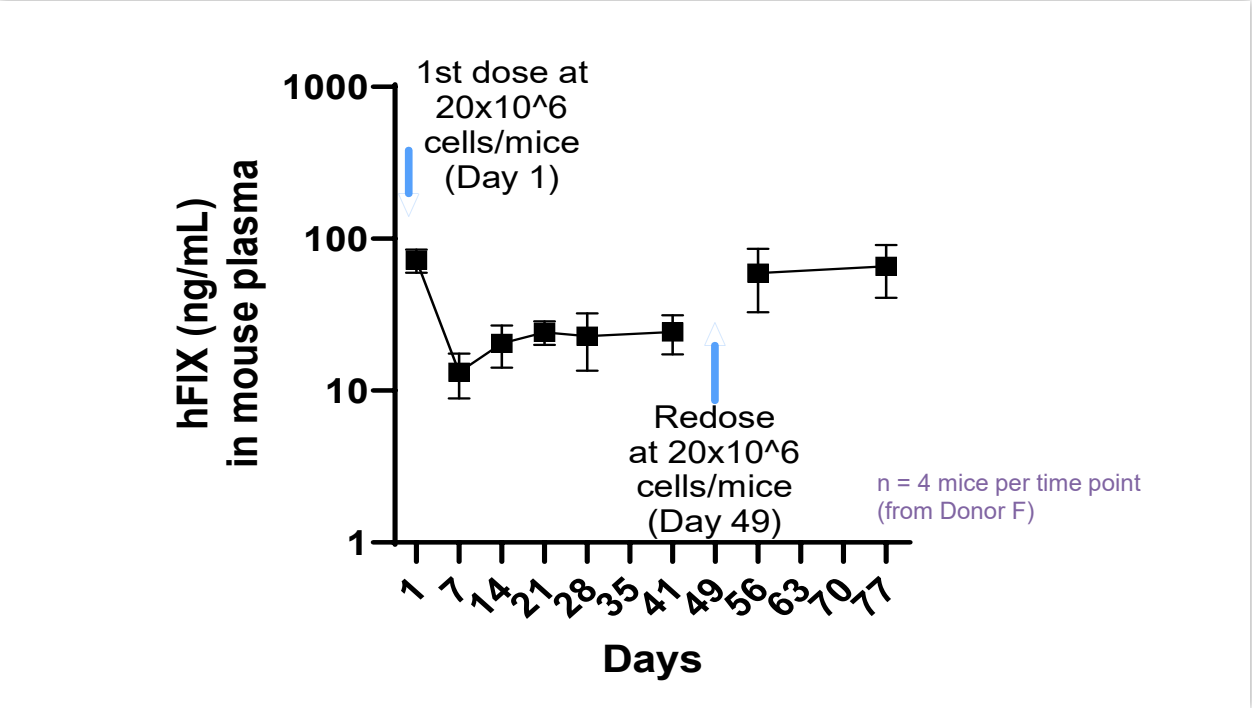
Padua FIX activity using immune-capture chromogenic assay



2 independent measurements at days 126 (A) and pooled sample from d98/d126 (B)

hFIX: human FIX as measured by immune capture MSD assay

BE-101 Is Re-dosable, Leading to a Predictable Increase in Engraftment and FIX Levels

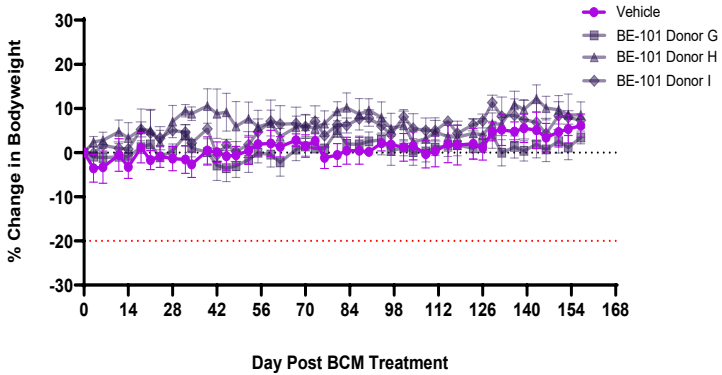


Note: hFIX levels on Day 77 were the mean values between week 2 and week 4 after re-dose

Nonclinical Safety Evaluation

- No BE-101 related short- or long-term safety findings observed in **168/168 mice (**at the highest feasible dose of 20x10^6 viable cells).
- No BE-101-related adverse events observed across multiple *in vivo* studies out to **5 months**, including assessments of:
  - Survival and body weight
  - Clinical pathology (complete blood count (CBC), serum chemistry)
  - Histopathology of selected organs including brain, lungs, heart, spleen, liver, kidneys, testes, and femur with bone marrow.
- GLP toxicology and off-target evaluation studies are on-going with no concerns identified to date.

No change in bodyweight compared to the vehicle group in long-term studies



N = 3 mice per time point / donor

Summary and Next Steps

- We have developed an *ex vivo* precision gene engineered B cell medicine, BE-101, that produces continuous and durable levels of active FIX *in vivo*.
- The therapeutic application of this unique cellular medicine, that does not require pre-conditioning, and offers the flexibility for re-dosing (if needed), has the potential to be a paradigm shift in the treatment of hemophilia B in both adults and children.
- A Pre-IND meeting has been completed and a robust package of preclinical studies is nearing completion in anticipation of a **first-in-human** clinical trial in **2024** for people with moderately severe to severe hemophilia B.

Beyond Hematology: BCMs Created Across Protein Classes and Product Applications

	Small Biologics		Multi-Target			Full Length Antibodies		
Protein Classes	 Peptides	 Non-Ab Proteins	 T Cell Engagers	 Bispecific	 Fusion Protein	 IgG	 IgA	 IgM
Be Bio Programs	Metabolic	Hem Rare	Onc	Hem Onc	Rare	Multiple (Inc. Onc. I&I)	Onc	In-progress (Onc, ID)

Acknowledgement

WE THANK ALL OF OUR BE BIO TEAM MEMBERS FOR THEIR SUPPORT!