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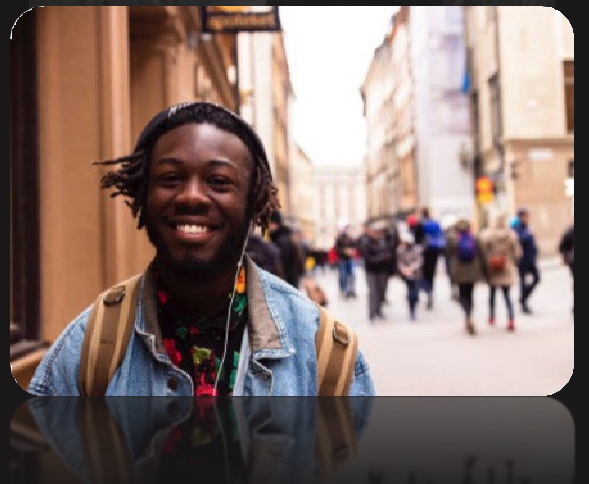
Ensoma

curative medicines through precision *in vivo* cellular engineering

October 2024



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Creating a new genetic medicine

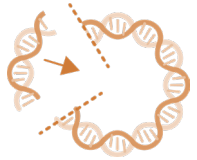
We engineer hematopoetic stem cells (HSC) *in vivo* to develop a durable source of therapeutic blood and immune cells that treat chronic disease.

Cell and genetic medicines are highly innovative… but opportunity to improve and expand therapeutic potential

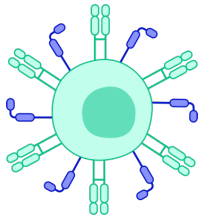
Current cell & genetic medicines challenges

- **High Burden of Treatment**
- **Concerns Over Treatment Durability**
- **Complex, Costly CMC & Supply Chain**
- **Few Qualified Treatment Centers**

Opportunity to expand therapeutic potential



Genetic diseases



Oncology

Immunology

Pipeline focus at the nexus of scientific validation & unmet need

	Indication	Target	Modification	Stage of development: Research	IND-enabling	Clinical	Rights
Genetic diseases	Chronic granulomatous disease (CGD)	HSC	CYBB (gene insertion)	→	→ **IND H1 '25**		ensoma
	Sickle cell disease	HSC	HbF reactivation & antibody enrichment (multiplex editing)	→			ensoma, Bill & Melinda Gates foundation
Oncology	Solid-tumor I/O	T, NK, M, HSC	Multi-lineage CAR (gene insertion)	→			ensoma
	Heme Oncology	T, NK, HSC	Multi-lineage CAR (gene insertion)	→			ensoma

Experienced team and top-tier investors

Our Leadership Team

Jim Burns, PhD
President &
Chief Executive Officer

Hans-Peter Kiem, MD, PhD
Founder, Chief Clinical &
Scientific Advisor

Robert Peters, PhD
Chief Scientific Officer

Daniel Leblanc
Chief Technology Officer

Stephanie Fedak
Senior Vice President,
People & Culture

Elinor Shin, PhD, JD
Senior Vice President, Legal
& Intellectual Property

Patrick Au, PhD, DABT
Vice President, Translational
Research & Early Development

Betsy Bogard
Vice President, Program &
Alliance Management

Drew Dietz, MD
Vice President,
Head of Clinical R&D

Joe Salas, PhD
Vice President,
Biology

Stefano Stella, PhD
Vice President,
Gene Editing

Chapman Wright, PhD
Vice President, Process &
Analytical Development

$205 Million Raised

5AM VENTURES

F-PRIME

BILL & MELINDA GATES foundation

GILEAD

Takeda
TAKEDA VENTURES, INC.

Kite

SOLASTA VENTURES

BIOLUMINESCENCE VENTURES

SymBiosis

ALEXANDRIA Venture Investments

Cormorant Asset Management

rtw

MIRAE ASSET

DELOS CAPITAL

Viking

CATALIO CAPITAL MANAGEMENT

RIT Capital Partners plc

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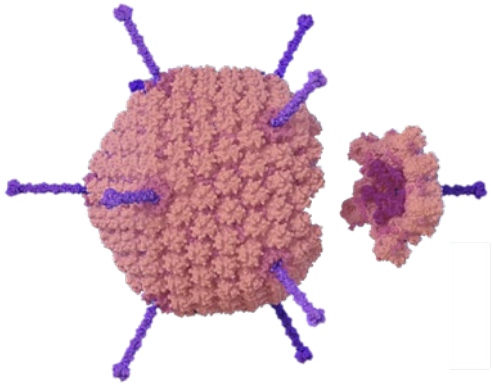
Ensoma technology

Engenious: High-capacity, HSC targeting, multi-plex genetic engineering

Ensoma's proprietary VLP

Helper-dependent adenovirus (HDAd) 5/35++

Ad35++ fiber knob:
CD 46 targeting



Ad5

Ad35

Large payload capacity:

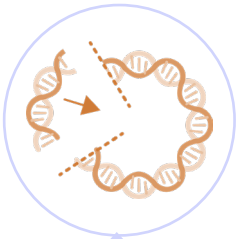
VLP: 35 kb

Lentivirus: ~8 kb

AAV: 4.7 kb

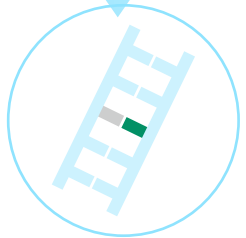
Gene Insertion

- Efficient large gene insertion (engineered sleeping beauty)
- Favorable insertion profile



Gene Editing

- Highly efficient base editing with proprietary CRISPR-Cas
- Class-leading specificity & safety profile (no nicks on either strand)



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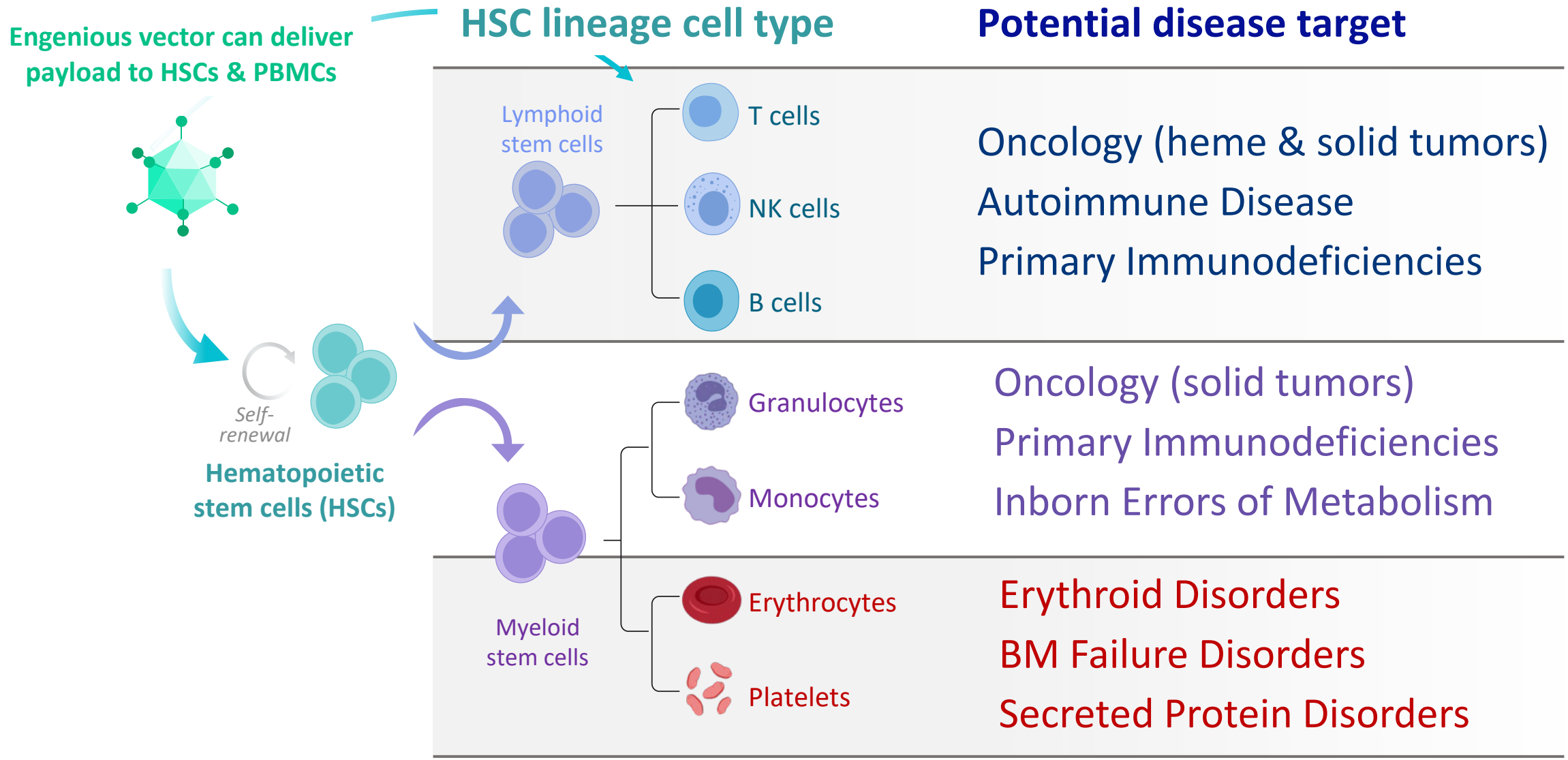
Engineering HSCs through *in vivo* gene therapy creates a durable source of blood and immune cells to treat chronic disease



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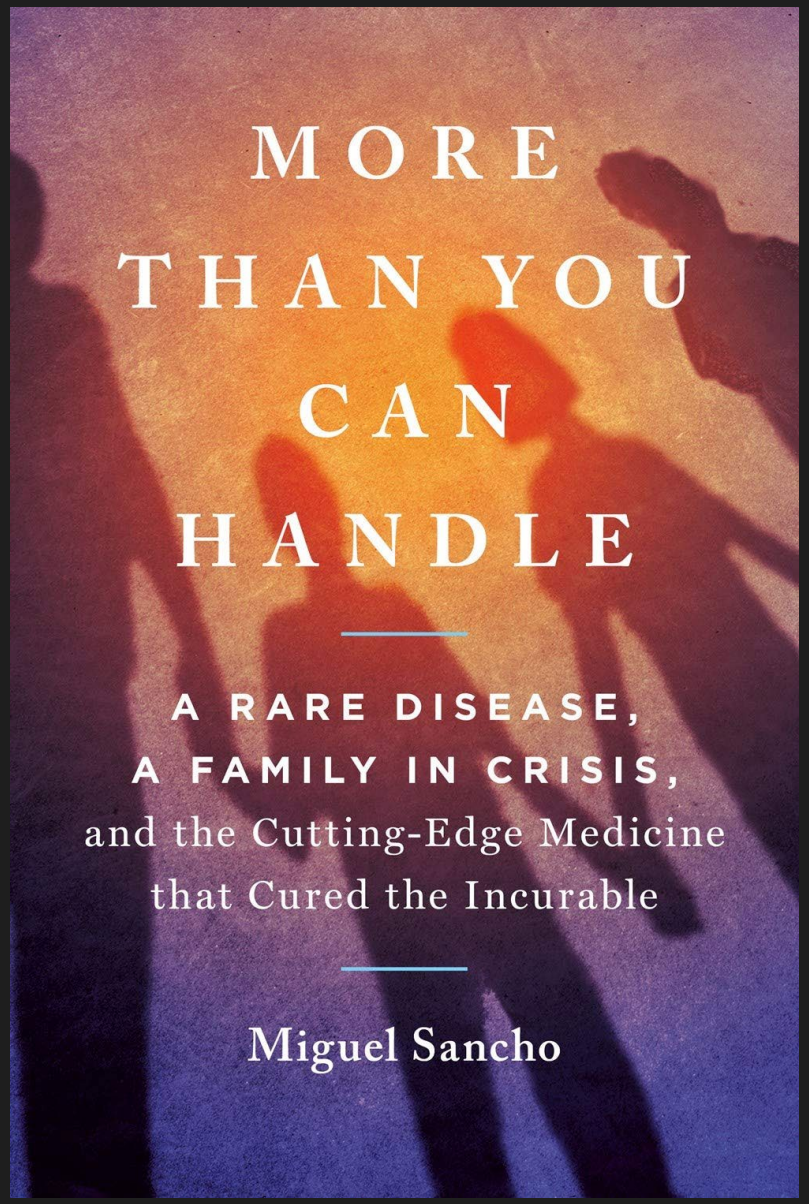
Chronic Granulomatous Disease



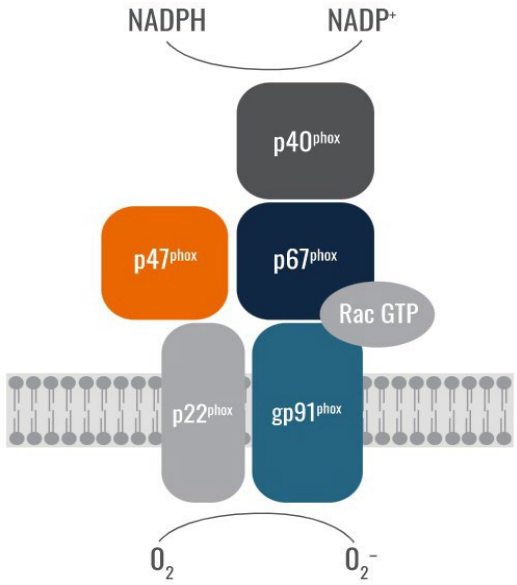
About chronic granulomatous disease (CGD)

CGD overview

- Estimated incidence: 1 in 200,000 live births
- Caused by a defect in NADPH oxidase
- Patients experience recurrent and severe bacterial or fungal infections; dysregulated inflammation is common
- Median life expectancy is ~45 years
- Treatment options include: antibiotics, antifungals, interferon gamma, and allo-HSCT; *ex vivo* HSC-targeted gene therapies have been evaluated in clinical trials

CGD has two sub-types: X-linked and autosomal recessive

The NADPH Complex[1]



Subunit (gene)	Mode of inheritance	Frequency
gp91^{phox} (CYBB)	X-linked	65-70%
p47^{phox} (NCF1)	Autosomal recessive	20-25%
p67^{phox} (NCF2)	Autosomal recessive	5-6%
p22^{phox} (CYBA)	Autosomal recessive	3-5%
p40^{phox} (NCF4)	Autosomal recessive	<1%

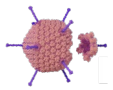
CYBB NOTES

- X-linked CGD tends to be more severe, earlier onset than autosomal recessive[2]
- Over 500 mutations have been described in CYBB

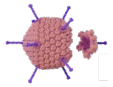
Sources: 1) https://www.cgdpathways.com/; 2) Winkelstein et al., Medicine 2000

X-CGD candidate: *in vivo*, HSC-directed gene insertion

Our approach

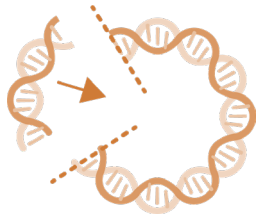


Sleeping Beauty

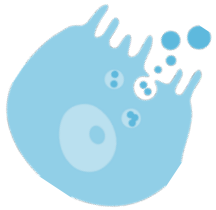


Neutrophil | CYBB | Enrichment cassette

In vivo CYBB expression



Functional CYBB insertion

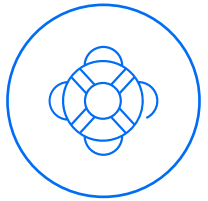


Drives *in vivo* CYBB expression

Key points of differentiation

One, time *in vivo* functional cure for CGD

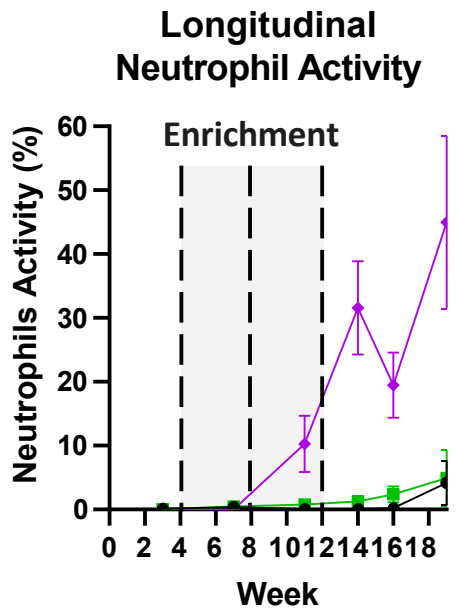
Greatly reduced treatment burden versus *ex vivo* approaches

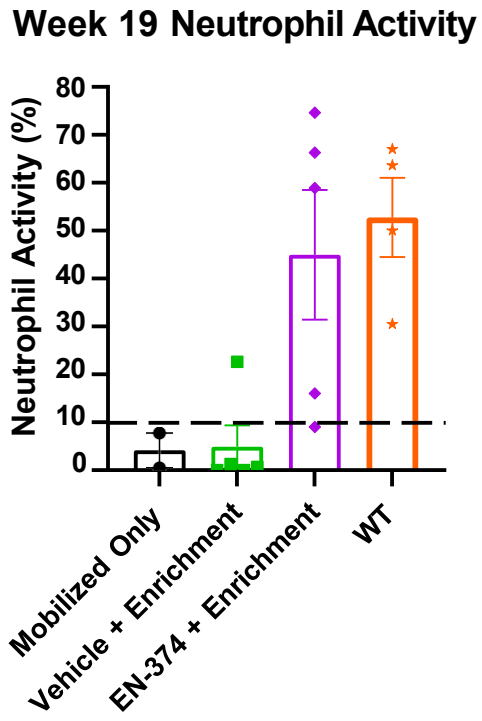


Safety advantage relative to transplant (no GVHD risk)

EN-374 restores oxidative burst function in CGD mouse neutrophils

CYBB activity (DHR) present in ~45% of total circulating neutrophils





Relevant threshold for clinical impact is estimated to be ≥10% CYBB activity

LETTERS
https://doi.org/10.1038/s41591-019-0735-5
nature medicine

Lentiviral gene therapy for X-linked chronic granulomatous disease

Donald B. Kohn[1*], Claire Booth[2], Elizabeth M. Kang[3], Sung-Yun Pai[4], Kit L. Shaw[1], Giorgia Santilli[2], Myriam Armant[4], Karen F. Buckland[2], Uimook Choi[3], Suk See De Ravin[3], Morna J. Dorsey[5], Caroline Y. Kuo[1], Diego Leon-Rico[2], Christine Rivat[2], Natalia Izotova[2], Kimberly Gilmour[2], Katie Snell[2], Jinhua Xu-Bayford Dip[2], Jinan Darwish[2], Emma C. Morris[6], Dayna Terrazas[1], Leo D. Wang[4,15], Christopher A. Bauser[7], Tobias Paprotka[7], Douglas B. Kuhns[8], John Gregg[9], Hayley E. Raymond[9], John K. Everett[9], Geraldine Honnet[10], Luca Biasco[2], Peter E. Newburger[11], Frederic D. Bushman[9], Manuel Grez[12], H. Bobby Gaspar[2,13], David A. Williams[4], Harry L. Malech[3], Anne Galy[10,14], Adrian J. Thrasher[2*] and the Net4CGD consortium[16]

Prior clinical data with *ex vivo* showed restoring ≥10% of neutrophils with NADPH oxidase activity confers clinically meaningful improvements in infection outcomes

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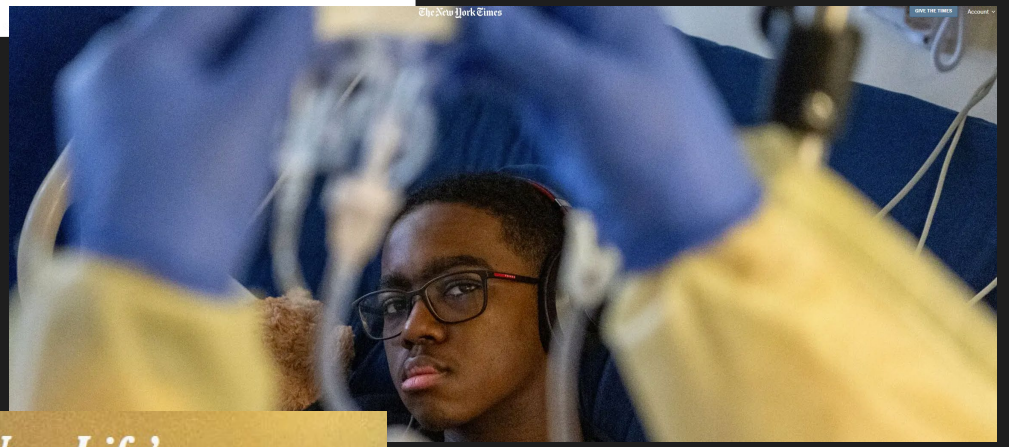
Sickle Cell Disease



First Day of a 'New Life' for a Boy With Sickle Cell

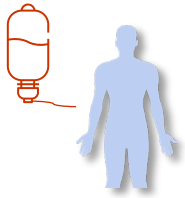
Kendric Cromer, 12, is among the first patients to be treated with gene therapy just approved by the F.D.A. that many other patients face obstacles to receiving.

Article headlines from: Timmerman Report, The New York Times (both Sep. 17, 2024)

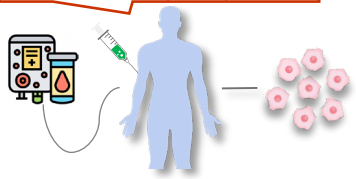
SCD | How Ensoma will solve *ex vivo* challenges

Today's *Ex Vivo* SCD Patient Journey

Prophylactic blood transfusions → **Mobilization & cell collection (apheresis)** → **N-of-1 manufacturing, testing, and release** → **Myeloablative conditioning** → **Hospitalization for severe side effects** → **Lengthy immune recovery**



2+ cycles; 2-3 days of collection per cycle



Infertility risk

e.g., severe mucositis requiring opioids / ketamine

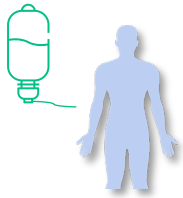
High infection risk

~2 months + ~6 weeks + 6+ months + ~1 week + ~4 weeks + 4+ months = **1 yr+**

Our Vision: *In Vivo* Patient Journey

Simple outpatient infusion → **2-3 outpatient infusions of enrichment agent**

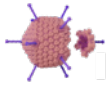
1 day



1 day per enrichment cycle

SCD Candidate: *in vivo* base editing to induce HbF expression

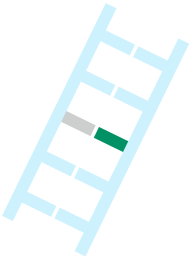
Our approach



ENS-BE:HbF & enrichment

Transient editor creates **permanent** correction

In vivo HbF expression



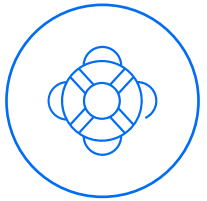
In vivo base editing

Drives HbF expression

Key points of differentiation

One, time *in vivo* functional cure for SCD

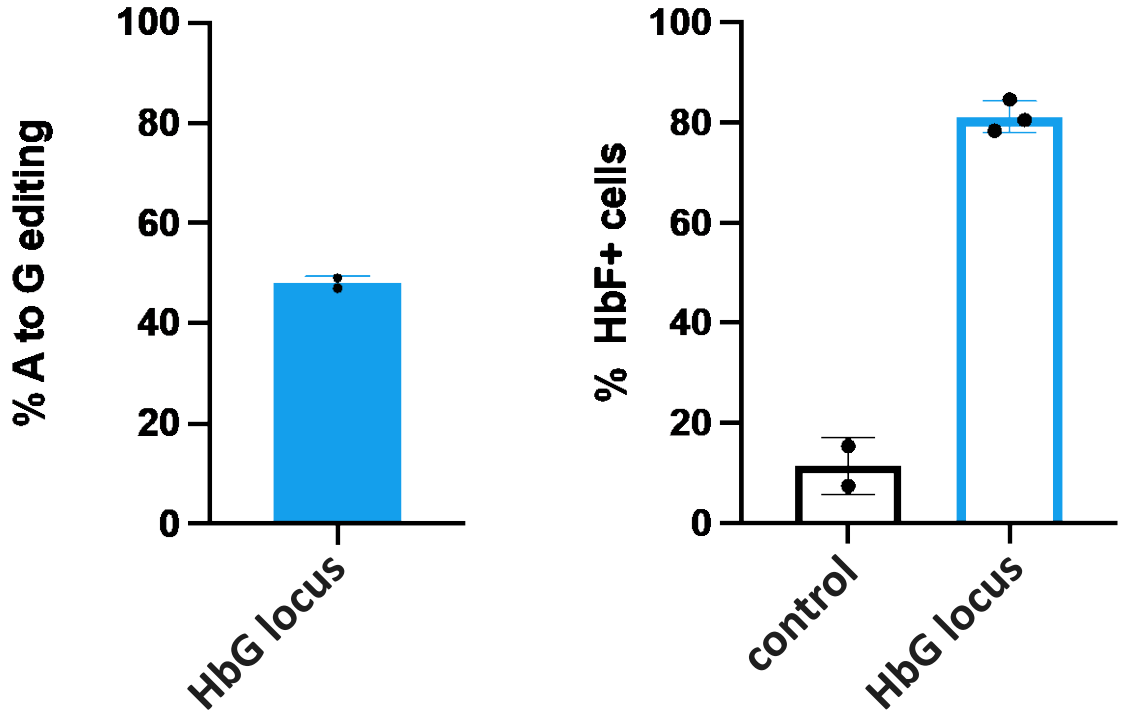
Greatly reduced treatment burden versus *ex vivo* approaches
No chemotherapeutic enrichment



Safety advantage relative to transplant (no GVHD risk)

Robust HbF induction with Ensoma's base editor

- High level of HbG locus editing in primary CD34+
- High level of HbF induction in fully differentiated erythrocytes



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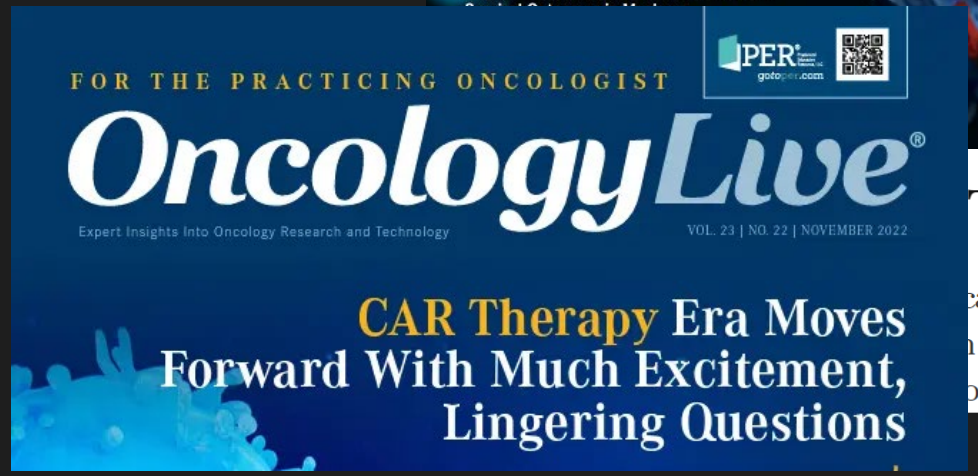
Immune Oncology Solid Tumor



Toxicity of Illness

cancer into a chronic disease with
extended period of time, financial
onic, too.

Differentiated Solid Tumor Approach Addresses Current Barriers

Challenges Limiting Solid Tumor Cell Therapies To Date	Ensoma's differentiated approach
Lack of efficacy due to immunosuppressive tumor microenvironment	Engineered HSCs deliver CAR-T, NK, M to bring full immune system to the tumor microenvironment
Durability issues	HSC editing provides durability via *in vivo* replenishment
N-of-1 manufacturing	Highly scalable, off-the-shelf therapy

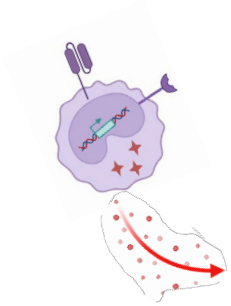
Solid Tumor Candidate: Durable, multi-cellular approach

Our approach

Lineage-specific CAR generation

1 CAR-Myeloid cells

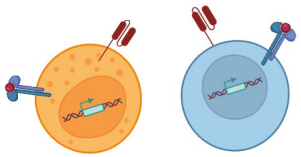
Infiltrate & inflame tumor → kill targets & prime endogenous immunity



Re-program TME & augment potency

2 CAR-T & NK cells

Engineer potency & long-term persistence



Key points of differentiation

Multi-cellular CAR approach (T, NK, and myeloid)

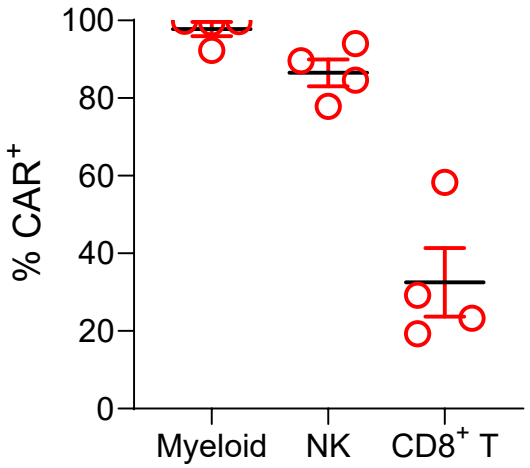
Ability to **modulate the tumor microenvironment**

Built-in **durability** (due to ability to target HSCs)

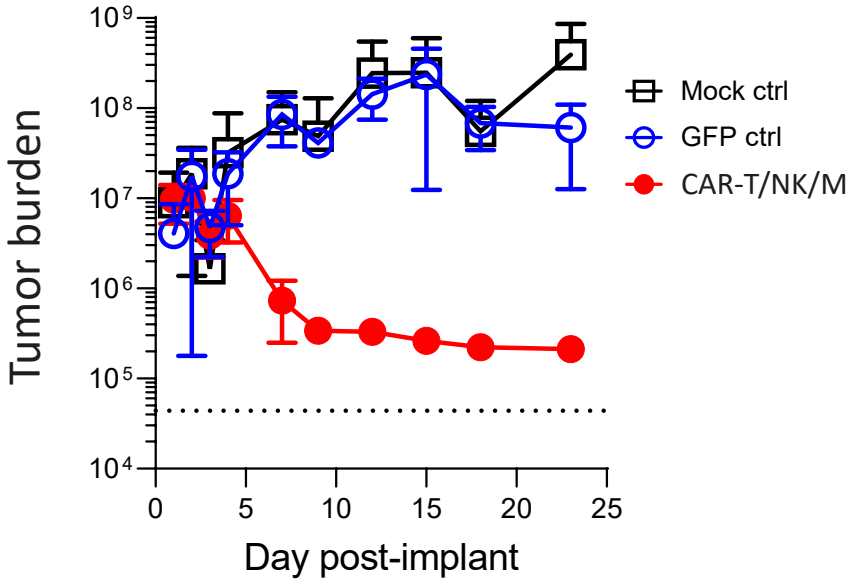
Differentiated, multi-cellular *in vivo* CAR approach mediates potent & durable solid tumor control

4/4 pan-lineage CAR mice cause regression in aggressive prophylactic solid tumor model

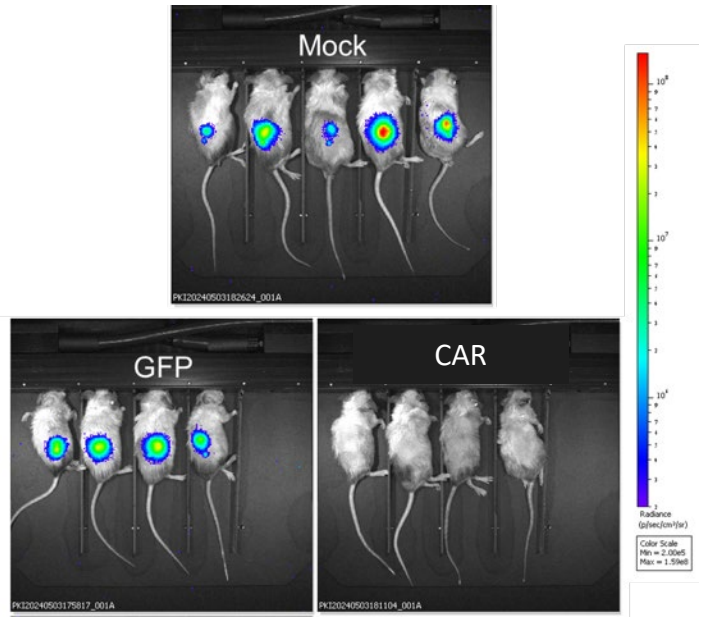
Established mice with CAR-T/NK/M



Reduced Tumor burden with pan lineage CAR-T/NK/M



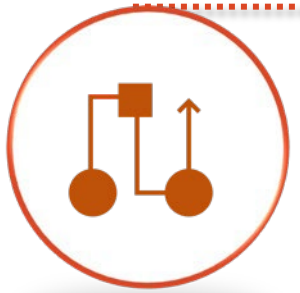
Day 12 Imaging



We are Building a Leading *in vivo* Gene Therapy Company

What We Have Built

- Delivery of large payloads up to 35KB and multiplex capability
- Best-in-class base editing – no DNA nicks
- Ability to do large gene insertion
- Focused on genetic, oncological, and immune diseases



Progress to the Clinic

- X-CGD IND scheduled H1 2025 – *1st in vivo HSC gene therapy*
- Positive pre-IND meeting, IND enabling studies ongoing
- GMP drug product being manufactured for clinical trial

Future Opportunities

- Advance our portfolio of programs – *2 development candidates in '25*
- Continue to innovate in our platform
- Explore partnerships that expand our platform's potential

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The future of medicine lies within us.