

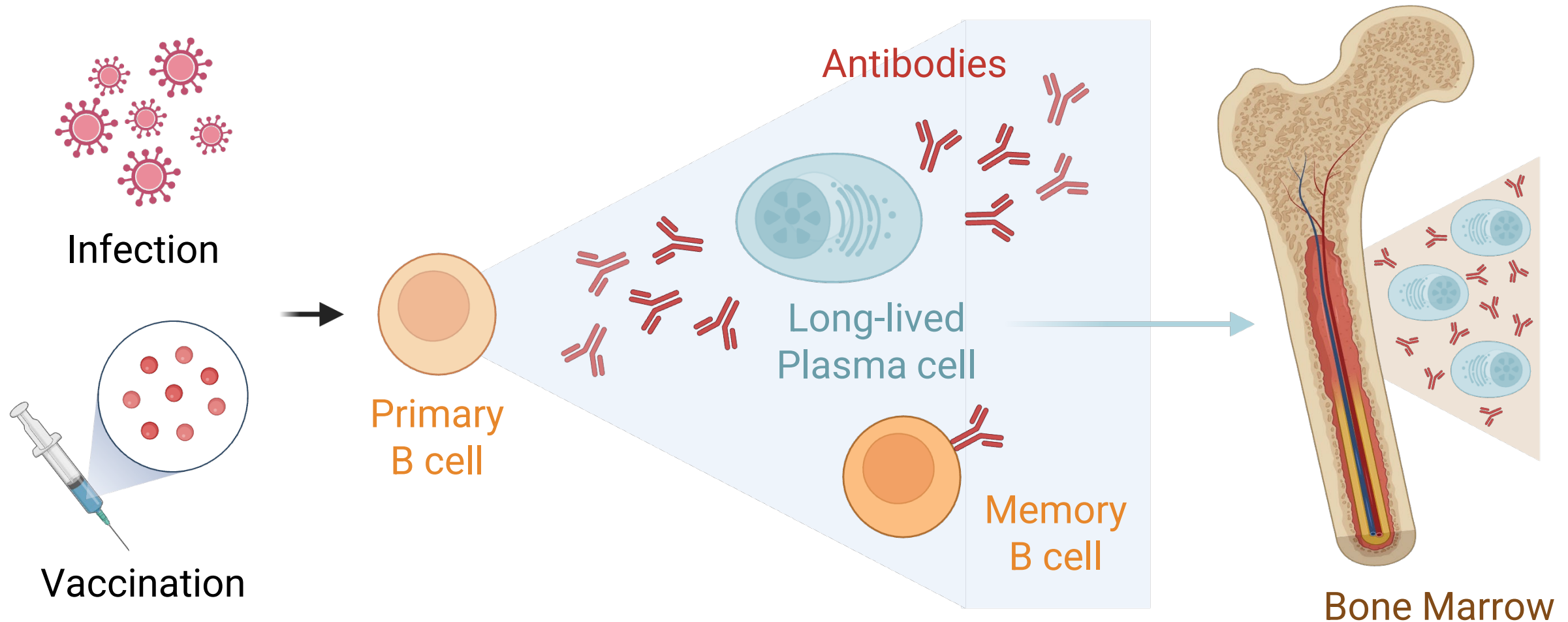


A versatile B cell engineering platform enables development of B Cell Medicines for sustained delivery of therapeutic biologics

Anja Hohmann, PhD; Be Biopharma

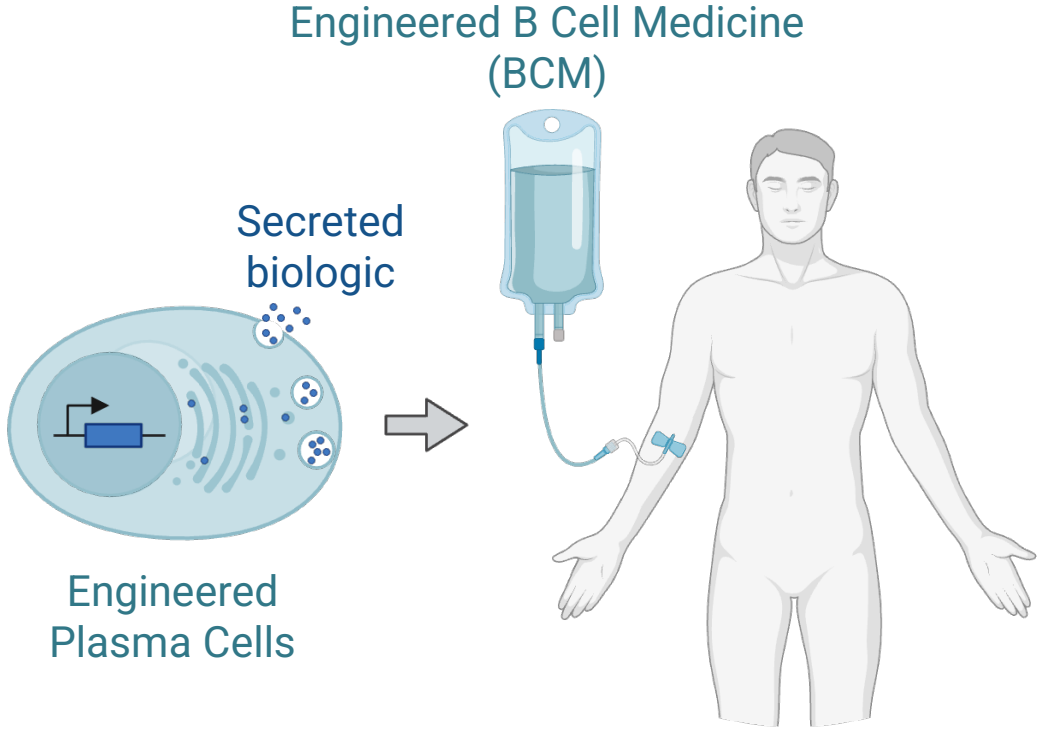
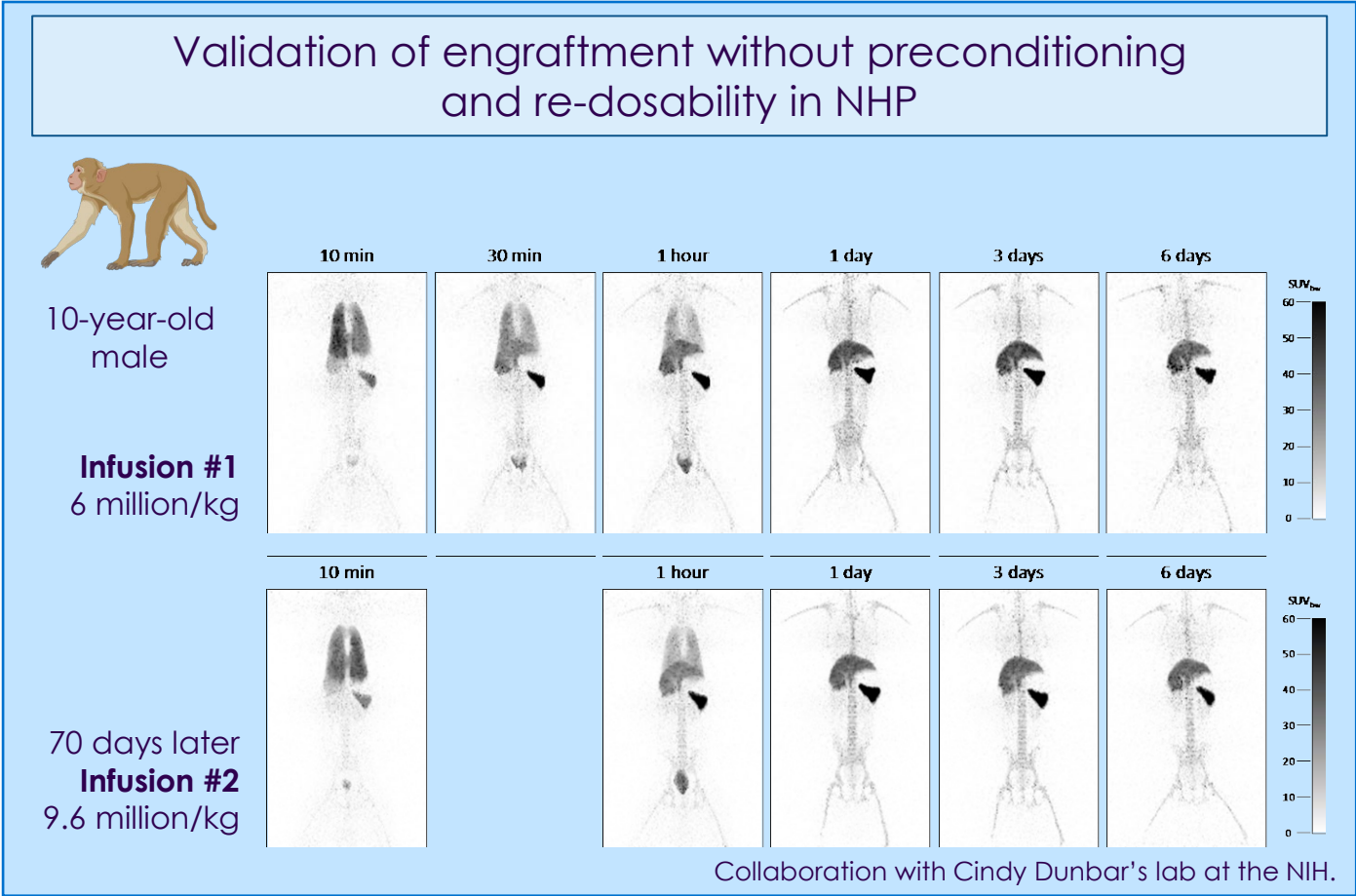
ASH Annual Meeting 2024

B cell biology enables a new class of cellular medicines



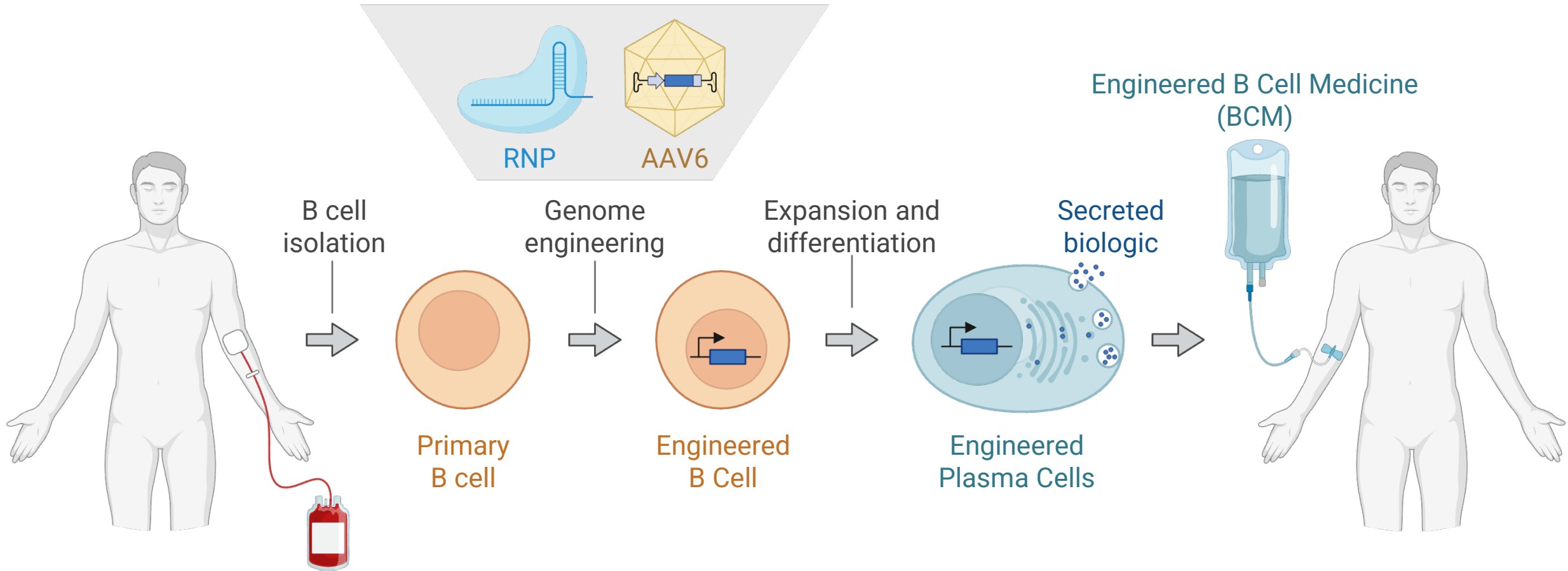
Capacity for protein production: 1000s of molecules/sec/cell¹
Longevity: Natural human plasma cells can persist for decades²

B cell biology enables a new class of cellular medicines



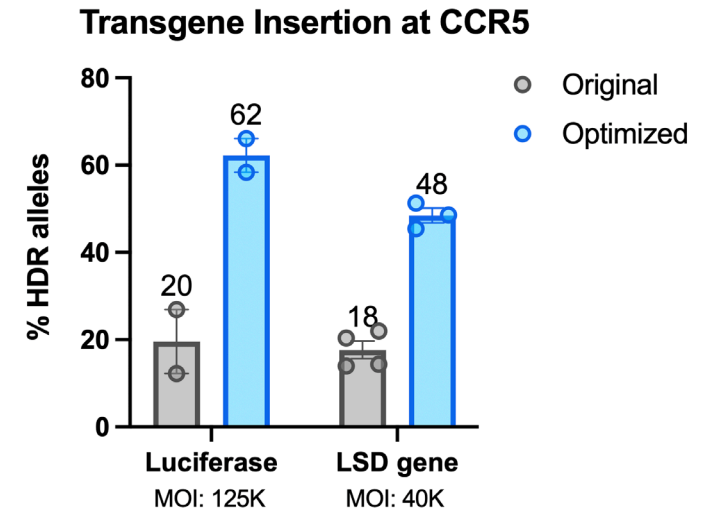
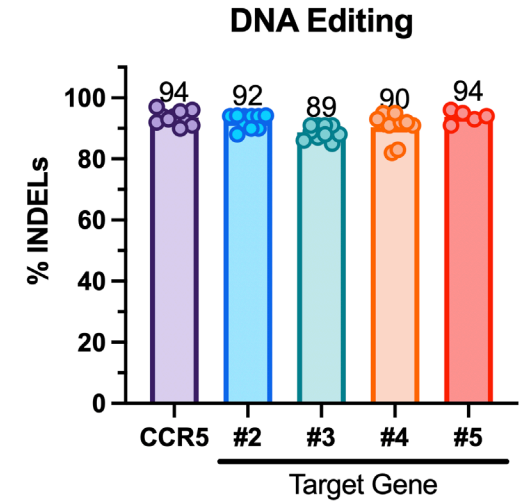
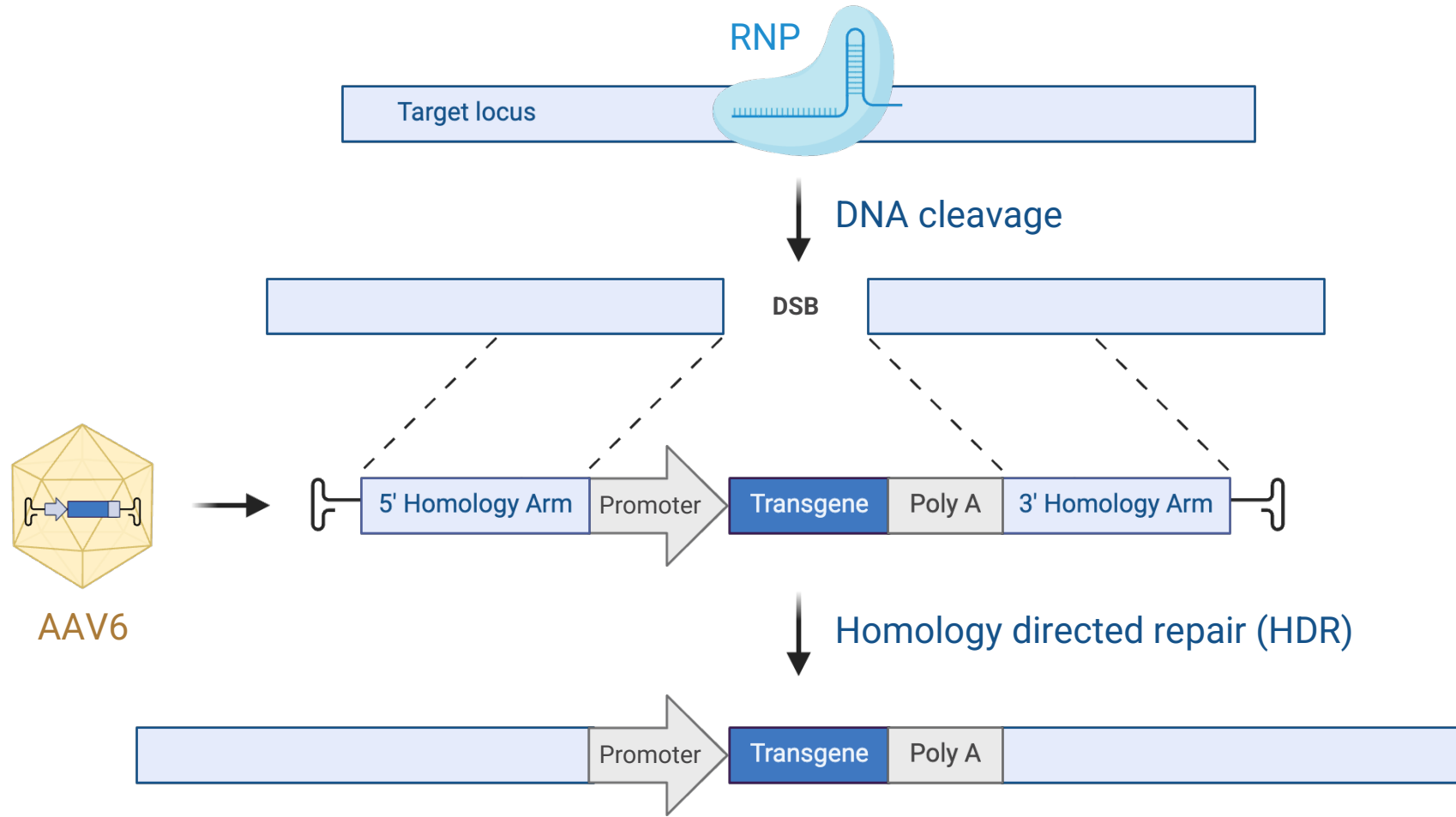
BCMs are unique suited for the sustained supply of biologics
Capable of making versatile proteins; Stable protein secretion
Engraftment without pre-conditioning; Long-term persistence; Re-dosable

BCMs are engineered and differentiated *ex vivo* to serve as protein factories in the body upon infusion



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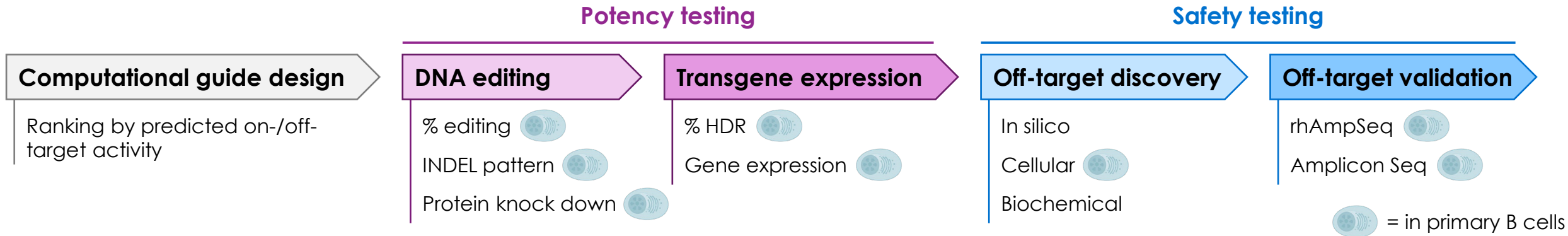
Our engineering strategy stably and efficiently inserts transgenes at defined genomic sites



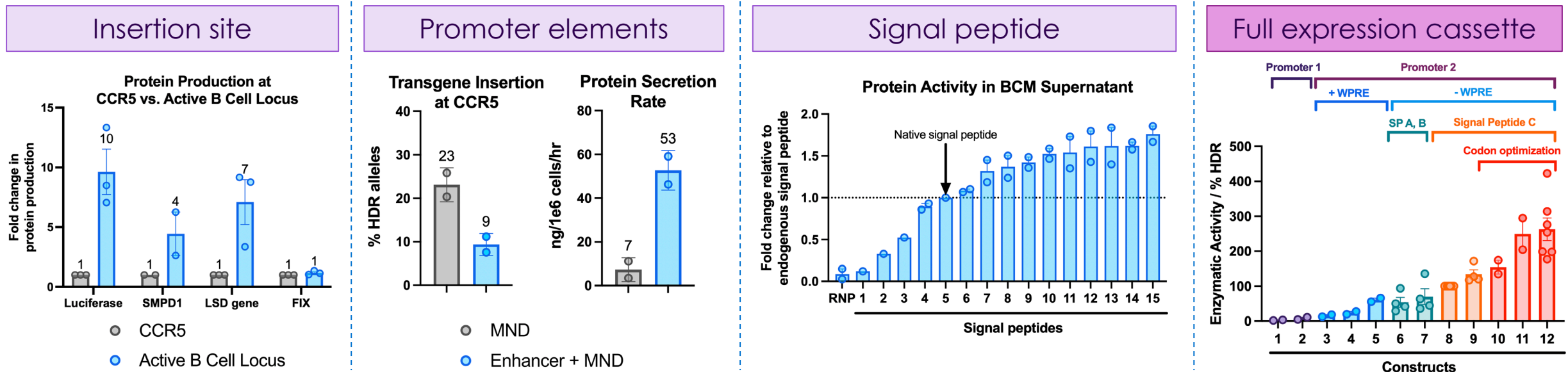
Optimized B cell engineering protocol achieves DNA editing with greater than 90% efficiency and targeted HDR-mediated gene insertion up to 60% without selection.

Guide selection and construct optimization processes are designed for enhanced potency and safety

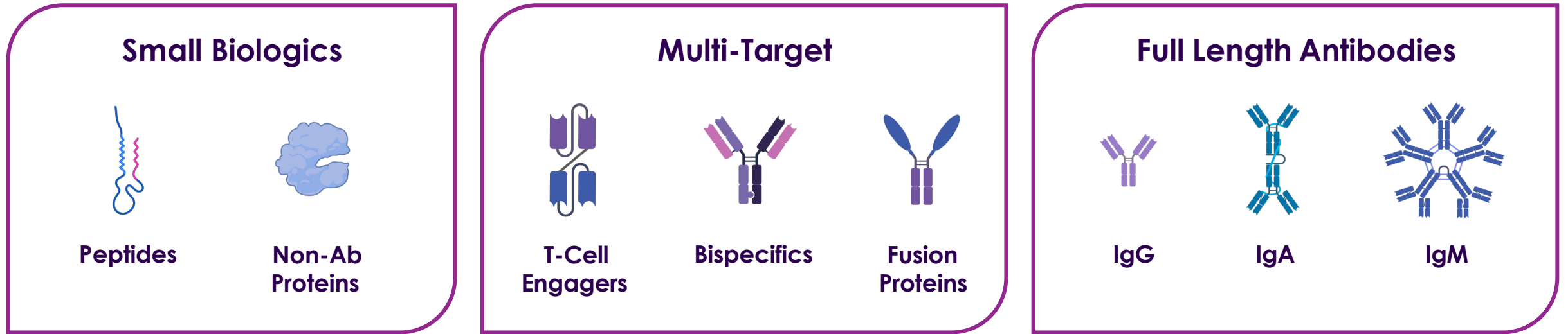
Guide RNAs for clinical use are selected via potency and specificity testing directly in primary human B cells



Choice of target locus and optimization of regulatory and coding sequences can enhance protein production



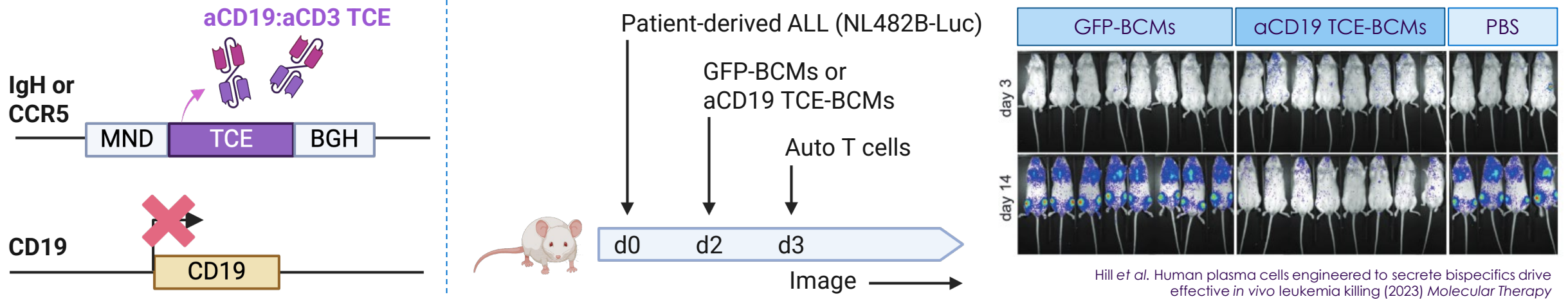
Our B cell engineering platform supports the generation of BCMs expressing versatile biologics across protein classes



- 1 **Anti-CD19:Anti-CD3 TCE** for Acute Lymphoblastic Leukemia (ALL)
- 2 **Alkaline Phosphatase (ALP)** for Hypophosphatasia (HPP)
- 3 **Factor IX (FIX)** for Hemophilia B (Hem B)

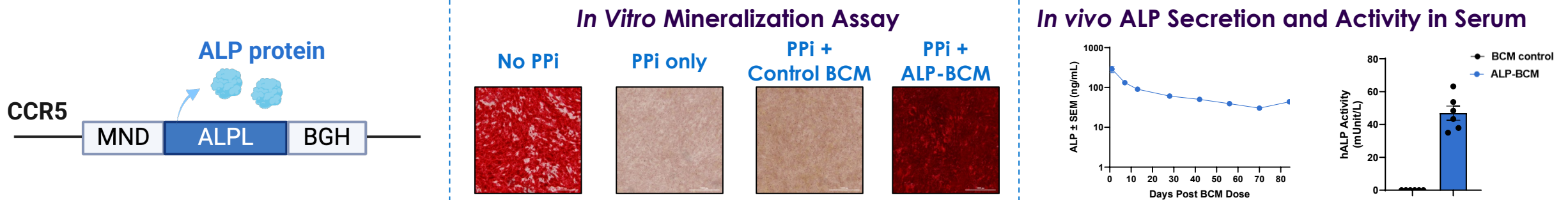
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1 Anti-CD19:anti-CD3 TCE for Acute Lymphoblastic Leukemia (ALL)



TCE-secreting BCMs show efficacy in patient-derived B-ALL xenograft model

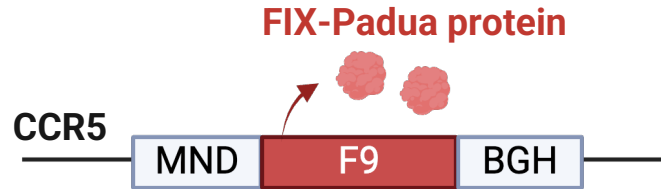
2 Alkaline Phosphatase (ALP) for Hypophosphatasia (HPP)



ALP-secreting BCMs rescue PPI-induced mineralization *in vitro* and stably produce active ALP in NOG-IL6 mice

BE-101: FIX-secreting BCMs for Hemophilia B

3 Factor IX (FIX) for Hemophilia B (Hem B)



Desired Criteria for 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 and redosable

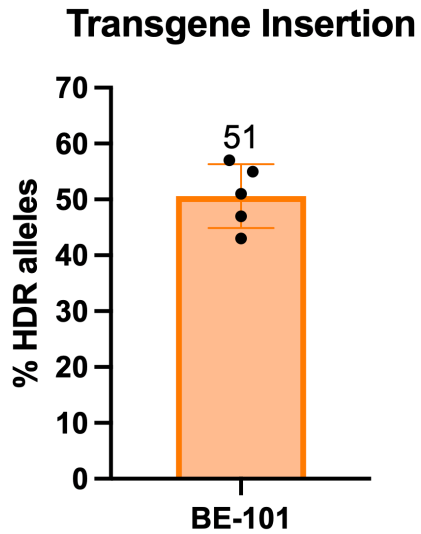


- Eliminates bleeds in childhood
- Prevents irreversible joint damage / pain
- Enables patient-specific FIX management

**Not possible
with AAV
Gene Therapy**

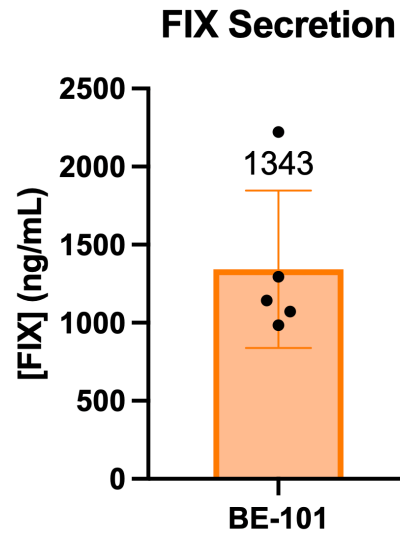
Optimized editing and culture methods reproducibly generate >50% FIX-engineered plasma cells in closed process at scale

Integration efficiency



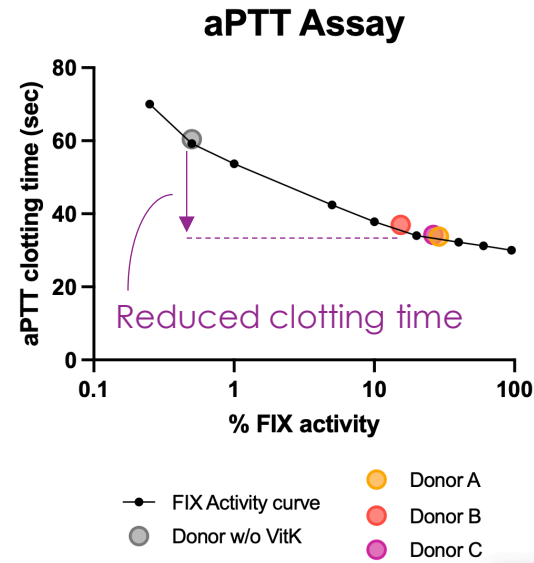
Average FIX insertion of 50% in closed process at scale

Protein production



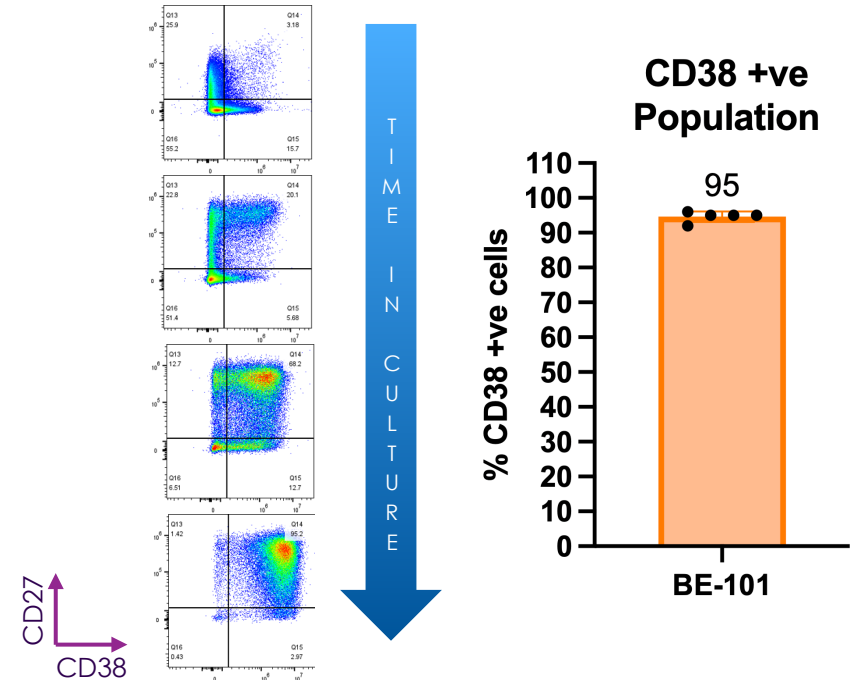
Confirmation of prolific FIX secretion in closed process at scale.

FIX biological activity



BCM-derived FIX decreases clotting time in aPTT assay in Vitamin K-dependent manner

Plasma cell differentiation

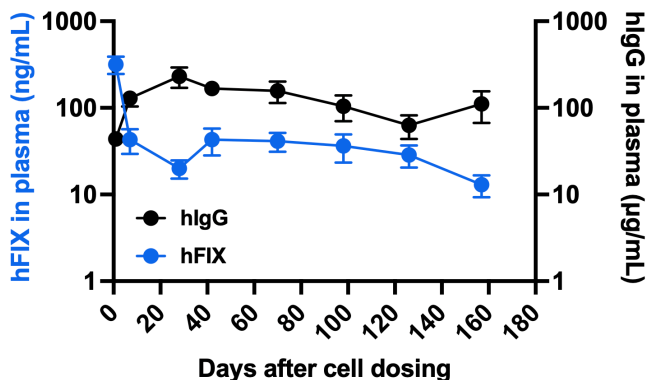


CD38+/CD27+/CD138+ Phenotype in closed process at scale

FIX secretion is durable in NOG-hIL6 mice showing no BE-101 related safety findings

Durability *in vivo* (NOG-IL6)

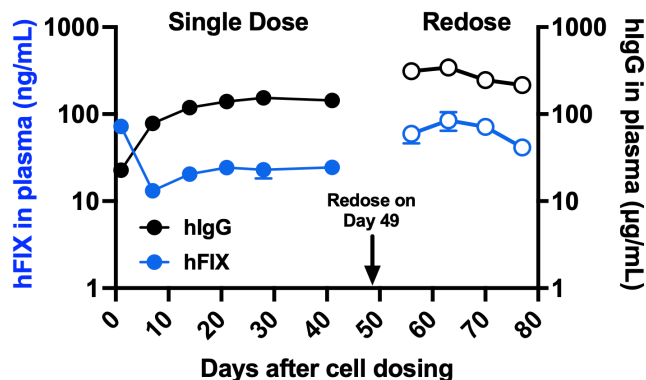
hFIX and hIgG Levels in Mouse Plasma (n=9 mice; 3 donors)



Sustained hFIX levels in mouse plasma following single IV administration

Redosability

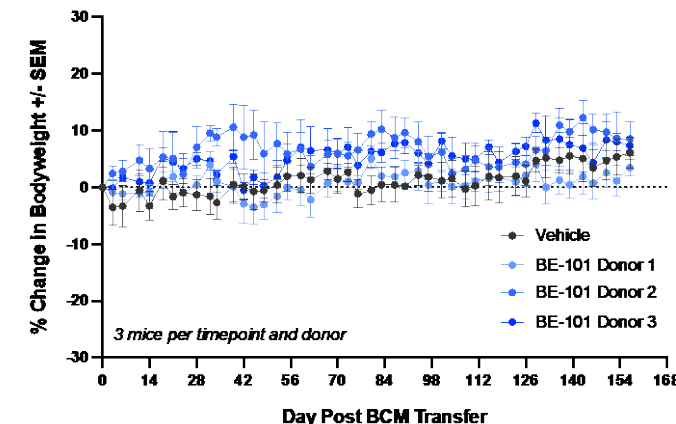
hFIX and hIgG Levels in Mouse Plasma (n=4 mice; 1 donor)



Repeat dosing achieves predictable increase in FIX levels *in vivo*

Long-term *in vivo* studies

Mouse Body Weight Changes Over Time



No change in body weight compared to vehicle control group

Nonclinical safety evaluation

- No BE-101 related safety findings in 168/168 mice
- Genotox package identified no concerning off-targets or other liabilities

- ✓ IND clearance
- ✓ Orphan Drug Designation
- ✓ Fast Track Designation
- ✓ Canada CTA clearance

BeCoMe-9 clinical trial is recruiting participants in the US.

Poster 2593.1
Tomorrow 6 – 8pm; Halls G-H

A versatile CRISPR-based B cell engineering platform...

- ✓ CRISPR-mediated DNA editing >90% and gene insertions up to 60%
- ✓ Rapid screening of guides and constructs directly in primary B cells
- ✓ Optimized construct design for transgene expression and secretion
- ✓ Prototypes with demonstrated biological activity across protein classes
- ✓ BeCoMe-9: FIX-BCM clinical trial for Hem B currently enrolling

Poster 2593.1
Tomorrow 6 – 8pm
Halls G-H
Session 322

...enables a new class of cellular medicines designed for sustained delivery of therapeutic biologics.

Thanks to the Be Bio Team!



Thanks also to our **SAB members** for valuable input and suggestions

Paula Cannon

Jason Cyster

Stephen Gottschalk

Richard James

Eun-Hyung Lee

Shiv Pillai

Glenn Pierce

David Rawlings