VOR33: A Clinic-Ready CRISPR/Cas9 Engineered Hematopoietic Stem Cell Transplant for the Treatment of Acute Myeloid Leukemia

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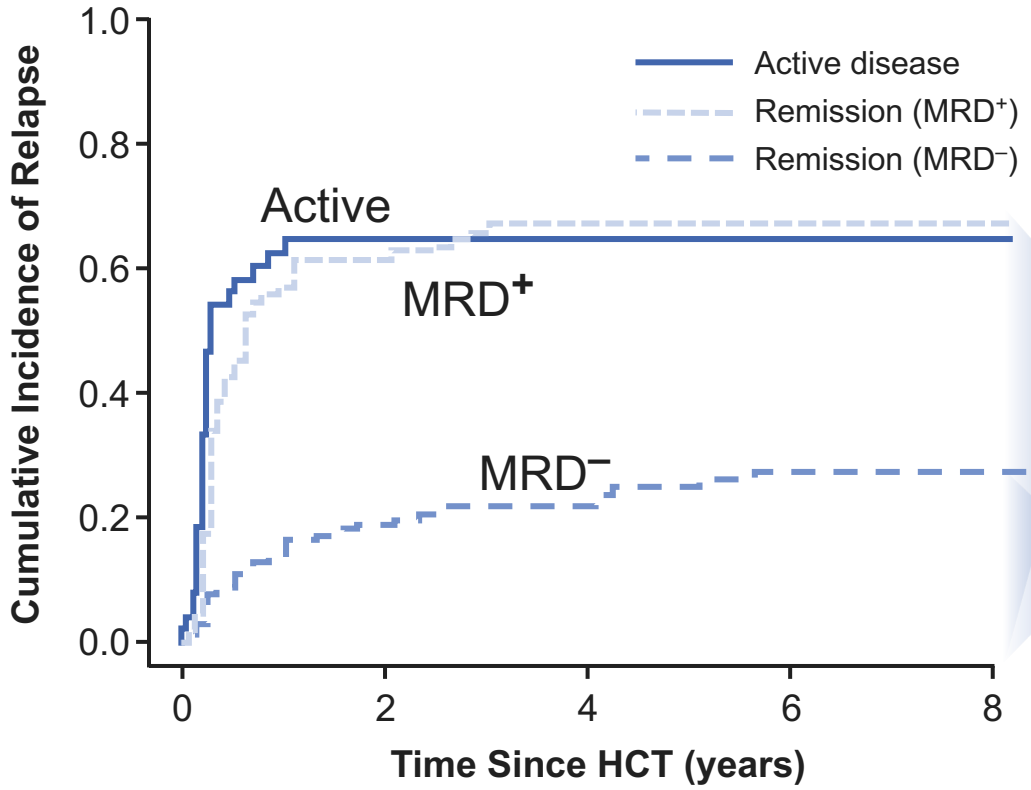
Disclosures

John Lydeard is a salaried employee of Vor Biopharma and holds an equity interest in the company.

>60% of Patients With AML With MRD+ Remission Will Relapse Within 1 Year After Transplantation

Cumulative Incidence of Posttransplant Relapse



Cumulative Risk of Relapse After Transplantation

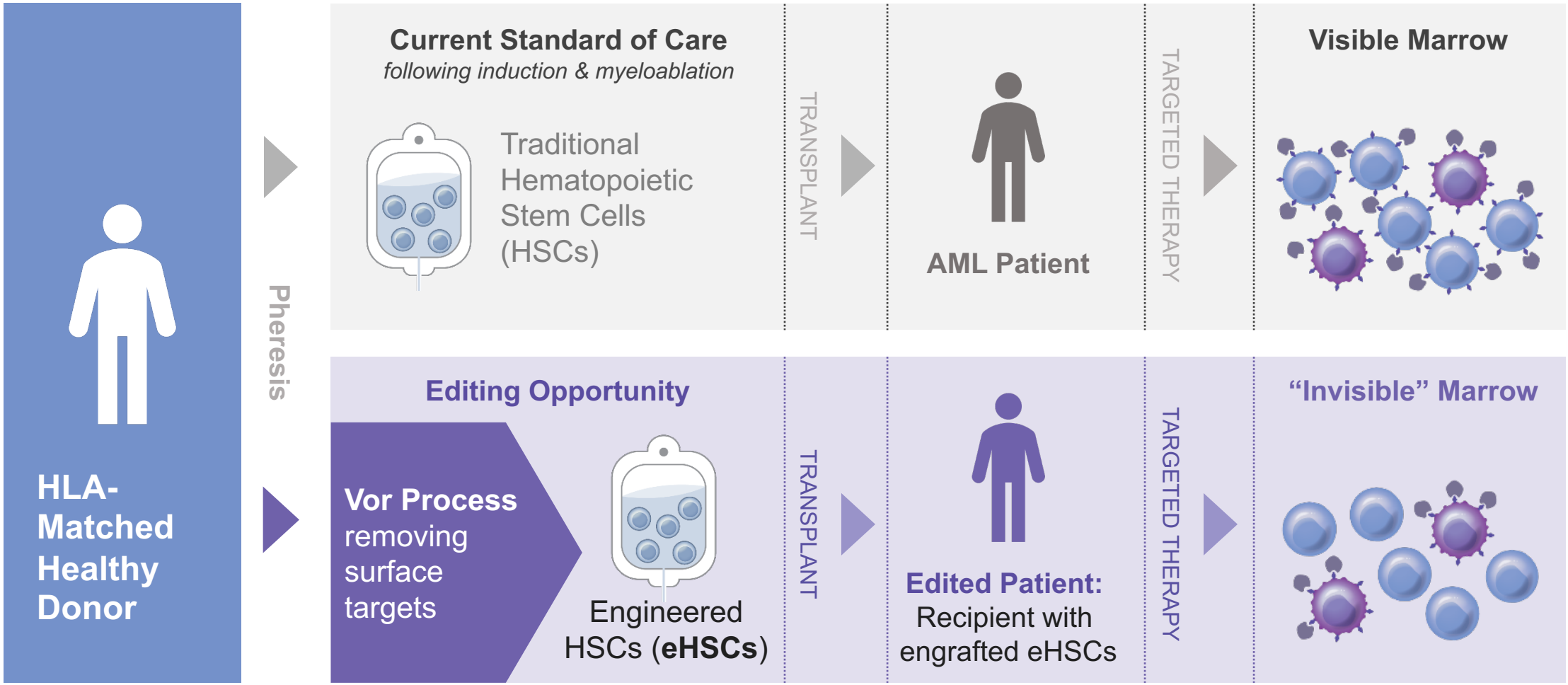
Highest unmet need and initial focus — **>60%** of patients with active disease and MRD+ relapse within 3 years

Substantial need remains in "low risk" — **~25%** of MRD− cases relapse in 5 years

In relapsed patients, the 2-year survival rate is **<20%**

AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; MRD, measurable residual disease.
Araki D, et al. *J Clin Oncol.* 2016;34(4):329-336.

VOR33: Engineering the Patient to Make Treatment-Resistant Transplant



CD33 as a Therapeutic Target in AML

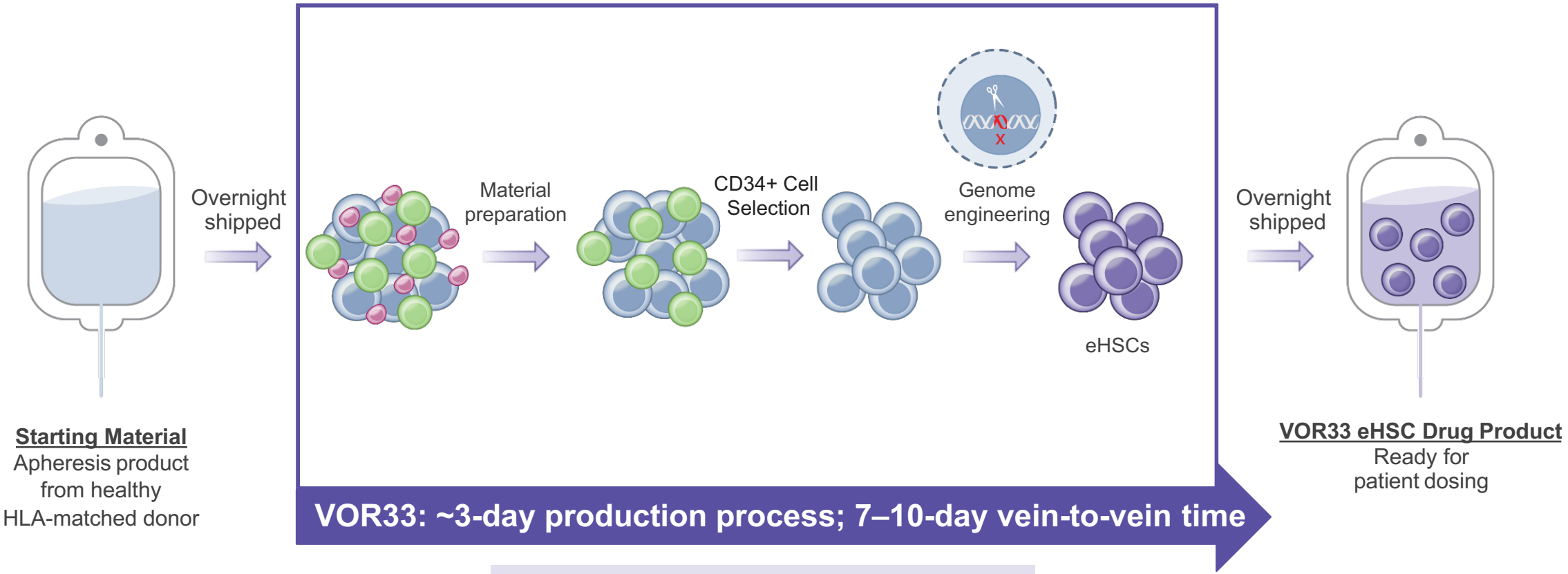
- Broadly expressed in AML Blasts and Leukemic Stem Cells
  - Expressed on normal myeloid cells
- Member of Siglec family (Siglec3), role unknown
- CD33 KO well tolerated in mouse and human
  - 65 individuals with homozygous loss-of-function (LOF) in gnomAD database[1]
- CD33 KO POC is well established
  - Borot et al, 2019[2]; Kim et al, 2018[3]; Humbert et al, 2019[4]

HSPC, hematopoietic stem and progenitor cell; POC, proof of concept; siglec, sialic acid-binding immunoglobin-like lectin.

1. Genome Aggregation Database. gnomAD v2.1.1. Accessed May 7, 2021. https://gnomAD.broadinstitute.org **2.** Borot F, et al. *Proc Natl Acad Sci USA*. 2019;116(24):11978-11987. Erratum in: *Proc Natl Acad Sci USA*. 2019 Jul 16;116(29):14780-14781. **3.** Kim MY, et al. *Cell*. 2018;173(6):1439-1453.e19. **4.** Humbert O, et al. *Leukemia.* 2019 Mar;33(3):762-808.

Efficient Deletion of CD33 at Clinical Scale Manufacturing

VOR33: Streamlined Cell Manufacturing Process



Starting Material
Apheresis product from healthy HLA-matched donor

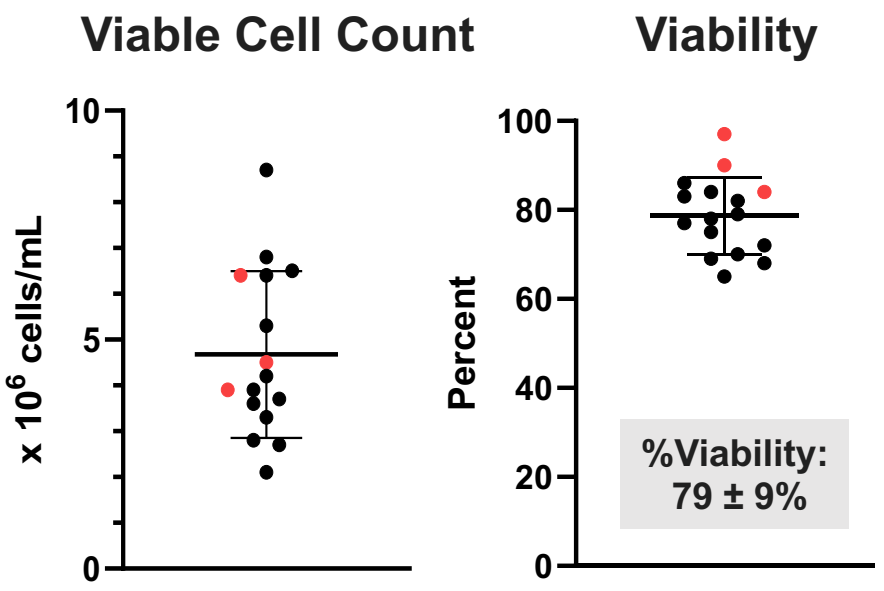
VOR33 eHSC Drug Product
Ready for patient dosing

- ✓ No new genetic material nor viral vectors
- ✓ No cell expansion

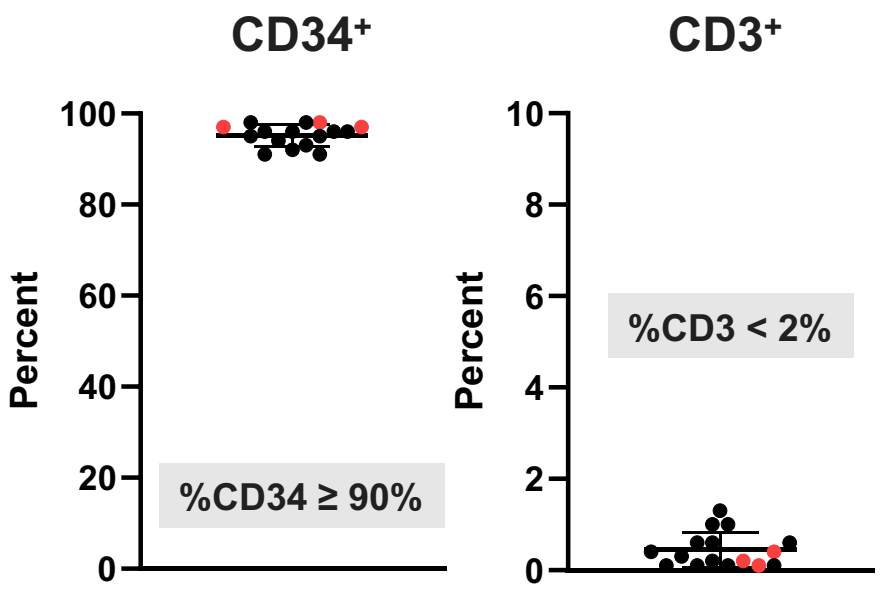
CAR-T, chimeric antigen receptor T-cell therapy.

VOR33 Manufacturing At Scale is Reproducible and Robust

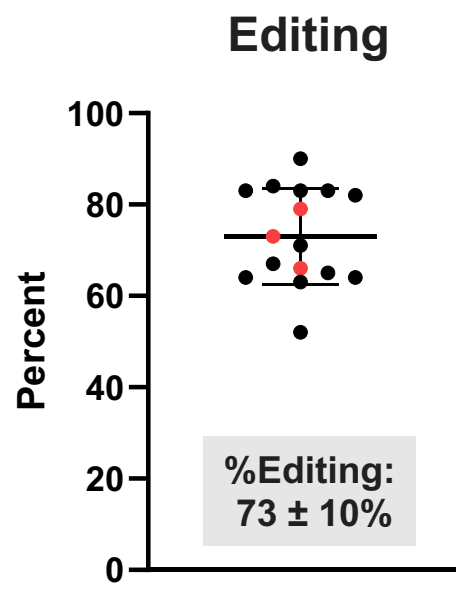
Cell Yield



Cell Purity (T-Cell Removal)



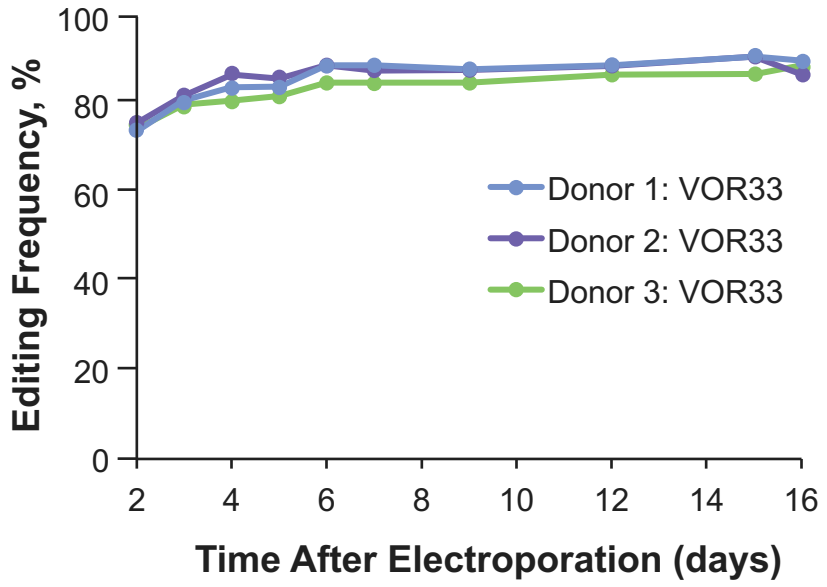
Editing ~73%



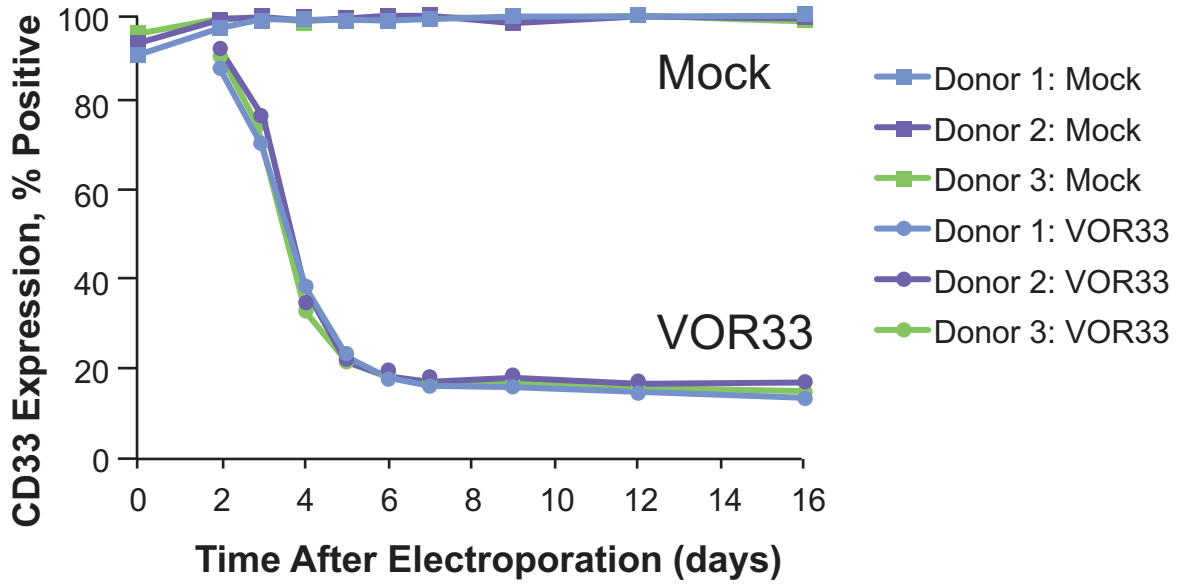
Data represents the results of at-scale manufacturing from 16 batches produced at 2 manufacturing sites. Symbols in red (●) indicate batches used in pharmacology and toxicology studies.

VOR33: CD33 Expression Protein Loss Upon Gene Editing

Gene Editing



Protein Expression



- Efficient gene editing stabilizes 4 days after delivery of the Cas9/gRNA RNP via electroporation
- Protein loss stabilizes 5 days after electroporation

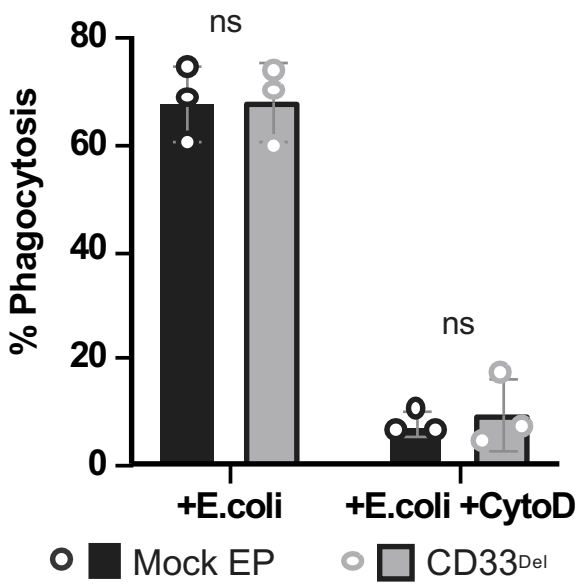
RNP, ribonucleoprotein.

Maintenance of Hematopoietic Function in CD33 Gene-Edited Cells

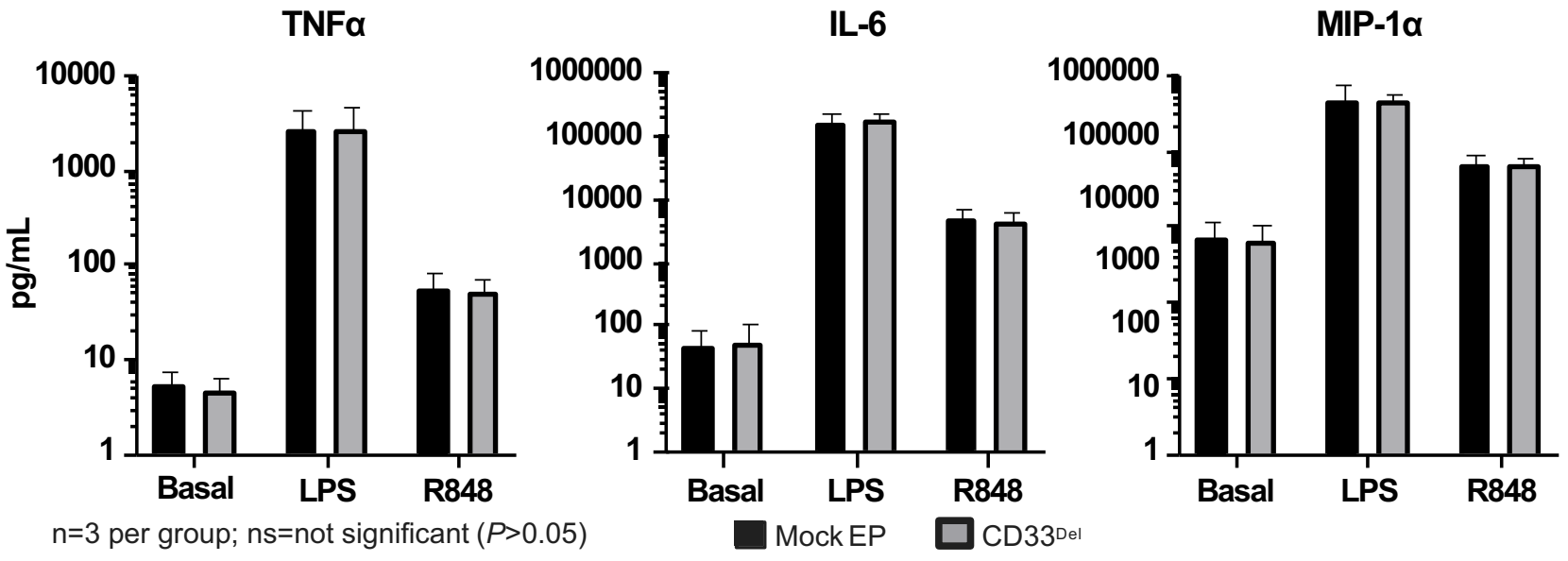
VOR33: No Observed Impact on Cell Function

In Vitro Cell Function Assays

Phagocytosis

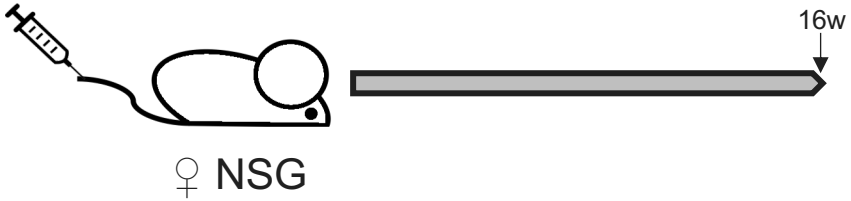


Cytokine production



CD33DEL, CD33 deleted; eHCS, engineered hematopoietic stem cell.; EP, electroporation; IL, interleukin; LPS, lipopolysaccharide; MIP, macrophage inflammatory protein; ns, not significant; TNF, tumor necrosis factor.

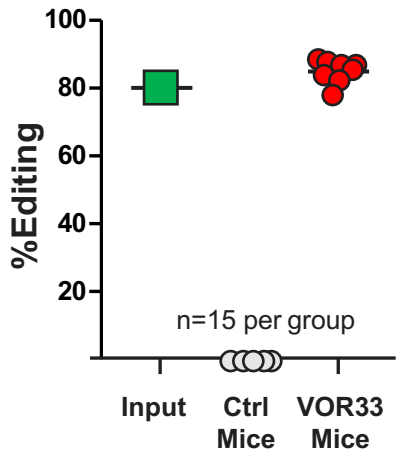
VOR33: No Impact on HSC Engraftment and Differentiation *in vivo*



- Multilineage engraftment
- Bone Marrow Editing %
- Hematopoietic progenitor potential

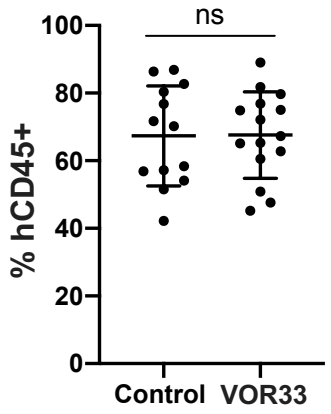
High Editing Maintained for 16-Weeks of Engraftment

Editing Efficiency

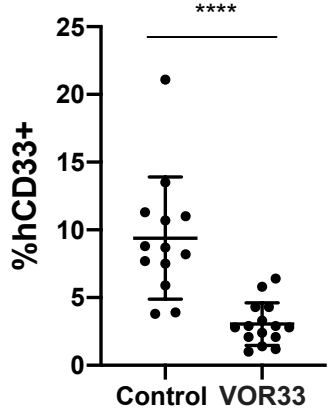


Xeno-Transplant in NSG Mouse Model: 16-Week Bone Marrow No Impact on Differentiation

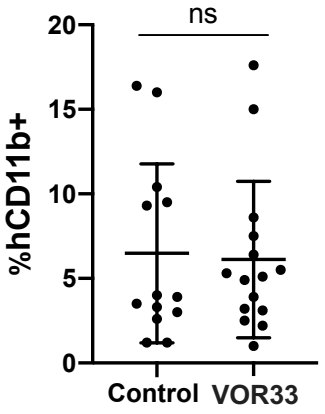
Human Chimerism



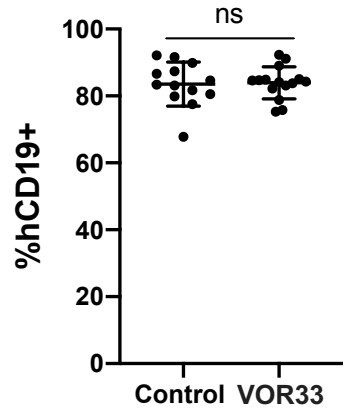
CD33 Frequency



Myeloid cell frequency



B-cell frequency



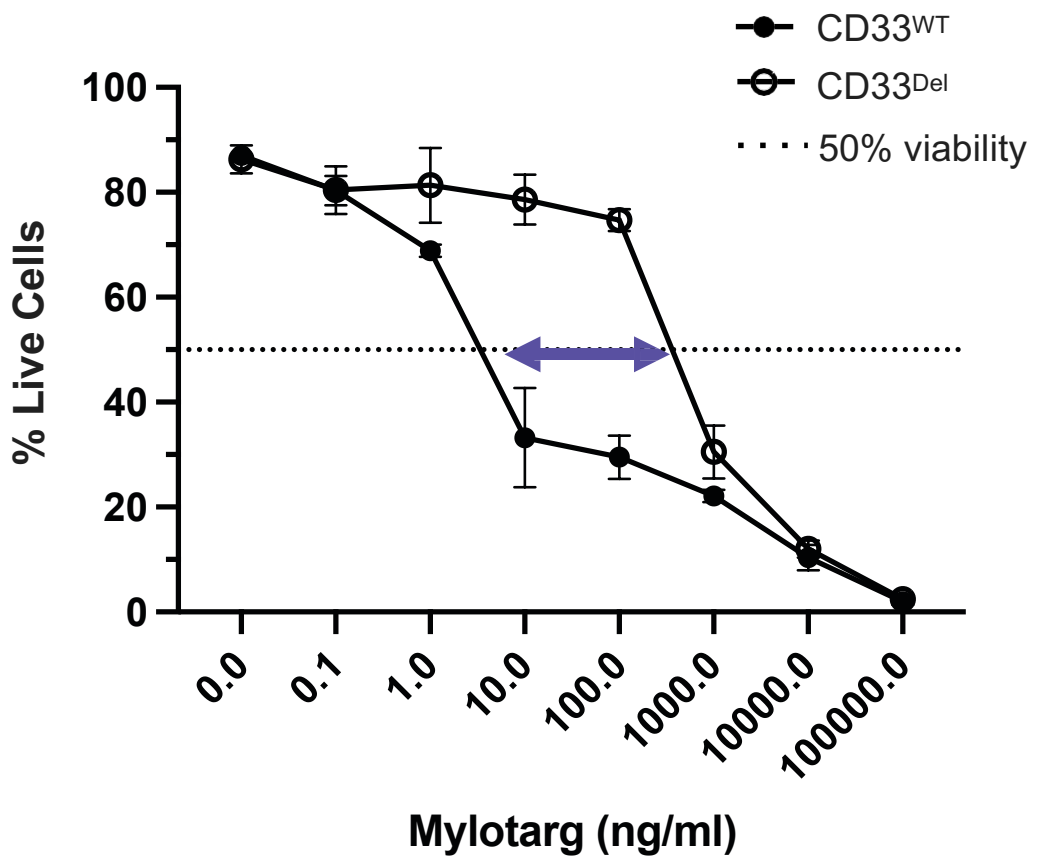
n=15, ns, not significant ($p > 0.05$); ****$p < 0.0001$ (ordinary one-way ANOVA)

HCS, hematopoietic stem cell; NSG, NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ; Ctrl,control

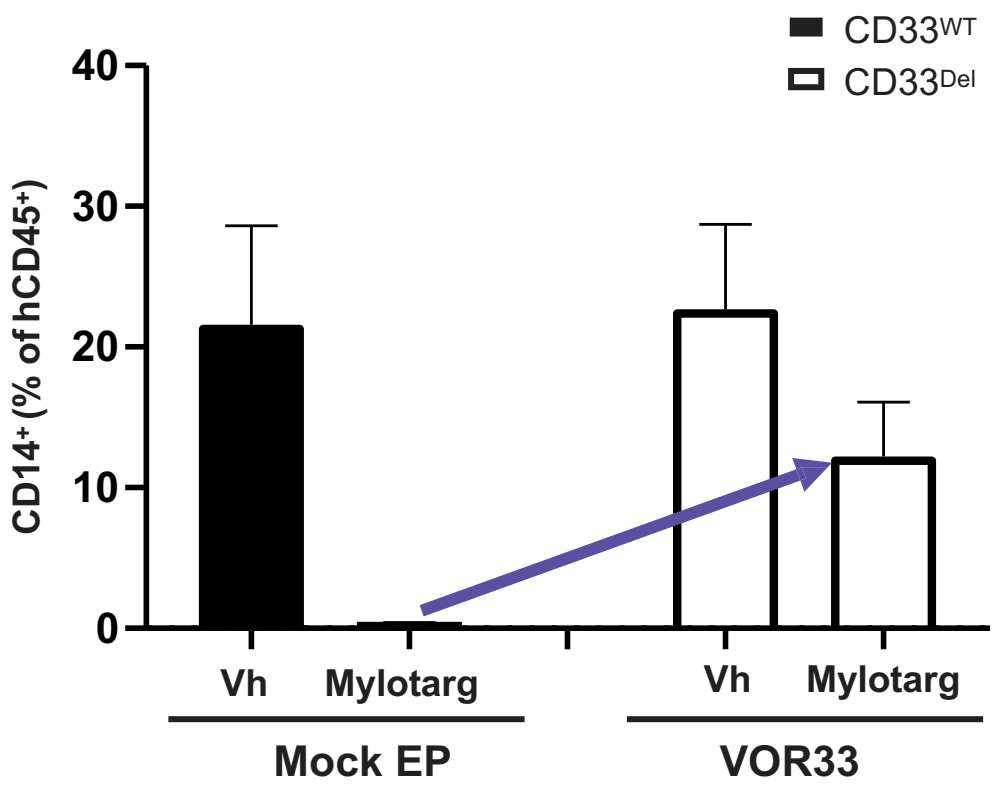
Pharmacology: CD33 Null Cells Are Protected From CD33-Directed Therapy

VOR33: Protected from CD33 Directed Therapy

In Vitro: Monocytes



In Vivo: 16-Week Engraftment



n=30 per arm (15 per donor)

EP, electroporation; Vh, vehicle; WT, wild-type.

Safety: Toxicology and Off-Target Results

Toxicology Assessment Did Not Reveal Significant Adverse Findings for VOR33

In life observations (every 3–6 days)

- Mortality
- Clinical signs
- Body weights
- Food/water consumption

Hematology (12)

- Cell morphology
- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration
- Platelet count & platelet/thrombocrit
- Red blood cell count
- Red cell distribution width
- Reticulocyte counts (absolute & relative)
- WBC
- WBC differential (absolute & relative)

Organ weights (11)

- Adrenals
- Brain
- Heart
- Kidneys
- Liver
- Ovaries
- Prostate
- Spleen
- Testes
- Thymus
- Uterus

Clinical Chemistry (19)

- Sample Appearance (when abnormal)
- A/G ratio (calculated)
- Alanine aminotransferase
- Albumin (A)
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin (total)
- Calcium (total)
- Chloride
- Cholesterol (total)
- Creatinine
- Globulin (G; calculated)
- Glucose
- Phosphorus (inorganic)
- Potassium
- Protein (total)
- Sodium
- Triglycerides
- Urea

Histopathology (43)

- Adrenals
- Aorta (thoracic)
- Brain
- Cecum
- Colon
- Duodenum
- Epididymis
- Esophagus
- Eyes
- Femur with marrow
- Gallbladder
- Heart
- Injection site
- Ileum
- Jejunum
- Kidneys
- Liver (2 lobes)
- Lungs with bronchi
- Lymph nodes (iliac, mesenteric and inguinal)
- Olfactory bulb
- Optic nerves
- Ovaries
- Pancreas
- Pituitary
- Prostate
- Rectum
- Salivary gland (mandibular)
- Sciatic nerve
- Seminal vesicles
- Skeletal muscle (thigh)
- Skin, subcutis & mammary gland (inguinal)
- Spinal cord (cervical)
- Spleen
- Sternum with marrow
- Stomach
- Testes
- Thymus
- Thyroids with parathyroids
- Tongue
- Trachea
- Urinary bladder
- Uterus
- Vagina

All assessment performed in compliance with GLP

WBC, white blood cell; GLP, good laboratory practice.

Assessment of Off-Target Edits: VOR33 Has No Significant Off-Target or Safety Concerns

Unbiased Assessment of Off-Target Sites	**GUIDE-seq** Low frequency genomic sites identified with no perceivable safety risk
In Silico Predicted Off-Target Sites	**Hybrid Capture NGS** No reproducible and reliably edited sites
Gross Chromosomal Abnormalities	**Karyotyping** No chromosomal abnormalities

See poster #112, Hazelbaker et al

NGS, next-generation sequencing.

Summary

- Clinical ready manufacturing process
- HSC engraftment and function are unaltered despite loss of CD33
- CD33 null cells are protected from CD33-directed therapy
- No toxicology or genomic off-target findings
- VOR33 IND and CTA have been cleared by FDA and Health Canada, respectively
  - Multicenter first-in-human Phase 1/2a clinical trial initiating in 2021 (NCT04849910)