

# GENOME SURGERY

THE NEXT WAVE OF GENE EDITING THERAPIES

**.HEAL**  
by ce:ctis



# FORWARD-LOOKING STATEMENTS

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This presentation contains “forward-looking” statements within the meaning of applicable securities laws, including the Private Securities Litigation Reform Act of 1995. Forward-looking statements may be identified by words such as “at this time,” “anticipate,” “believe,” “expect,” “on track,” “plan,” “scheduled,” and “will,” or the negative of these and similar expressions.

These forward-looking statements, which are based on our management’s current expectations and assumptions and on information currently available to management, include statements about our research and development projects and priorities, our pre-clinical project development efforts, the timing and progress of clinical trials (including with respect to patient enrollment and follow-up), the timing of our presentation of data, the adequacy of our supply of clinical vials, the timing of completion of construction of our Raleigh, North Carolina manufacturing facility, and operational capabilities at our manufacturing facilities, and the sufficiency of cash to fund operations.

These forward-looking statements are made in light of information currently available to us and are subject to numerous risks and uncertainties, including with respect to the numerous risks associated with biopharmaceutical product candidate development as well as the duration and severity of the COVID-19 pandemic and governmental and regulatory measures implemented in response to the evolving situation.

With respect to our cash runway, our operating plans, including product development plans, may change as a result of various factors, including factors currently unknown to us. Furthermore, many other important factors, including those described in our Annual Report on Form 20-F and the financial report (including the management report) for the year ended December 31, 2020 and subsequent filings Collectis makes with the Securities Exchange Commission from time to time, as well as other known and unknown risks and uncertainties may adversely affect such forward-looking statements and cause our actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

# ALLOGENEIC HSC TRANSPLANT IS A CURATIVE TREATMENT

## Allows to treat many human diseases

- **Hematological Disease** (SCD,  $\beta$ -Thalassemia, Anemias)
- **Autoimmune Disease** (Multiple Sclerosis)
- **Viral Disease** (HIV, HTLV)
- **Malignant Disease** (Multiple Myeloma, HL & NHL)

# 43,962

Number of total Allogeneic HSC transplants performed in US (2013-2017)

# 43%

Frequency of matched donor available in US (2013-2017)

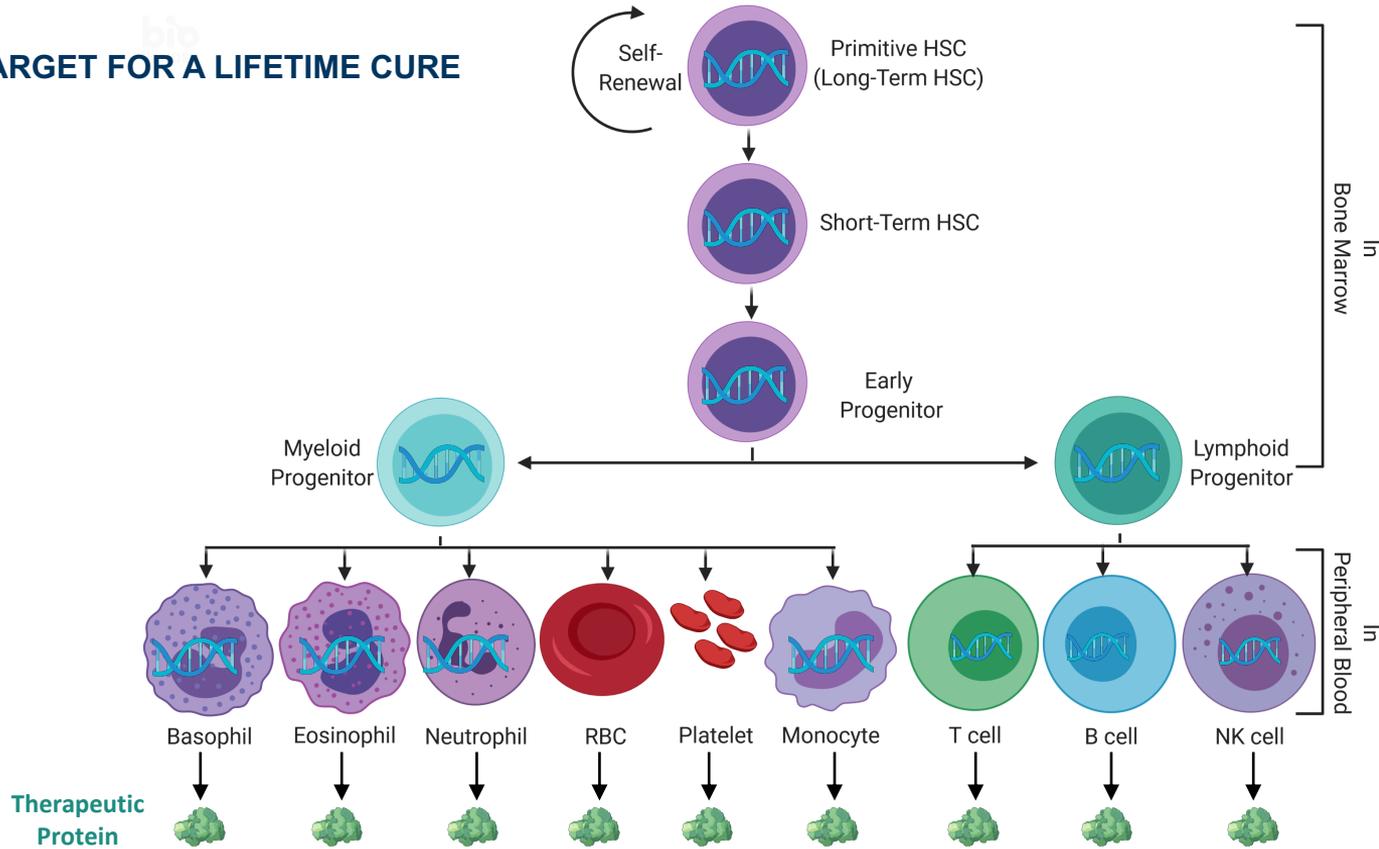
# 2.27X

Mortality risk of HLA-mismatched vs matched donor in age 55 or over

## Gene editing offers an unique opportunity to address the challenges

# HSC GENE THERAPY IS VERSATILE

TARGET FOR A LIFETIME CURE



# HSC GENE THERAPY POTENTIAL



HSPC

- Fanconi anemia



Platelets

- Haemophilia A
- Haemophilia B
- Haemophilia C
- Wiskott Aldrich Syndrome



Neutrophil

- Chronic Granulomatous disease
- Kostmann's Syndrome



RBC

- $\alpha$ -thalassemia
- $\beta$ -thalassemia
- Sickle cell disease
- Pyruvate kinase deficiency
- Diamond-Blackfan Anemia



Monocyte

- X-linked Adrenoleukodystrophy
- Metachromatic Leukodystrophy
- Gaucher disease
- MPS-I



B cells

- ADA-SCID
- X-linked SCID
- Wiskott Aldrich syndrom
- X-linked agammaglobulin emia

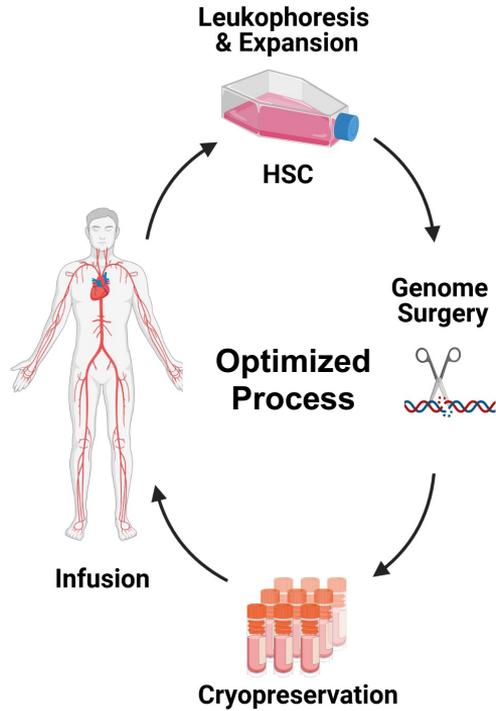


T cells

- ADA-SCID
- X-linked SCID
- Wiskott Aldrich syndrome
- X-linked hyper IgM syndrome
- Cancer
- HIV

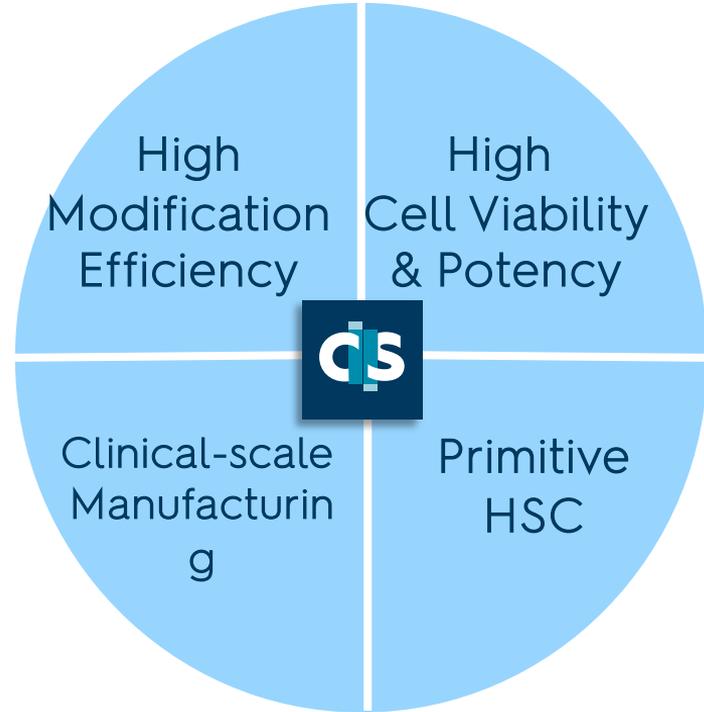
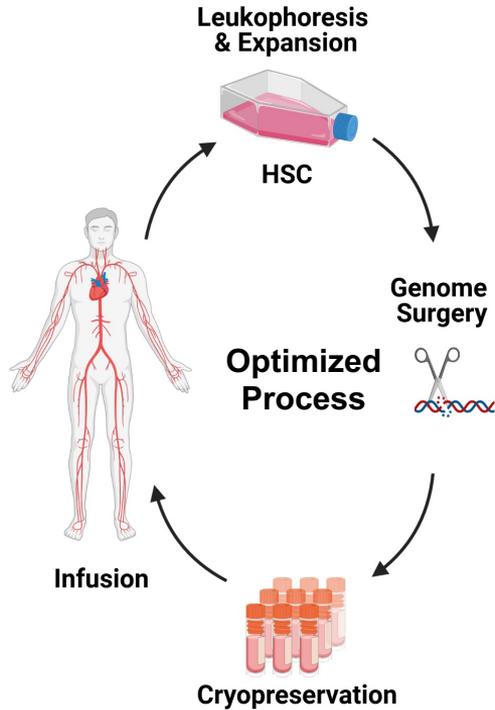
# PROCESS

## HSC GENOME SURGERY PLATFORM



# PROCESS

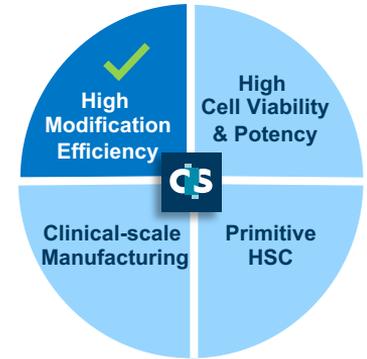
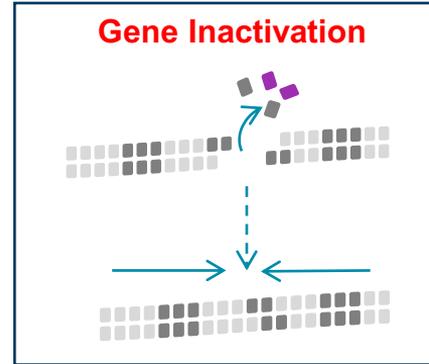
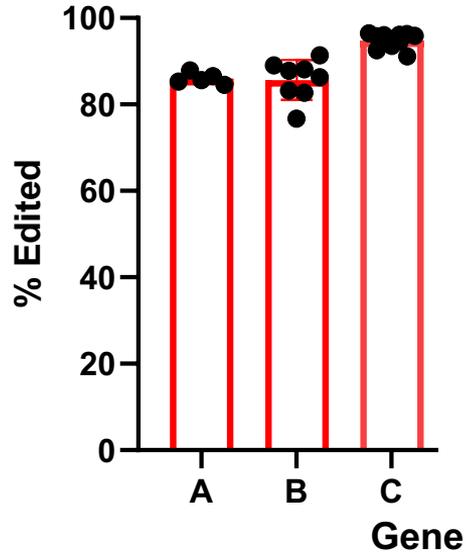
## KEY ASPECTS OF HSC ENGINEERING FOR GENOME SURGERY



# PROCESS

## HIGH MODIFICATION EFFICIENCY

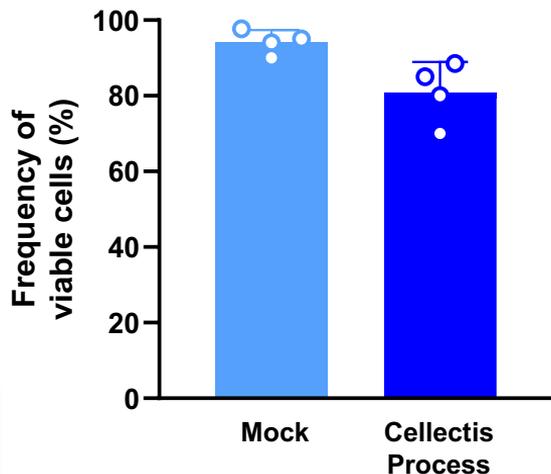
Allows for multiple type of modifications



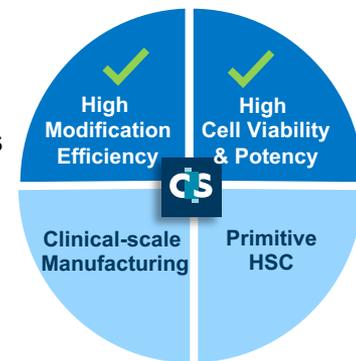
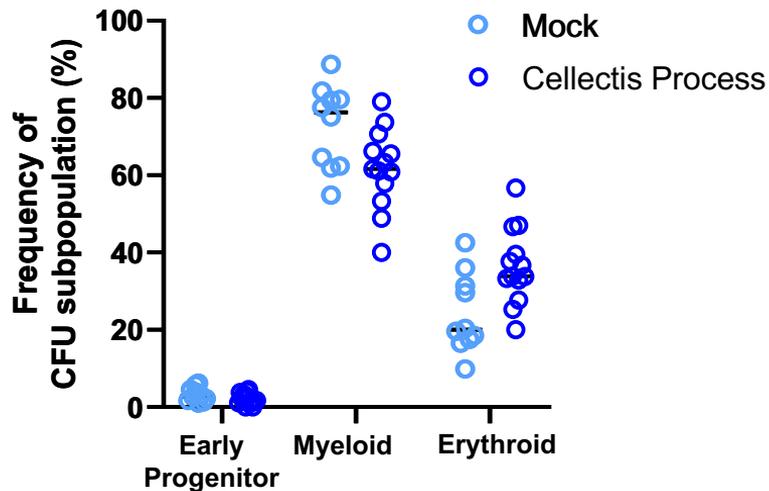
# PROCESS

## HIGH CELL VIABILITY & DIFFERENTIATION POTENCY

High viability



Maintains differentiation potency

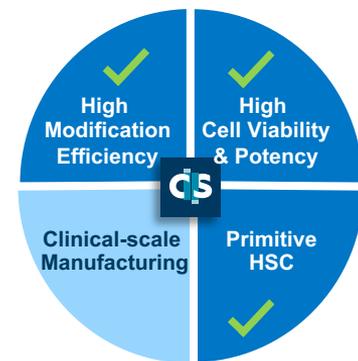
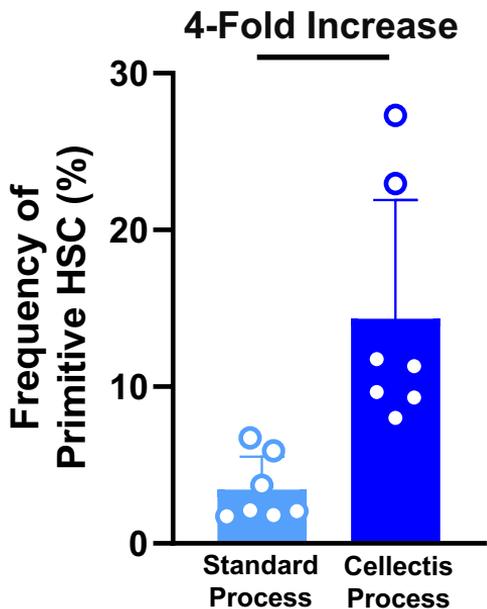
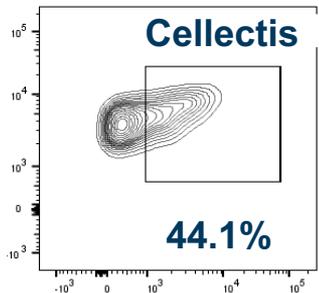
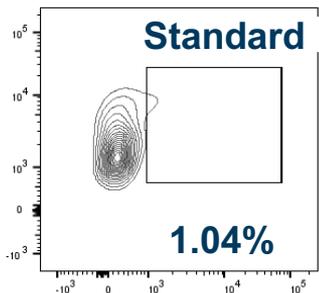


# PROCESS

## INCREASE IN PRIMITIVE HSC

Increases primitive HSC

CD90+CD133+  
in CD34+CD45RA<sup>low</sup>CD38-



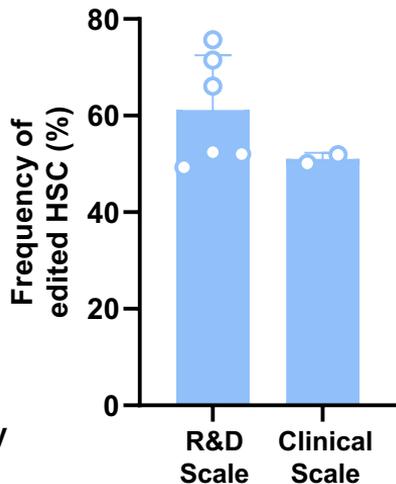
# PROCESS

## CLINICAL-SCALE MANUFACTURING

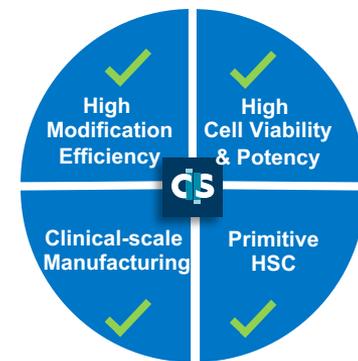
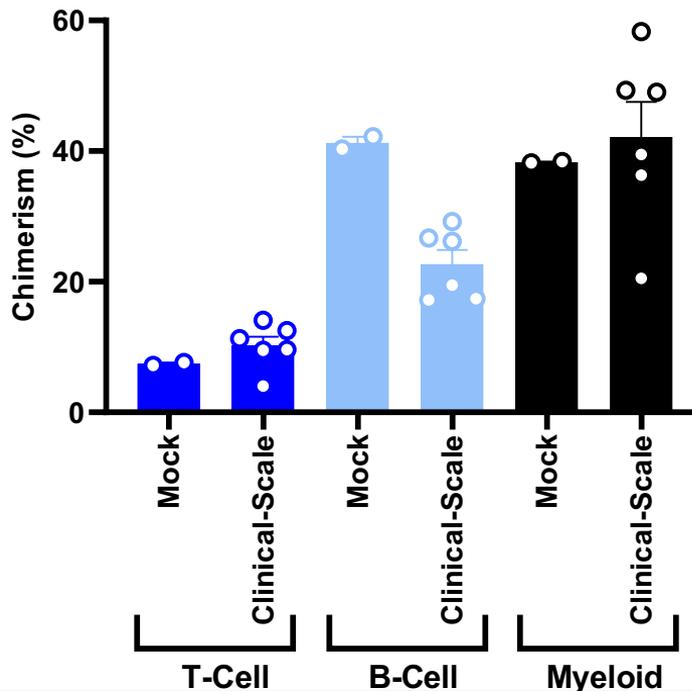
### Clinical-Scale Gene Correction



Clinical-Scale  
HSC Genome Surgery

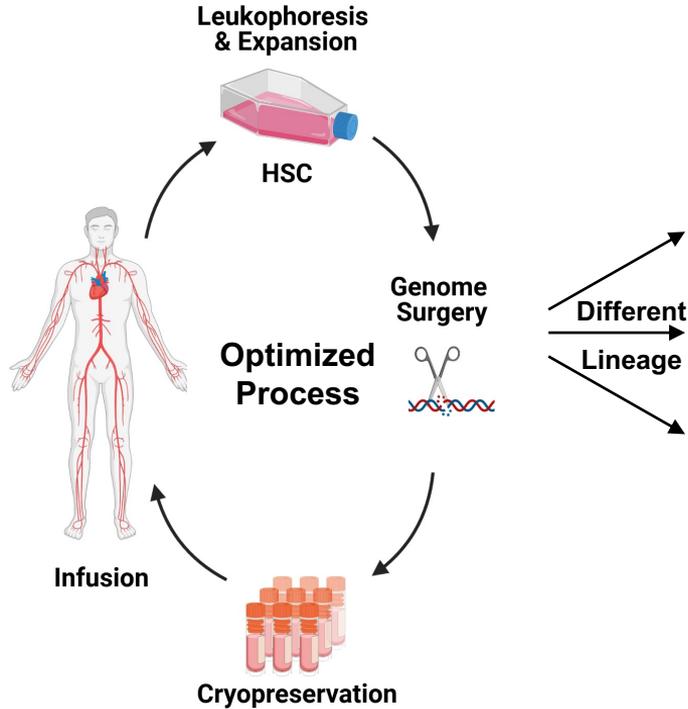


### In Vivo Engraftment

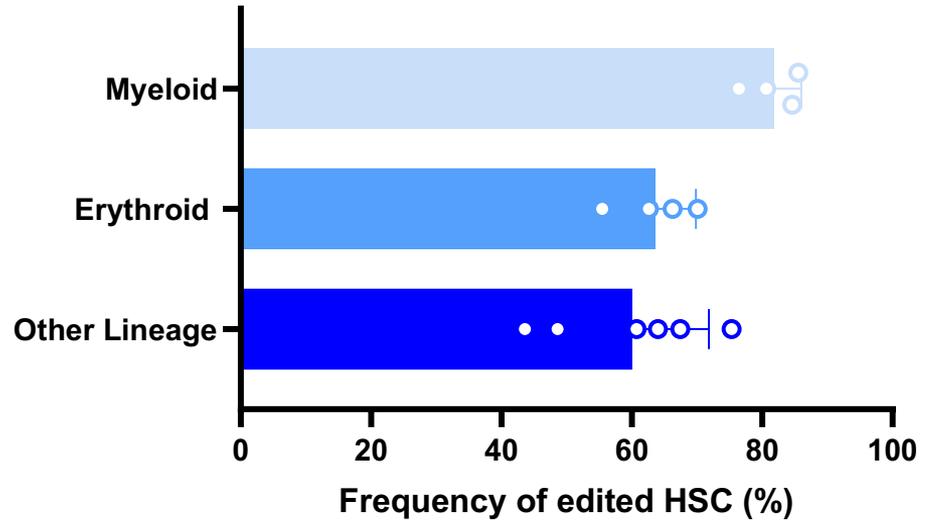


# PROCESS

## GENE EDITED HSC CAN DIFFERENTIATE INTO MULTIPLE LINEAGES

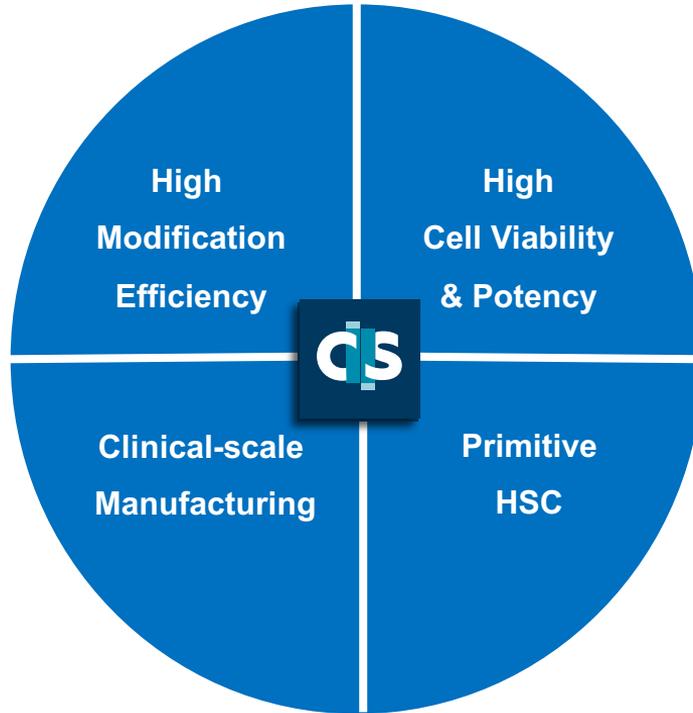


High rate of gene insertion in multiple lineages



# PROCESS

## CELLECTIS HAS DEVELOPED HIGH LEVEL OF GENOME SURGERY

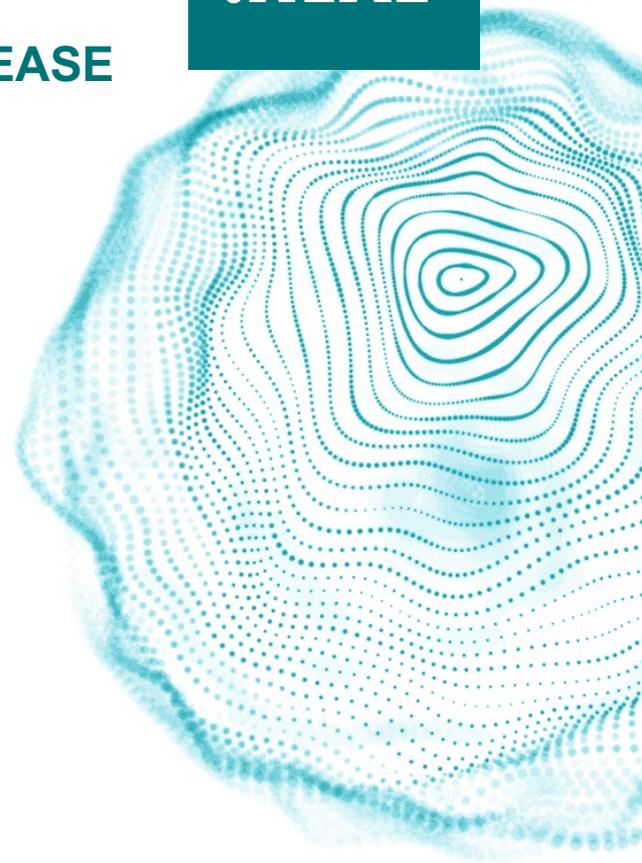


- **75-96% modification efficiency in multiple loci**
- **>80% cell viability & preserve differentiation potential**
- **>4-fold increase in primitive HSC**
- **Clinical-scale manufacturing without affecting key parameters**

**.HEAL**

**.HEAL GENE SURGERY TO CURE SICKLE CELL DISEASE**

**.TALGLOBIN01**



**.HEAL**  
by **cectis**

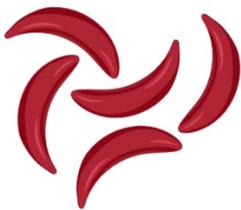
# SICKLE CELL ANEMIA

## Definition

SCA is an inherited genetic disorder affecting the shape and functions of red blood cells



Healthy RBC



SCA RBC

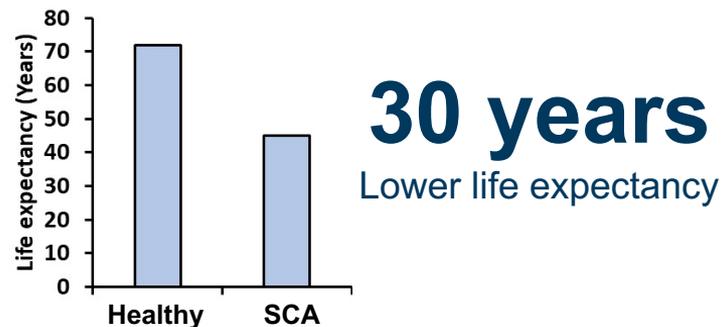
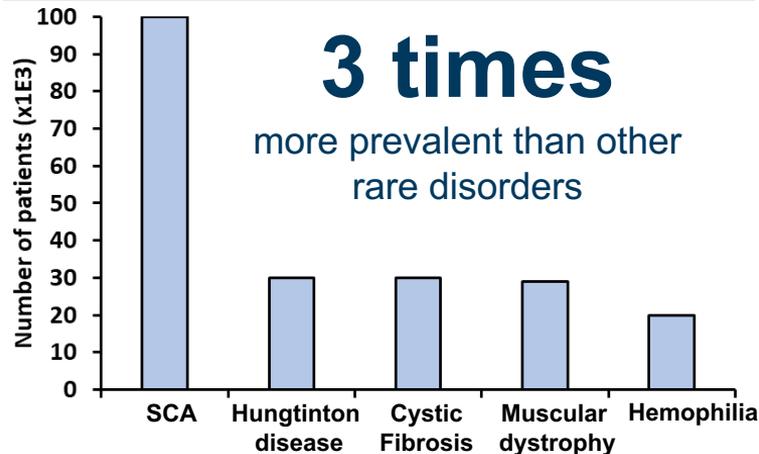
## Worldwide Epidemiology

**300K**  
Annual births<sup>1,2</sup>

**165K**  
Patients  
US/Europe

**>5M**  
Patients  
India/Africa

## US Epidemiology

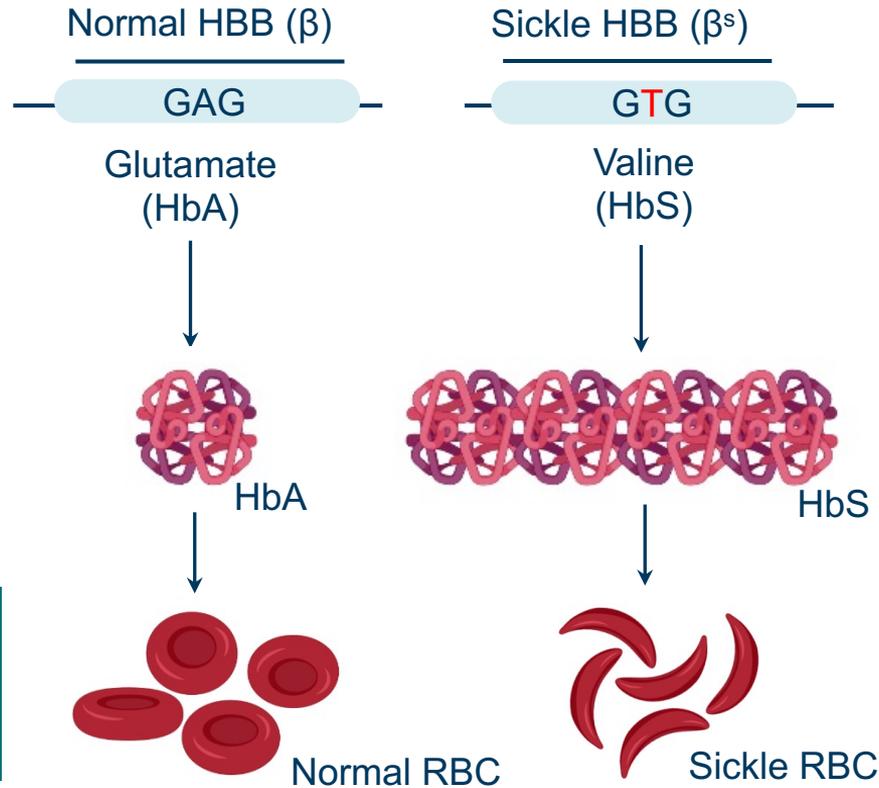


<sup>1</sup> Piel FB et al, Lancet 2013

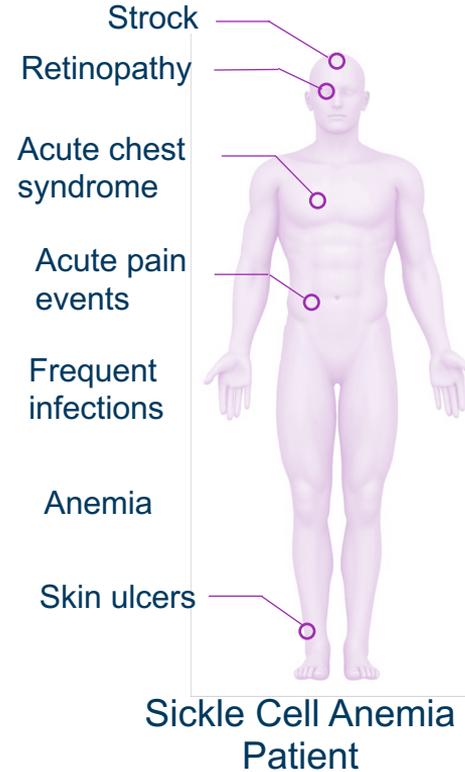
<sup>2</sup> Odame I, Nature 2014

# SICKLE CELL ANEMIA

## Genetic origin



## Pathological consequences



# SICKLE CELL ANEMIA TREATMENT OPTIONS

## Symptomatic treatments

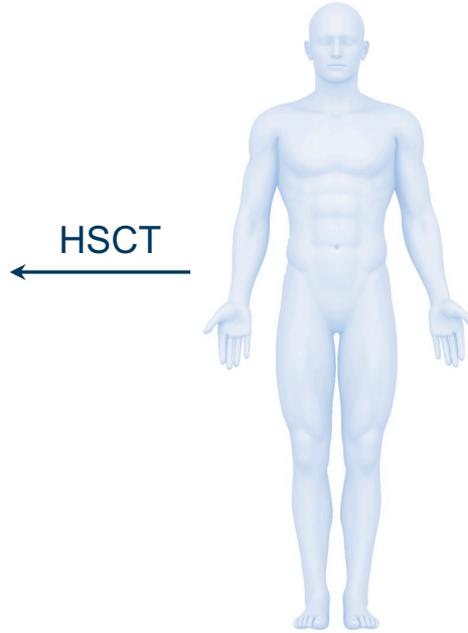
Chronic blood transfusion



Sickle Cell Anemia Patient

Hydroxyurea  
Anti oxidant  
Anti inflammatory  
Iron chelators  
Pain killers

## Curative treatment



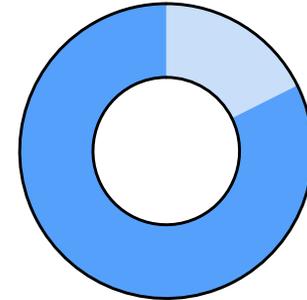
HLA-matched Healthy Donor

← HSCT

**91%**  
Overall survival rate<sup>2</sup>

**73%**  
Event free survival<sup>2</sup>

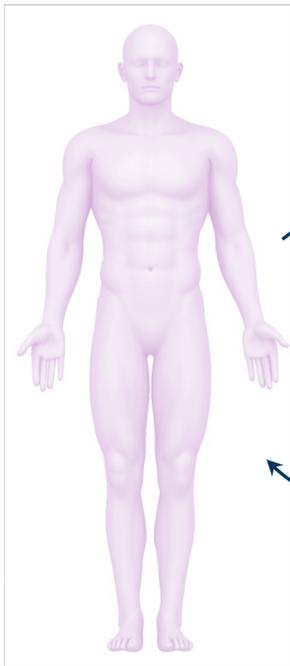
Legend:  
■ HLA matched HSCT  
■ HLA mismatched HSCT



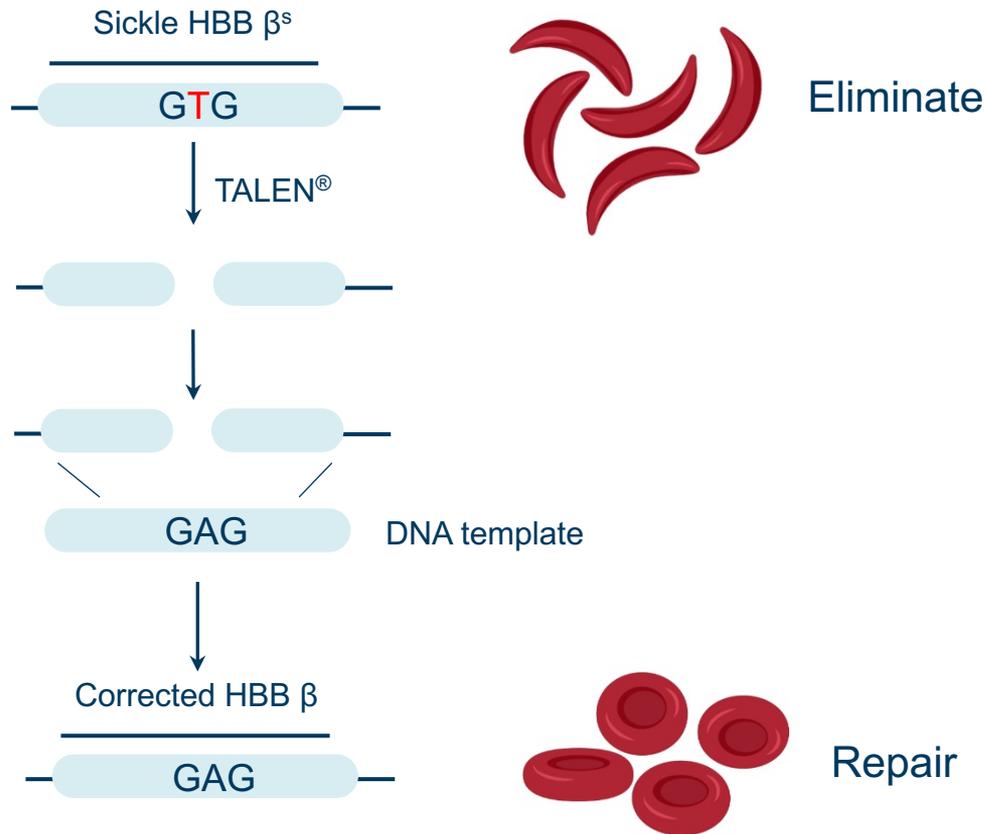
> 80 % of SCD patients are not eligible for HSCT <sup>4,5</sup>

# AUTOLOGOUS GENE SURGERY TO BYPASS HSCT AND CURE SCA

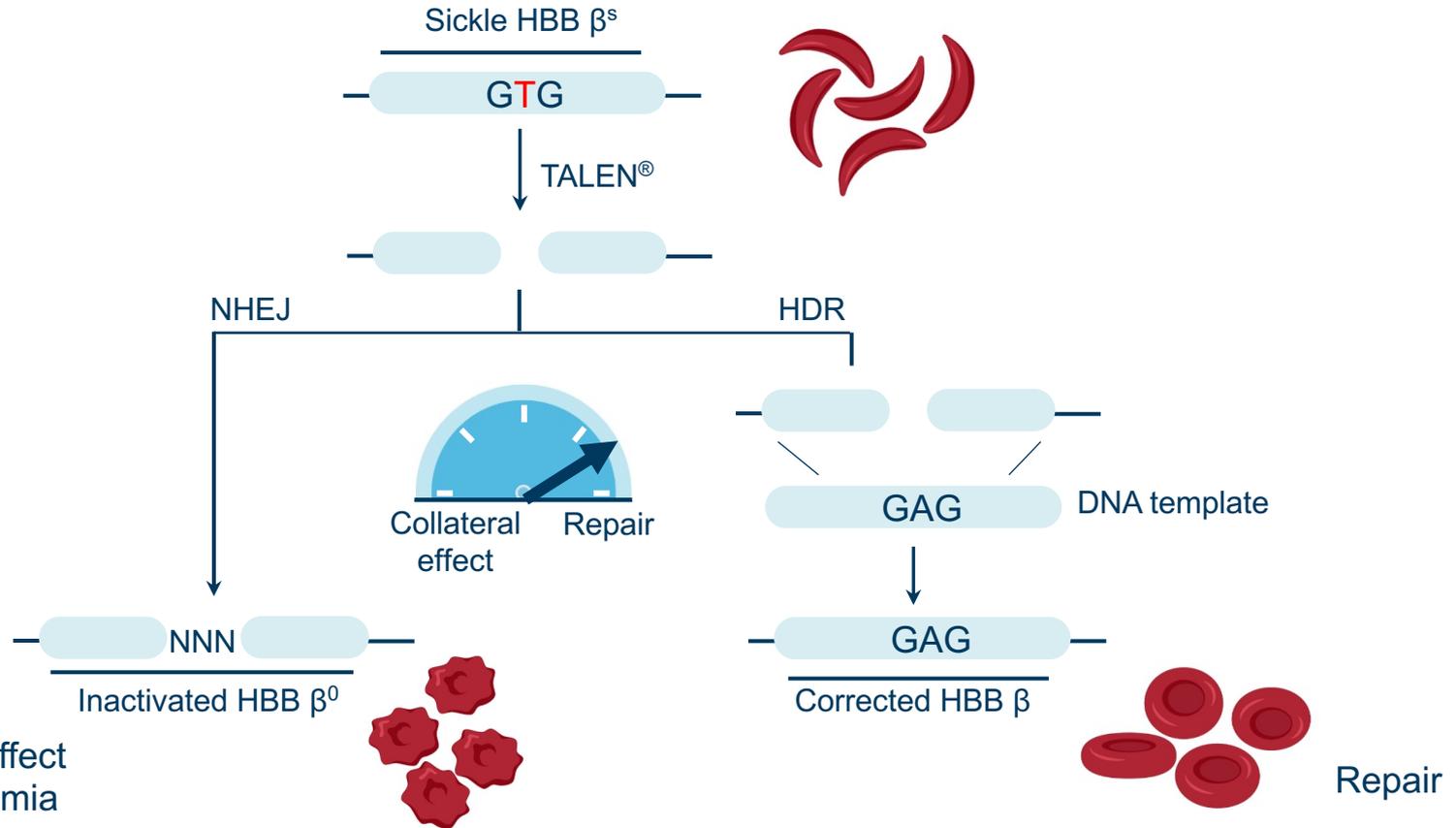
## Gene therapy treatment



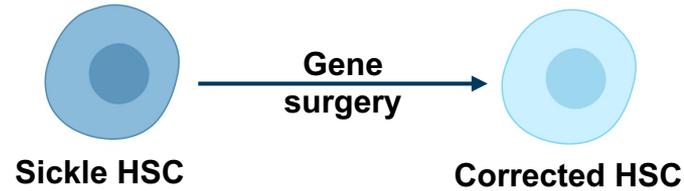
**.HEAL**



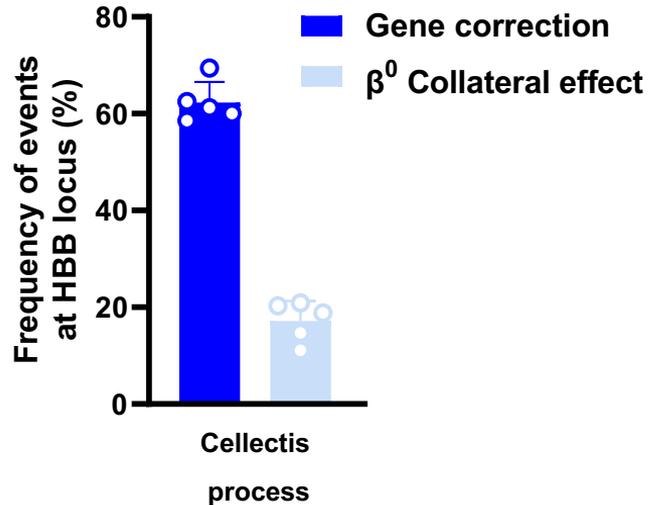
# A PRECISE GENETIC SURGERY OF HBB SICKLE MUTATION TO CURE SCD



# HIGHLY EFFICIENT HBB SURGERY AND MINIMAL COLLATERAL EFFECTS



## Potential advantage compared to competitors

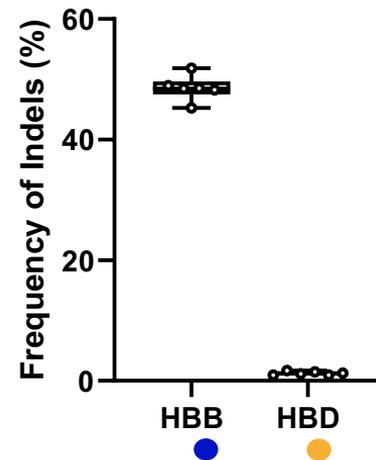


# HBB SURGERY PROCESS SHOWS MINIMAL OFF-SITE ACTIVITY

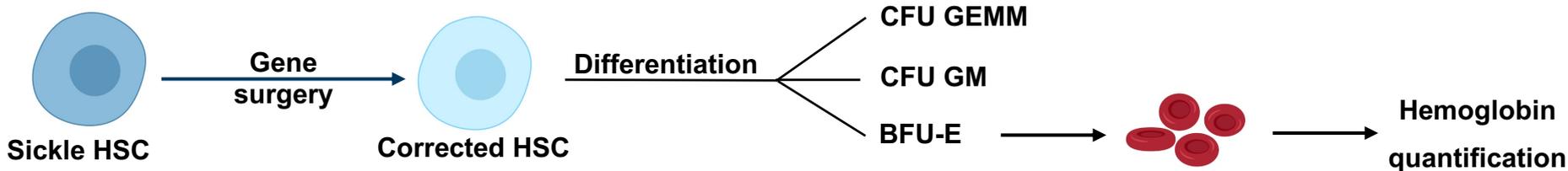
Exquisite specificity

One single off-site identified

Low off-site activity



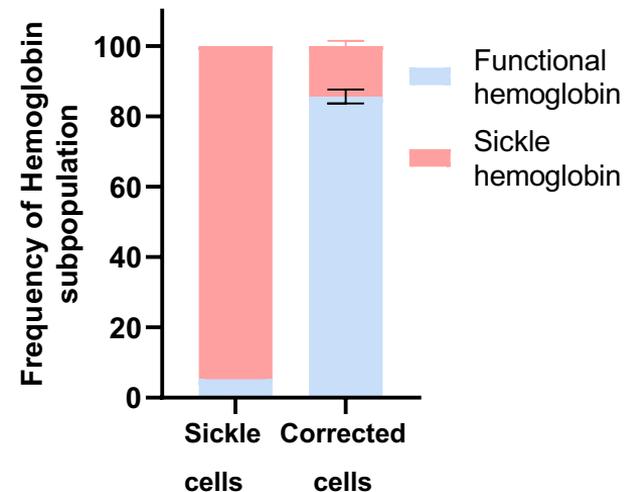
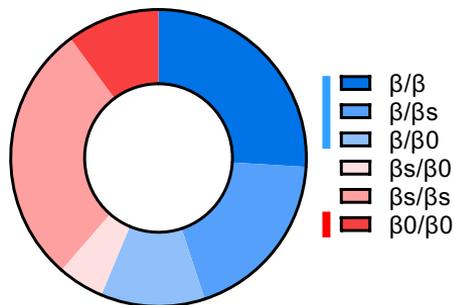
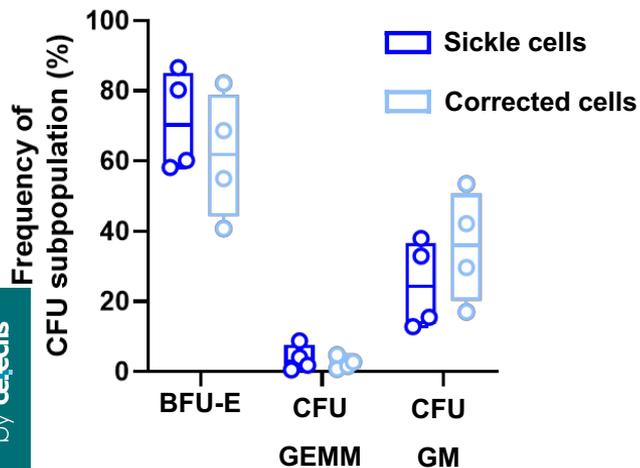
# HBB SURGERY EFFICIENTLY RESCUES HEMOGLOBIN IN RBC



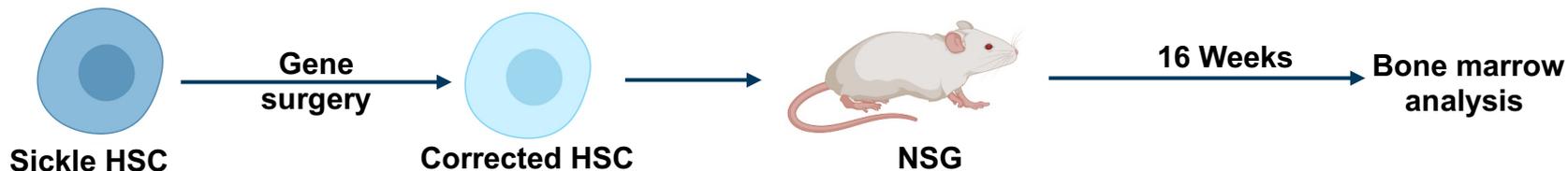
No effect on differentiation

Low collateral effect

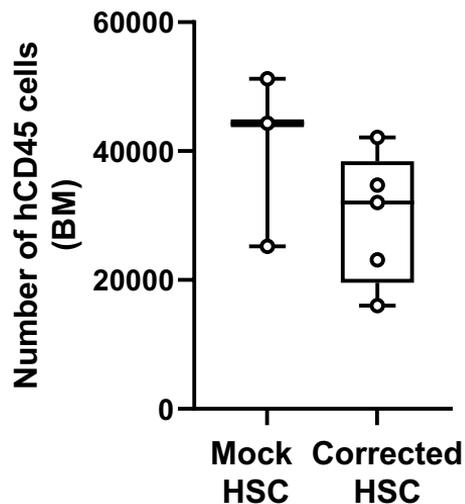
Hemoglobin rescue



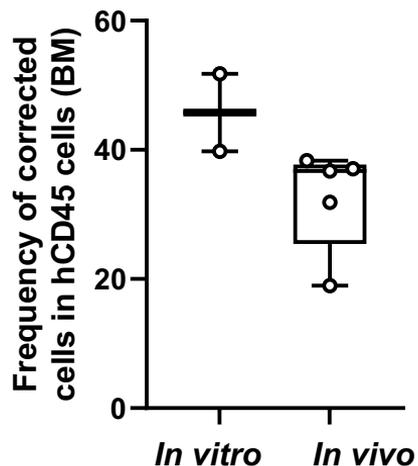
# HBB CORRECTED HSC EFFICIENTLY ENGRAFT *IN VIVO*



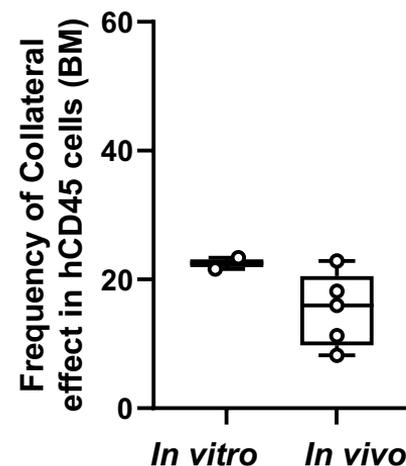
## Engraftment of corrected HSC in BM



## Stability of gene correction



## No competitive advantage of collateral effect



# .HEAL GENE SURGERY TO CURE SICKLE CELL DISEASE - TALGlobin01

.HEAL

**SCA HBB** surgery repairs hemoglobin and brings it back to its physiological level.

- Highly efficient correction of sickle HBB gene
- Hemoglobin rescued to therapeutic level
- Selection free process
- Low  $\beta^0$  collateral effect mitigates potential toxicity

**TALGlobin01 is ready to move forward to clinical development**

# DISCOVERY

**.HEAL**  
by ce:ctis

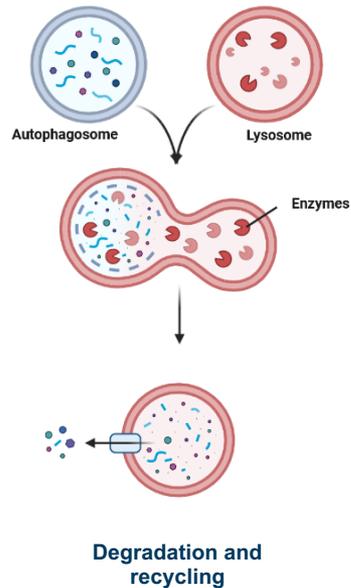
.HEAL GENE SURGERY TO CURE LYSOSOMAL STORAGE DISEASES



# LYSOSOMAL STORAGE DISEASES

## What are LSD?

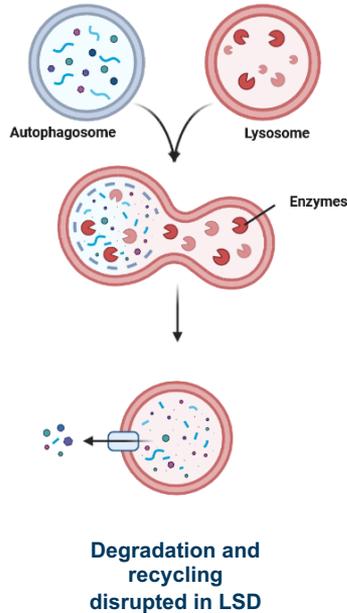
Over 70 diseases caused by genetic defects leading to **lysosomal dysfunction**



# LYSOSOMAL STORAGE DISEASES

## What are LSD?

Over 70 diseases caused by genetic defects leading to **lysosomal dysfunction**



## Clinical evolution

Accumulation of cellular waste leads to **multi-organ defects and systemic symptoms**

**Highly debilitating and life-threatening**

(life expectancy in severe cases is often < 12 months)

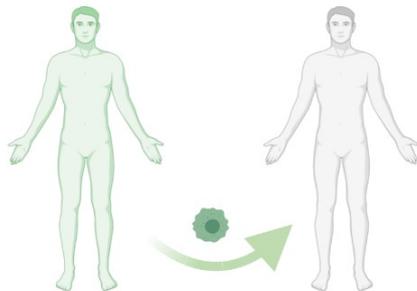


Combined frequency:  
**1 in 5000 newborns**



# URGENT NEED FOR EFFICIENT LSD TREATMENT AND CURE

## Current therapeutics for LSD



**Allogeneic  
stem cell  
transplantation**

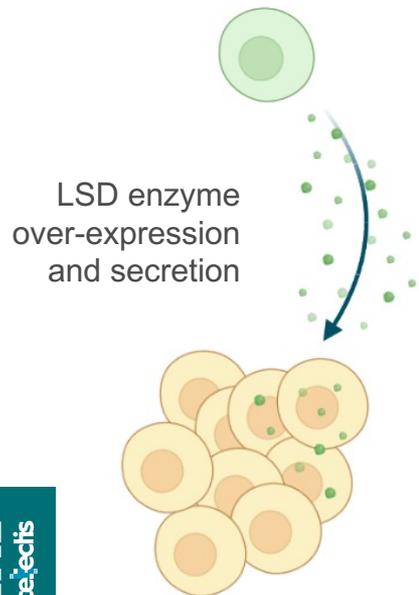


**Enzyme  
Replacement  
Therapy**

1. In most cases, treatment is only supportive.
2. Neurological symptoms remain untreated.
3. HSC genome surgery is a therapeutic strategy addressing unique LSD challenges.

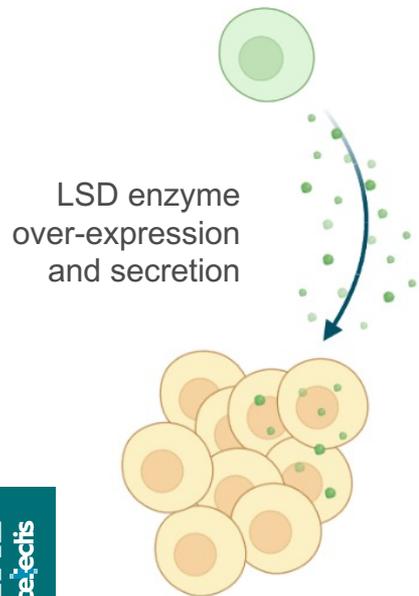
# HSC GENE THERAPY CAN SUITABLY TARGET LSD

Potent supra-endogenous  
LSD enzyme secretion

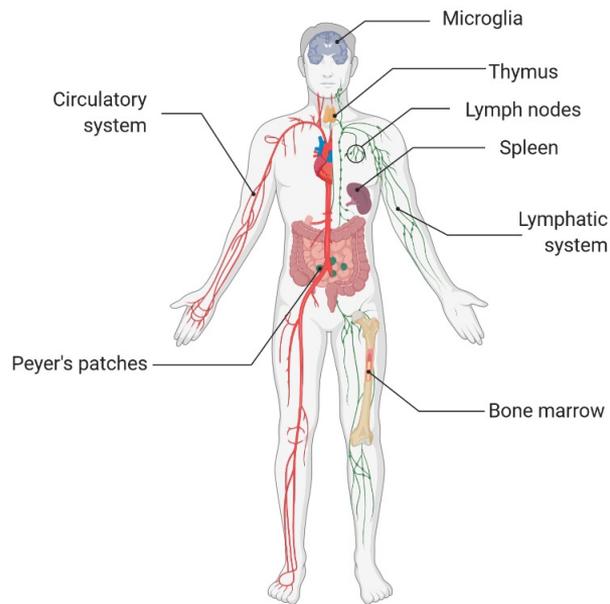


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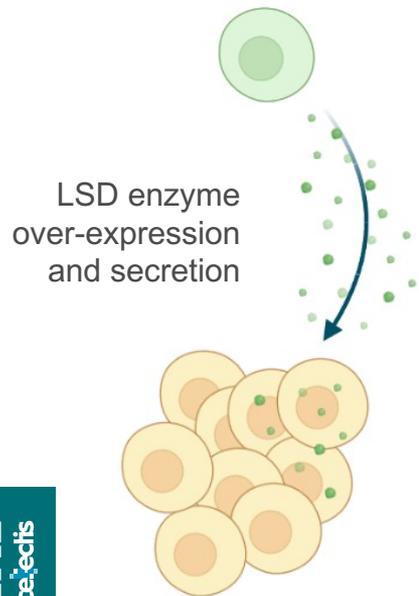


Systemic distribution

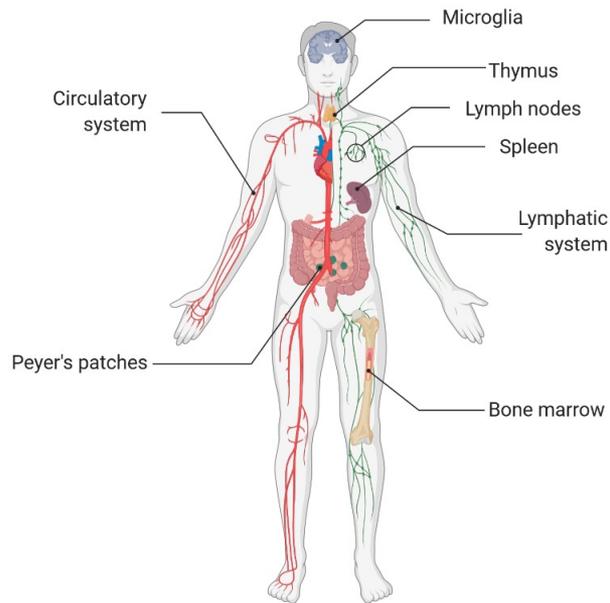


# HSC GENE THERAPY CAN SUITABLY TARGET LSD

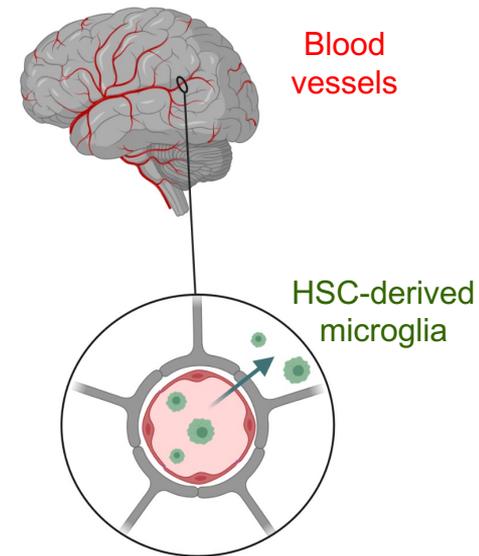
Potent supra-endogenous  
LSD enzyme secretion



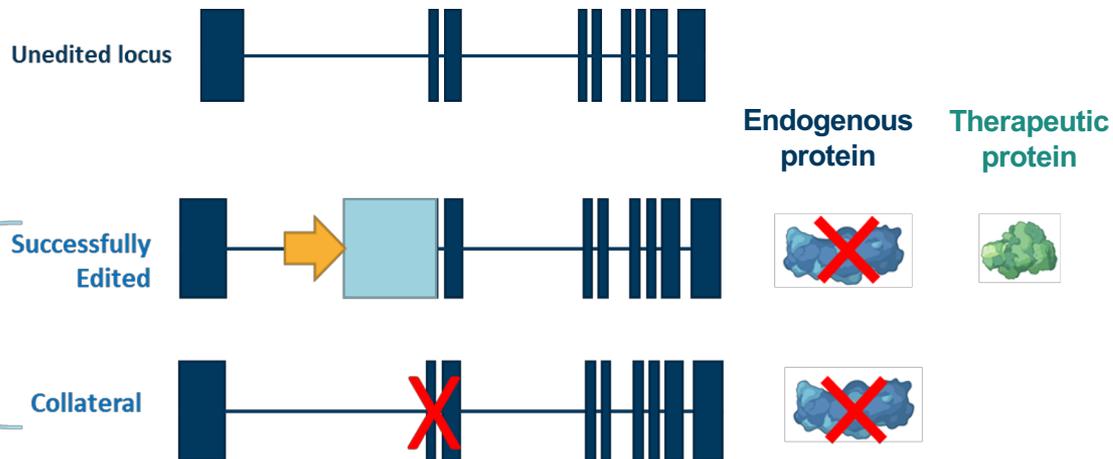
Systemic distribution



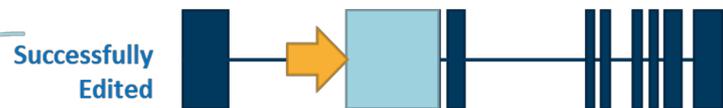
Myeloid cells  
can reach brain tissue



# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC



# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC



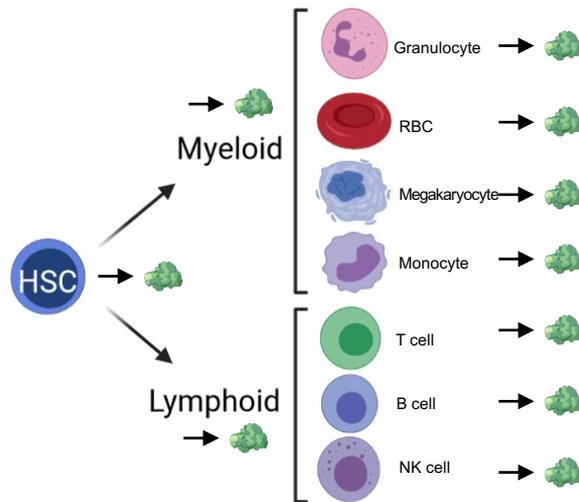
Endogenous protein



Therapeutic protein

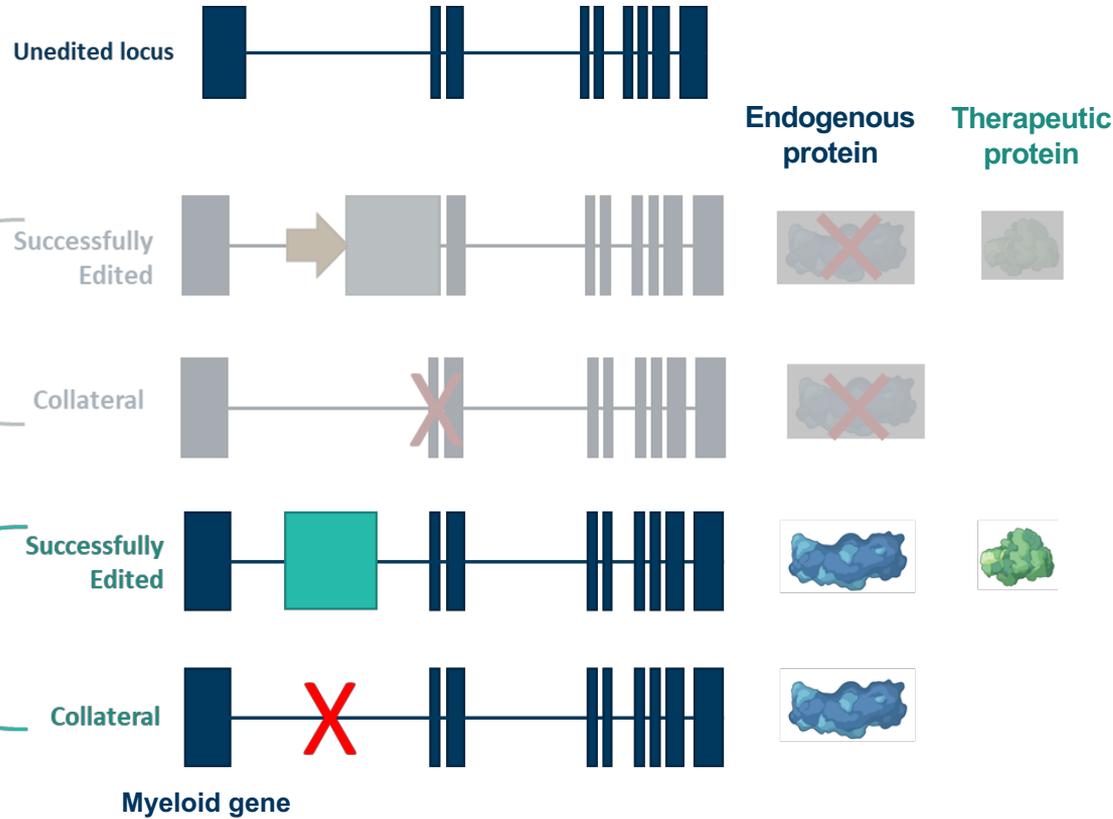


## Broad expression

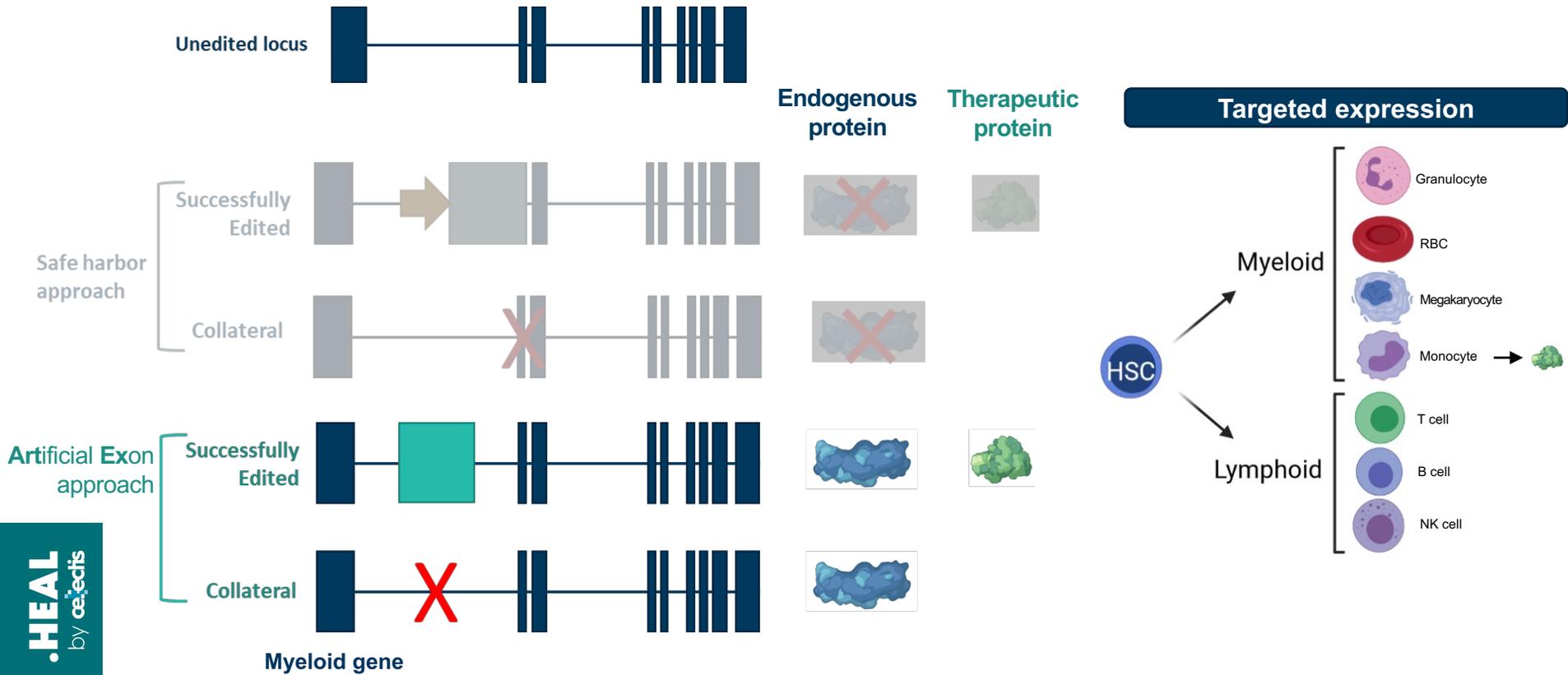


Safe harbor approach

# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC



# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC



# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC

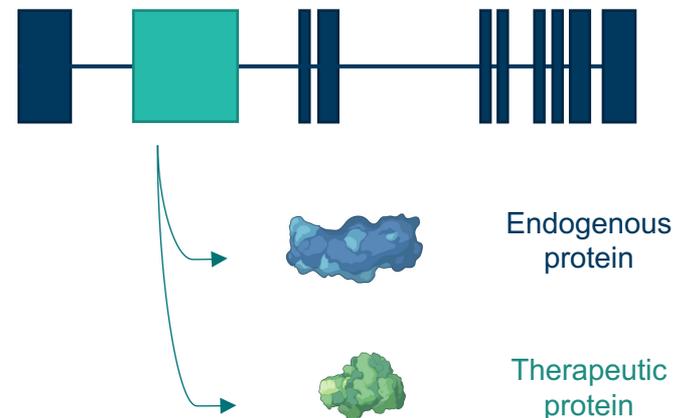
	ArtEx	Other gene therapy (lentiviral, safe harbor)
One-time treatment	Yes	Yes
Over-expression	Yes, depending on the targeted gene	Yes, depending on the promoter
Neurological benefit	Yes	Yes

Traditional LSD therapeutic options	
Allogenic transplantation	Enzyme Replacement Therapy
Yes + ERT if needed	No
No	N/A
Very limited	No

# HSC GENE THERAPY BY ARTEX: SAFE AND SPECIFIC

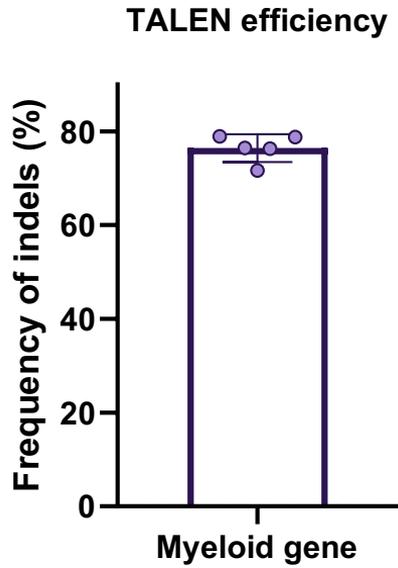
	ArtEx	Other gene therapy (lentiviral, safe harbor)
One-time treatment	Yes	Yes
Over-expression	Yes, depending on the targeted gene	Yes, depending on the promoter
Neurological benefit	Yes	Yes

Lack of collateral disruption risk	Yes	No
Lack of exogenous promoter	Yes	No
Cell type dependent expression	Yes	Challenging
Lack of overexpression in primitive HSC	Yes	No



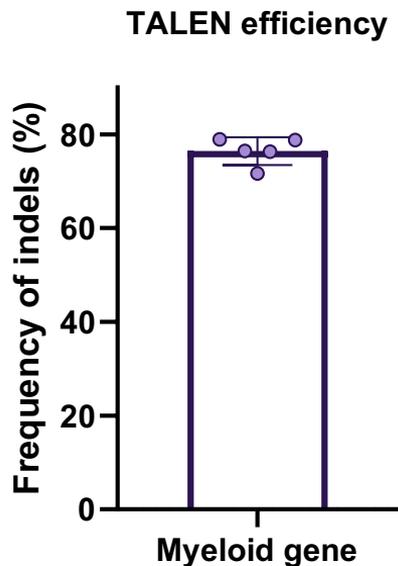
# POTENT AND SAFE TALEN®

## Efficient TALEN®

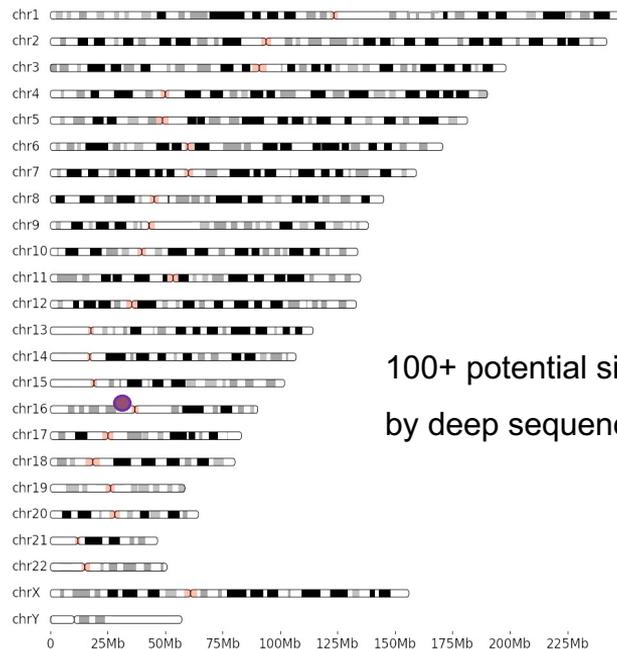


# POTENT AND SAFE TALEN®

## Efficient TALEN®



## With exquisite target specificity



100+ potential sites screened  
by deep sequencing

# ARTEX: SAFE AND LINEAGE SPECIFIC



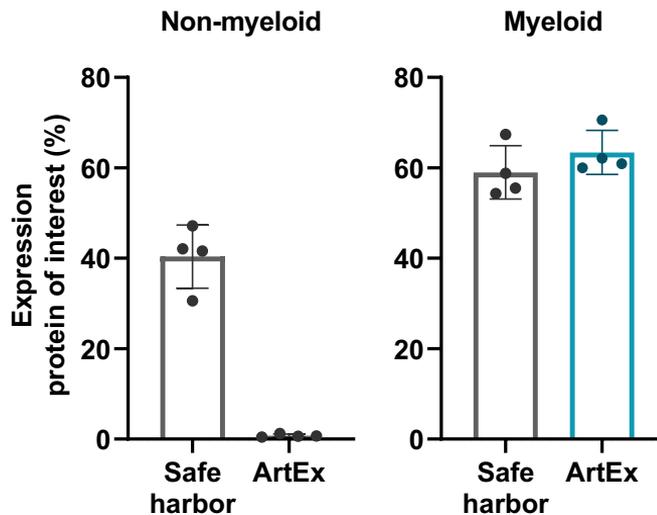
Endogenous protein



Protein of interest



Selective expression in the myeloid lineage

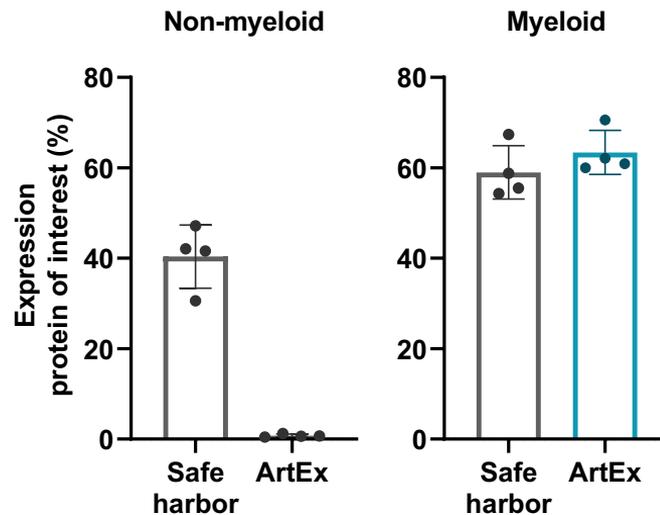
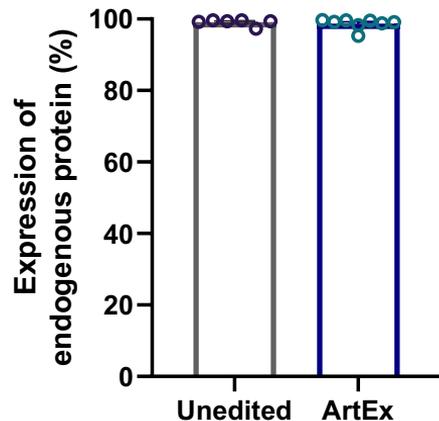


# ARTEX: SAFE AND LINEAGE SPECIFIC



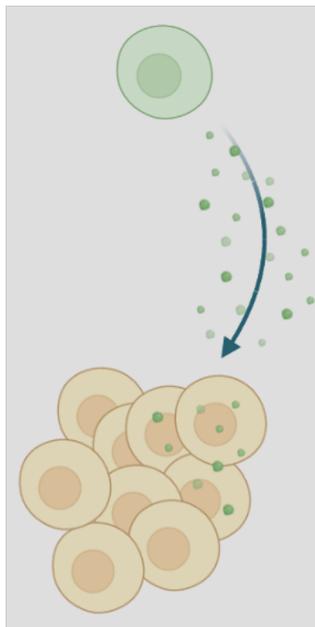
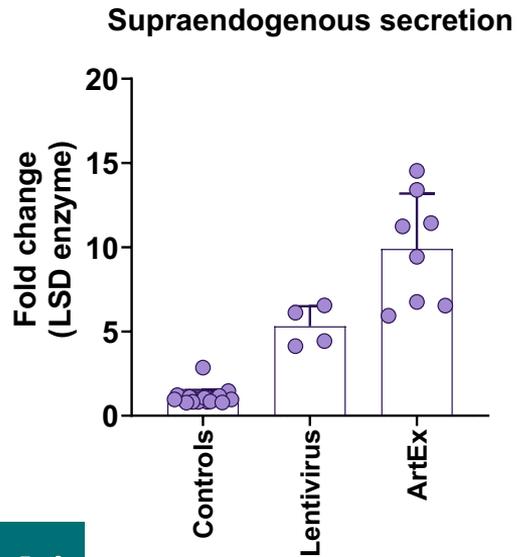
Endogenous protein expression maintained

Selective expression in the myeloid lineage



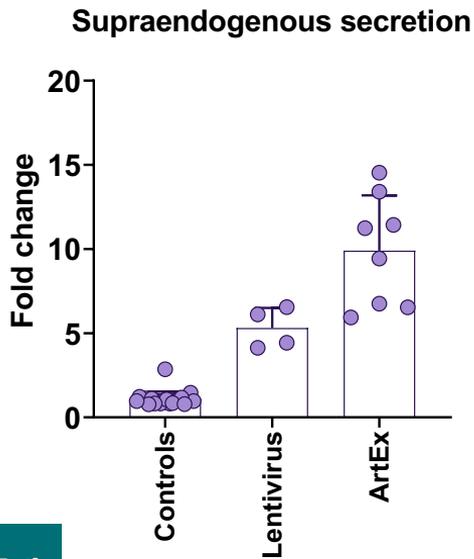
# ARTEX EDITED HSC ENGRAFT AND ITS PROGENY SECRETE THERAPEUTIC PROTEIN

## Therapeutic protein

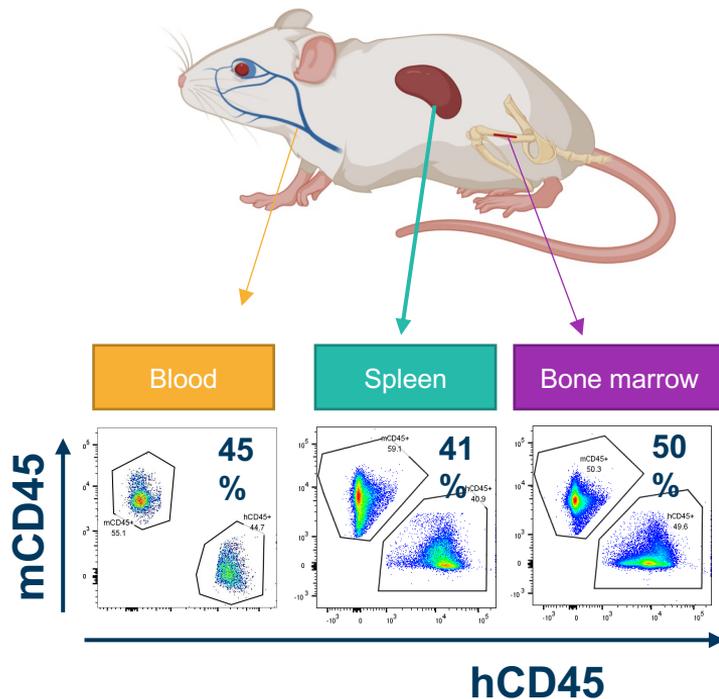


# ARTEX EDITED HSC ENGRAFT AND ITS PROGENY SECRETE THERAPEUTIC PROTEIN

## Therapeutic protein

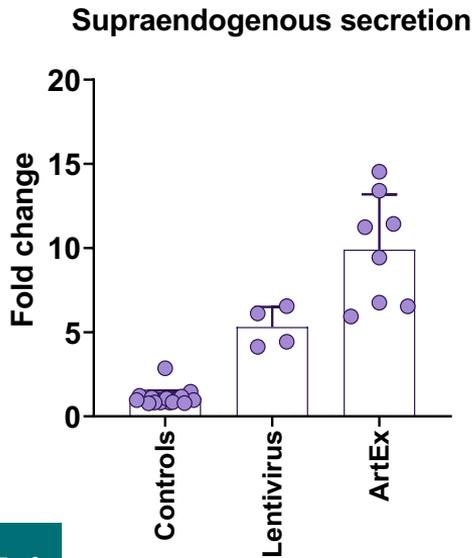


## Systemic distribution

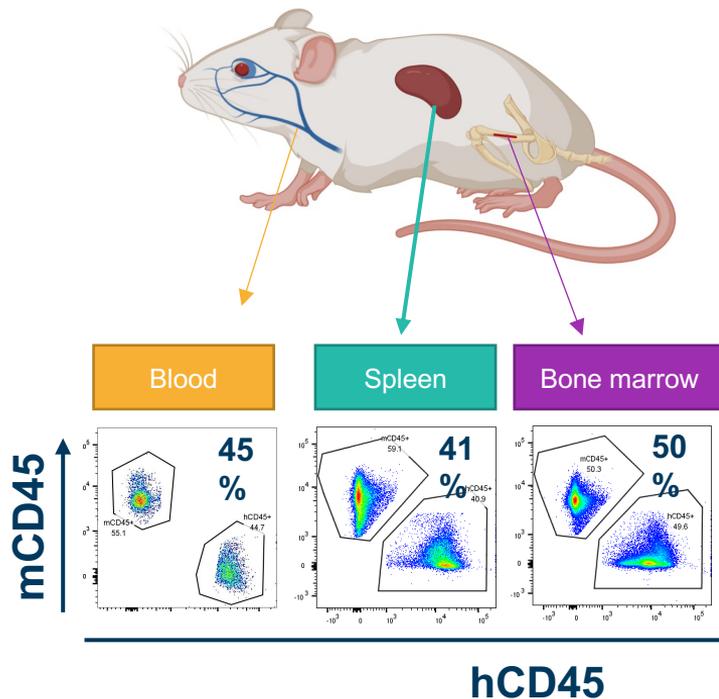


# ARTEX EDITED HSC ENGRAFT AND ITS PROGENY SECRETE THERAPEUTIC PROTEIN

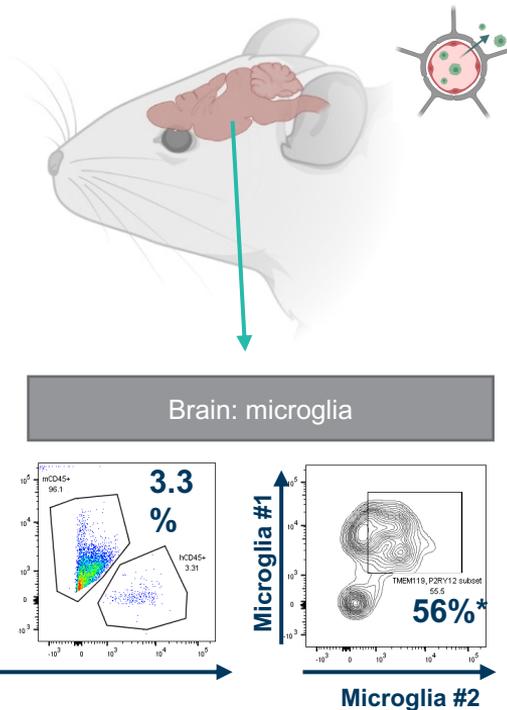
## Therapeutic protein



## Systemic distribution



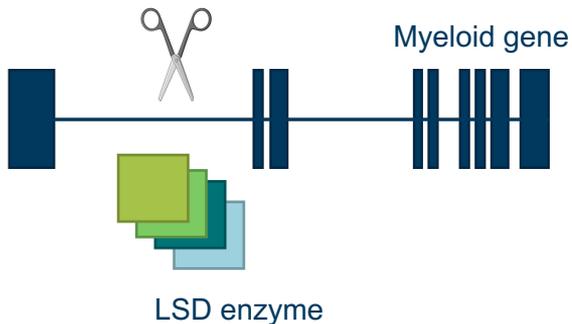
## Neurological presence



\*: within hCD45+/CD11b+

# HSC GENE THERAPY POTENTIAL FOR LSD

One shared TALEN<sup>®</sup> ...



	Enzyme	Disease	Estimated patients in US per year*
	$\alpha$ -galactosidase	Fabry disease	380-1900
	$\beta$ Glucocerebrosidase	Gaucher disease	38-342
	Lysosomal $\alpha$ -glucosidase	Pompe disease	38-342
	Arylsulfatase A	Metachromatic leukodystrophy	4-34
	$\alpha$ -L-Iduronidase	MPS-I	4-34
	Iduronate 2-sulfatase	MPS-II	4-34

...for Multiple Diseases

# DISCOVERY

## HSC GENOME SURGERY FOR LSD DISEASES

.HEAL



### HSC genome surgery for LSD

Potential single treatment cure

Proven systemic distribution, including neurological

Myeloid lineage specific expression

### Single TALEN<sup>®</sup> to treat multiple LSD

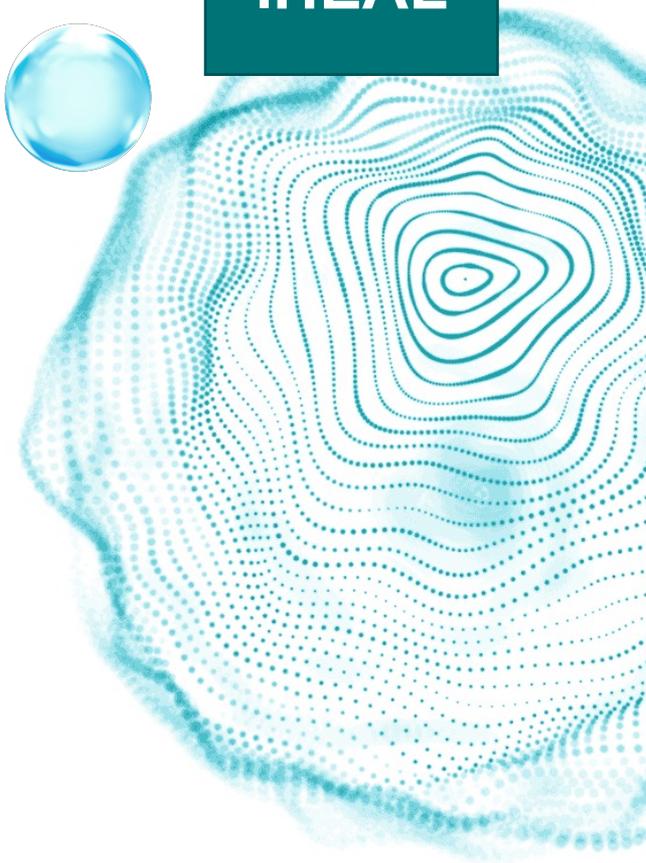
Easily adaptable platform: plug and play

Cost-effective development

Faster clinical track

# .HEAL PIPELINE HSC GENOME SURGERY FOR MULTIPLE GENETIC DISEASES

.HEAL



# .HEAL PIPELINE

## HSC GENOME SURGERY FOR MULTIPLE GENETIC DISEASES

.HEAL



Indications	Cell type	Candidate	Target	Discovery	Preclinical	IND-enabling
Sickle Cell Anemia	CD34+	TalGlobin-01	HBB	[Progress bar]		
Primary Immunodeficiency	CD34+	TalX-02	Undisclosed	[Progress bar]		
Lysosomal Storage Disease	CD34+	TalX-03	Undisclosed	[Progress bar]		
Primary Immunodeficiency	T-cell	TalX-04	undisclosed	[Progress bar]		
Primary Immunodeficiency	T-cell	TalX-05	undisclosed	[Progress bar]		

# GENOME EDITING TO TREAT IMMUNODEFICIENCIES

**.HEAL**  
by ce:ctis

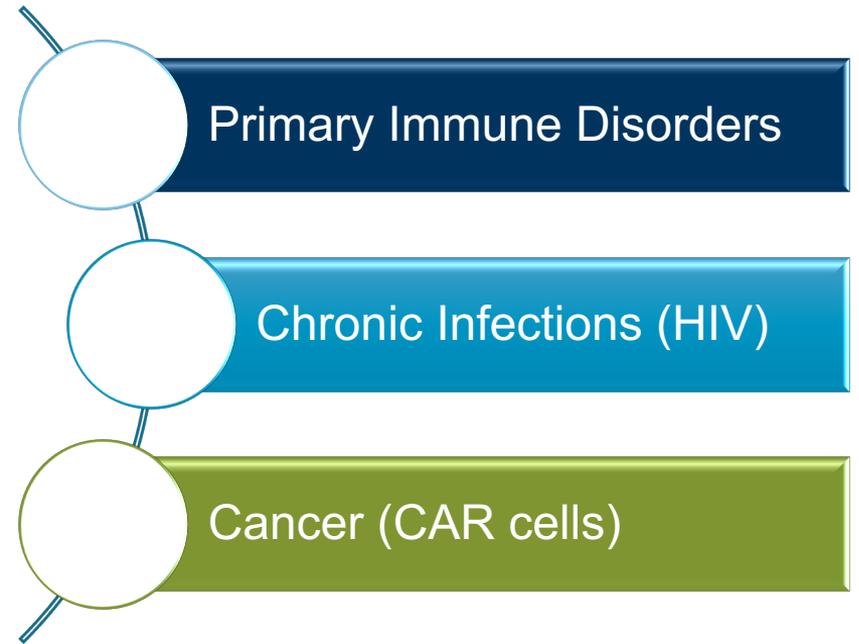


**TONI CATHOMEN**

**INSTITUTE FOR TRANSFUSION MEDICINE & GENE THERAPY  
MEDICAL CENTER – UNIVERSITY OF FREIBURG  
GERMANY**

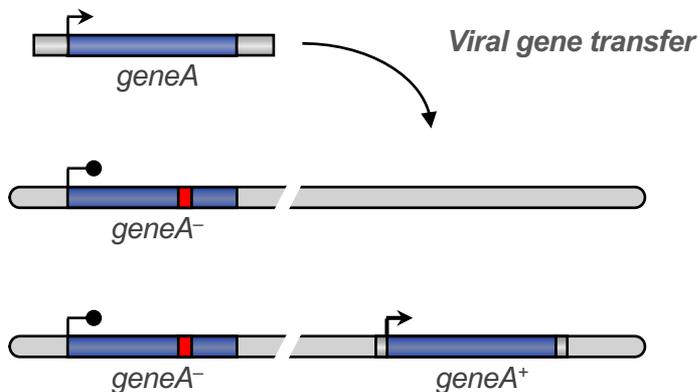
# R&D INTERESTS

## DEVELOPMENT OF INNOVATIVE CELL AND GENE THERAPIES



# CLINICAL SUCCESS OF GENE THERAPY

## CONVENTIONAL GENE TRANSFER

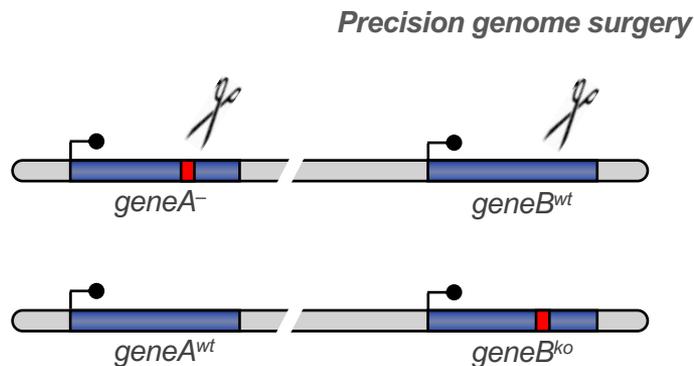
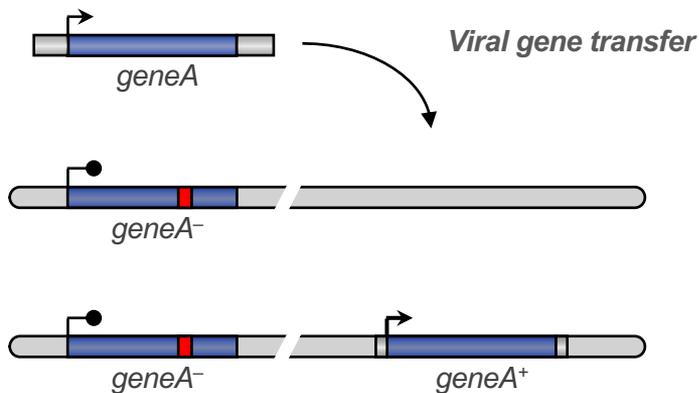


- ☺ Efficient gene transfer
- ☺ No SAE (SIN-γRV / LentiV / AAV)

	proven clinical benefit	marketing authorization EU
ex vivo	<b>HSC-based gene therapy</b> ADA-SCID β-thalassemia, SCD MLD	← Stimvelis® ← Zynteglo® ← Libmeldy®
	<b>T-cell immunotherapy (CAR)</b> B-ALL, CLL, DLBCL, NHL	← Kymriah® ← Yescarta® ← Tecartus®
in vivo	<b>Tumor (oncolytic)</b> Melanoma	← Imlygic®
	<b>Retina</b> Retinal dystrophy	← Luxturna®
	<b>Muscle</b> Spinal muscular atrophy	← Zolgensma®

# CLINICAL SUCCESS OF GENE THERAPY

## CONVENTIONAL GENE TRANSFER VS. GENOME EDITING



- ☺ Efficient gene transfer
- ☺ No SAE (SIN-γRV / LentiV / AAV)
- ☹ Gain-of-function mutations (e.g. *STAT3*)
- ☹ Levels of gene expression (e.g. *STAT3*)
- ☹ Spatio-temporal regulation of expression (e.g. *RAG1*)

- ☺ Correct disease causing mutations
- ☺ Disrupt disease-associated genes
- ☹ Biological consequences of off-target effects not well understood

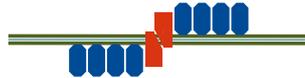
# INTERVENTIONAL GENOME EDITING STUDIES

## → OPPORTUNITIES

● DNA recognition

● DNA cleavage

Zinc-finger  
nucleases

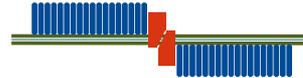


15 clinical studies (8):

- ✓ HIV
- ✓ Thalassemia
- ✓ Sickle cell dis.
- ✓ Hemophilia B
- ✓ MPS I / II
- ✓ HPV

*in clinical use*

TALE nucleases  
(TALEN)



6 clinical studies (4):

- ✓ CAR T cells
- ✓ HPV

*since 2016*

CRISPR-Cas  
nucleases

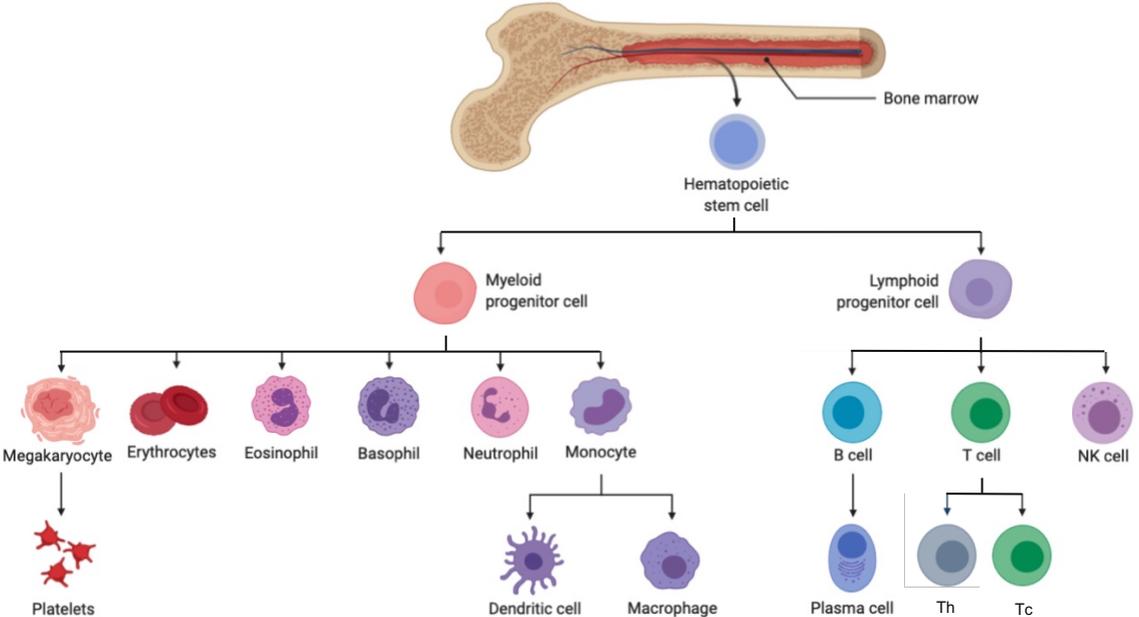


35 clinical studies (24):

- ✓ CAR/TCR-T cells
- ✓ HIV
- ✓ Thalassemia
- ✓ Sickle cell dis.
- ✓ Leber Congen. Amaurosis 10
- ✓ ...

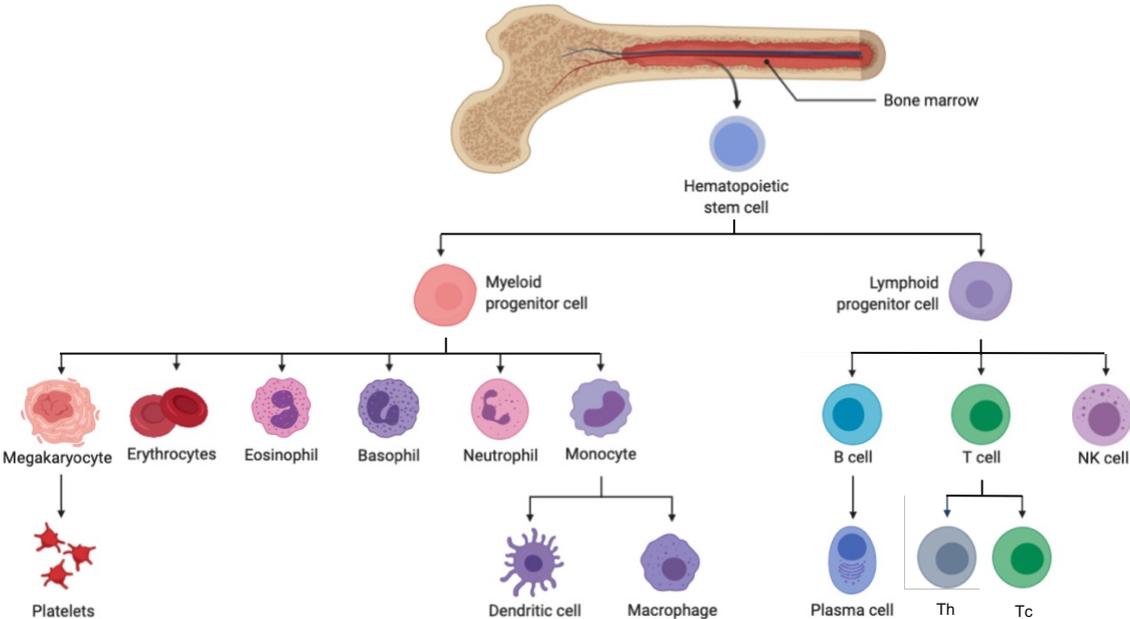
*since 2016*

# OUR BLOOD & IMMUNE SYSTEM



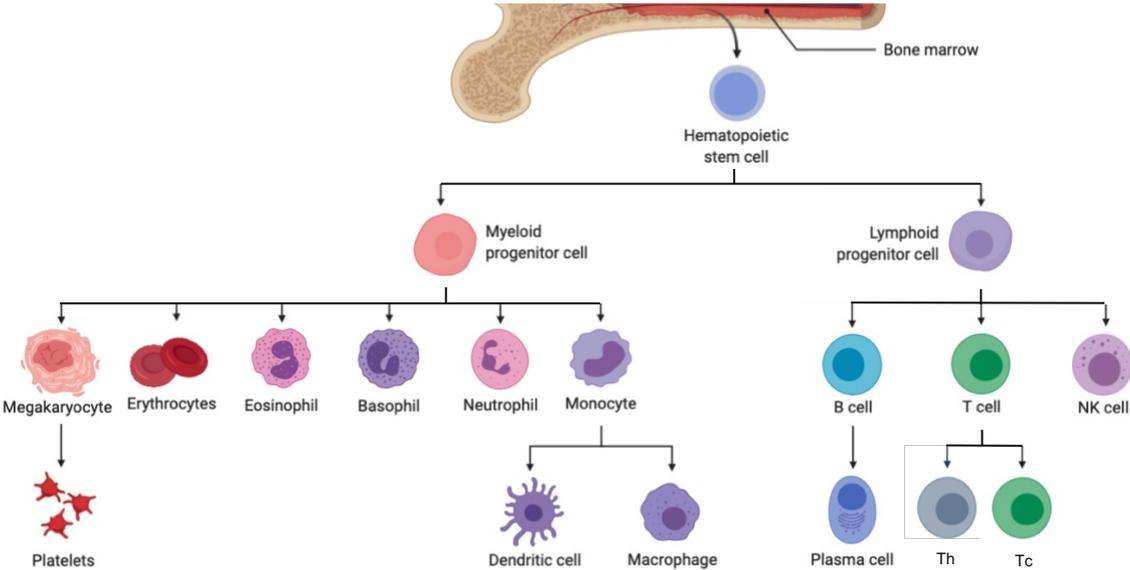
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM



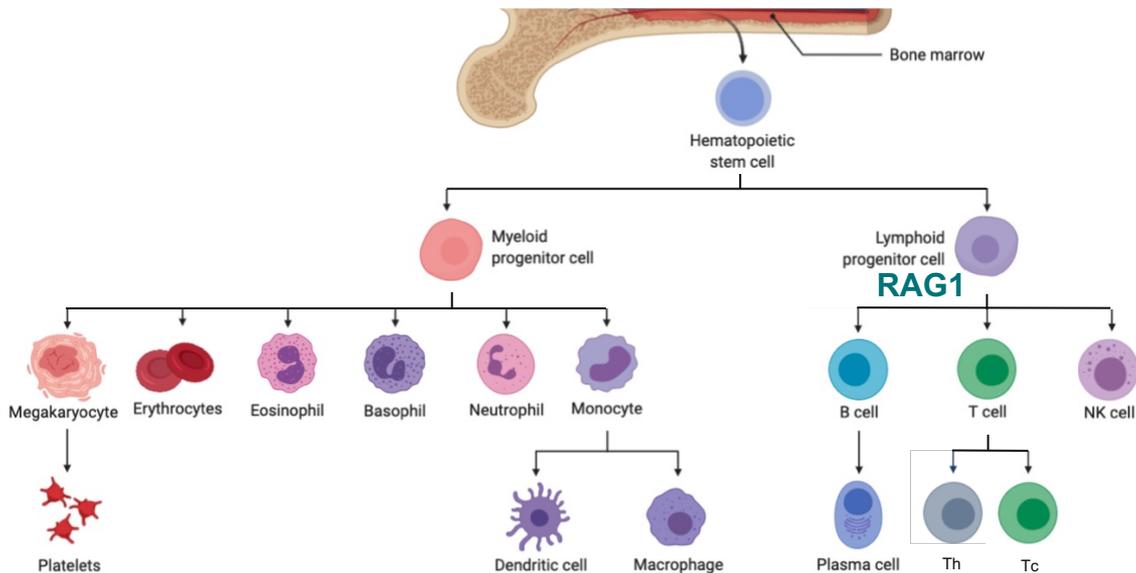
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM



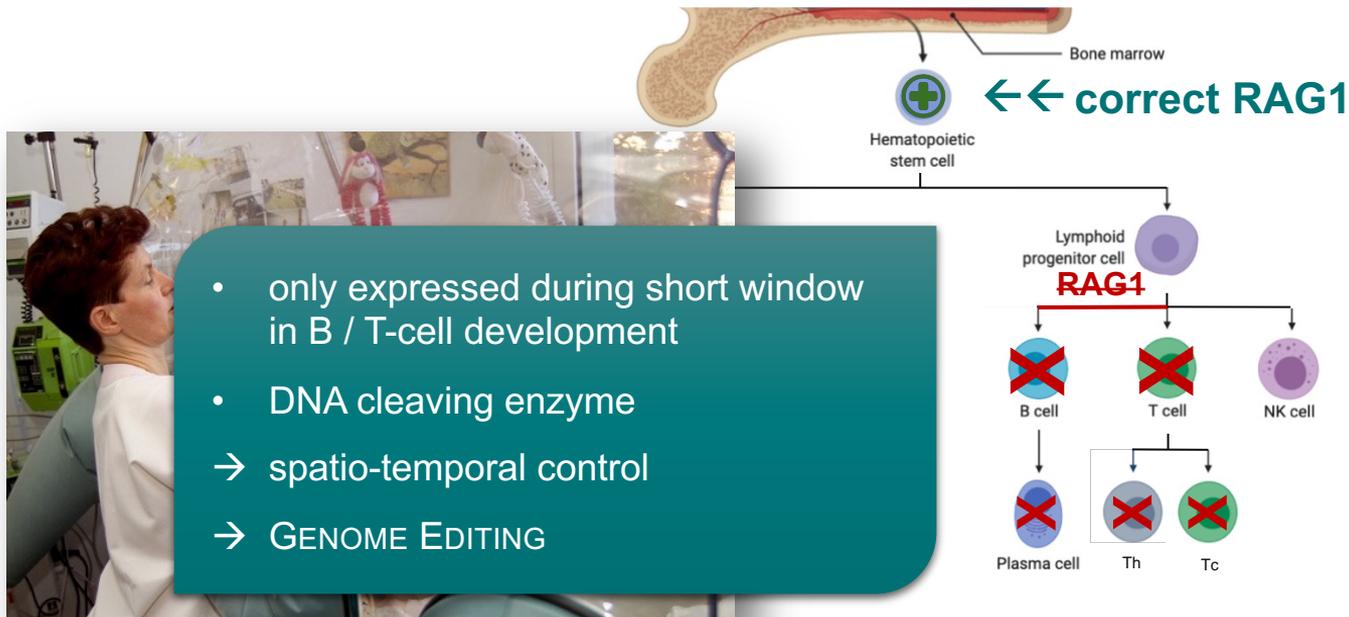
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT OF RAG1-SCID



# OUR BLOOD & IMMUNE SYSTEM

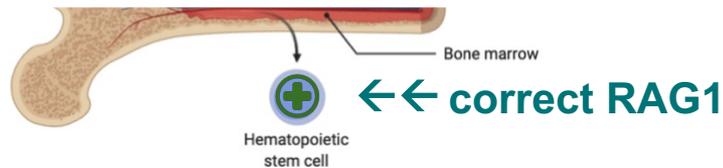
## EDITING THE IMMUNE SYSTEM – TREATMENT OF RAG1-SCID



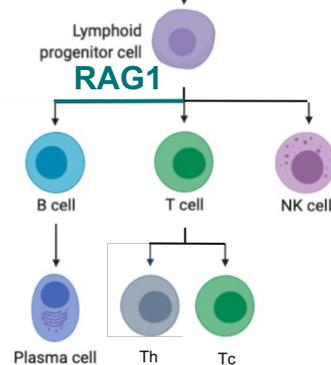
- only expressed during short window in B / T-cell development
- DNA cleaving enzyme
- spatio-temporal control
- GENOME EDITING

# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT OF RAG1-SCID



- only expressed during short window in B / T-cell development
- DNA cleaving enzyme
- spatio-temporal control
- GENOME EDITING



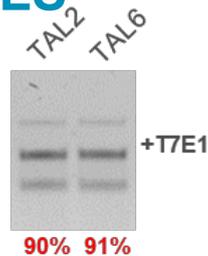
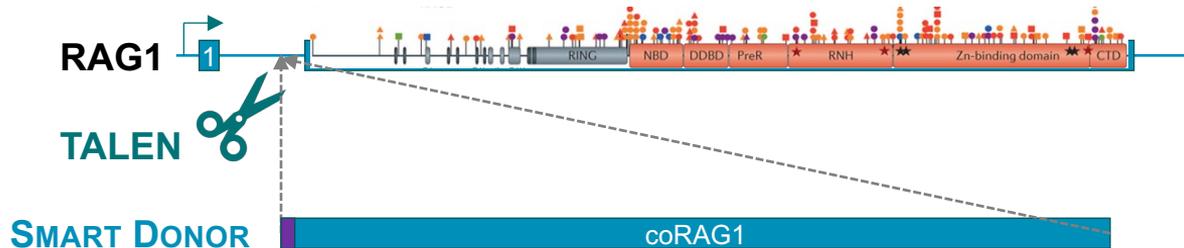
→ restore immune system

# RAG1 MUTATIONS IN RAG-SCID PATIENTS POSITION OF THE MUTATIONS

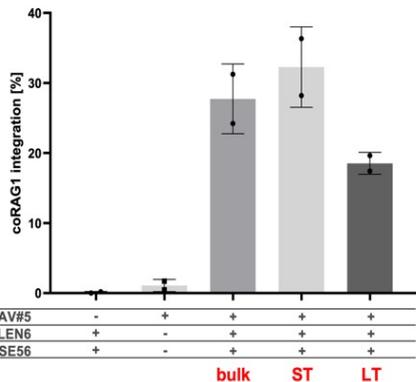


# RAG1 MUTATIONS IN RAG-SCID PATIENTS

## PROOF-OF-CONCEPT: *EX VIVO* IN CD34+ STEM CELLS

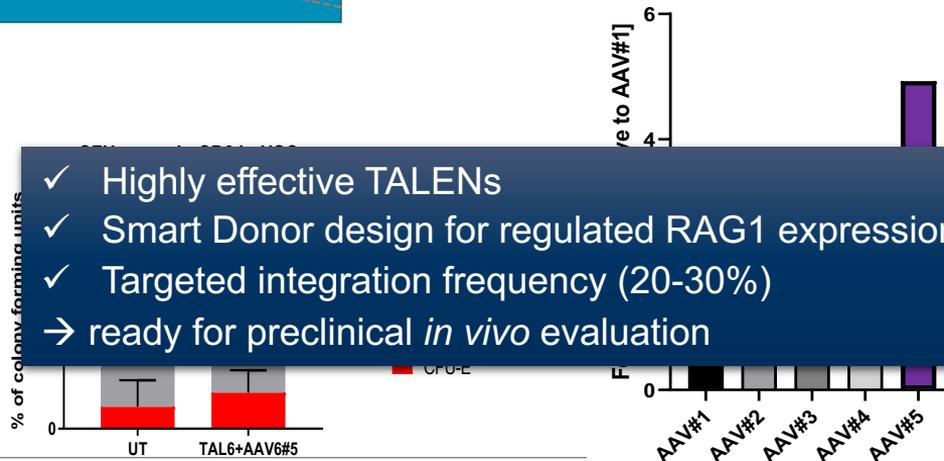


coRAG1 expression



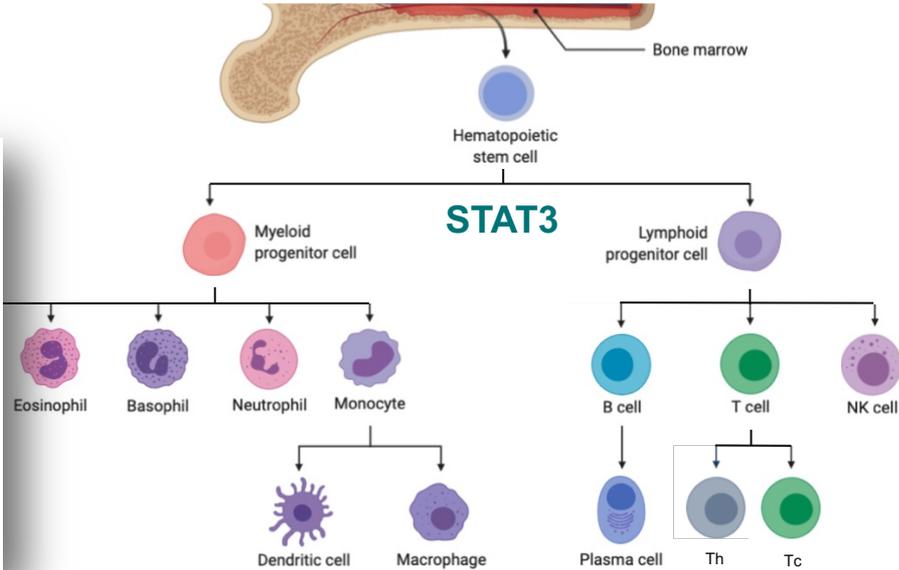
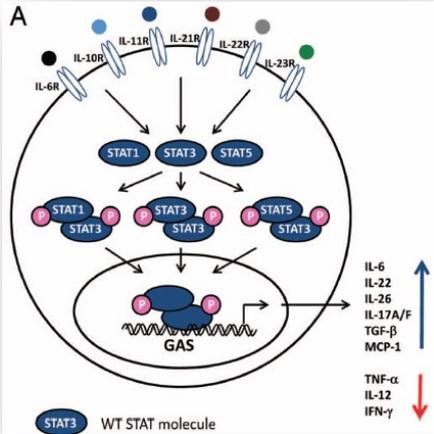
AAV#5	-	+	+	+	+
TAL6	+	-	+	+	+
GSE56	+	-	+	+	+

- ✓ Highly effective TALENs
- ✓ Smart Donor design for regulated RAG1 expression
- ✓ Targeted integration frequency (20-30%)
- ready for preclinical *in vivo* evaluation



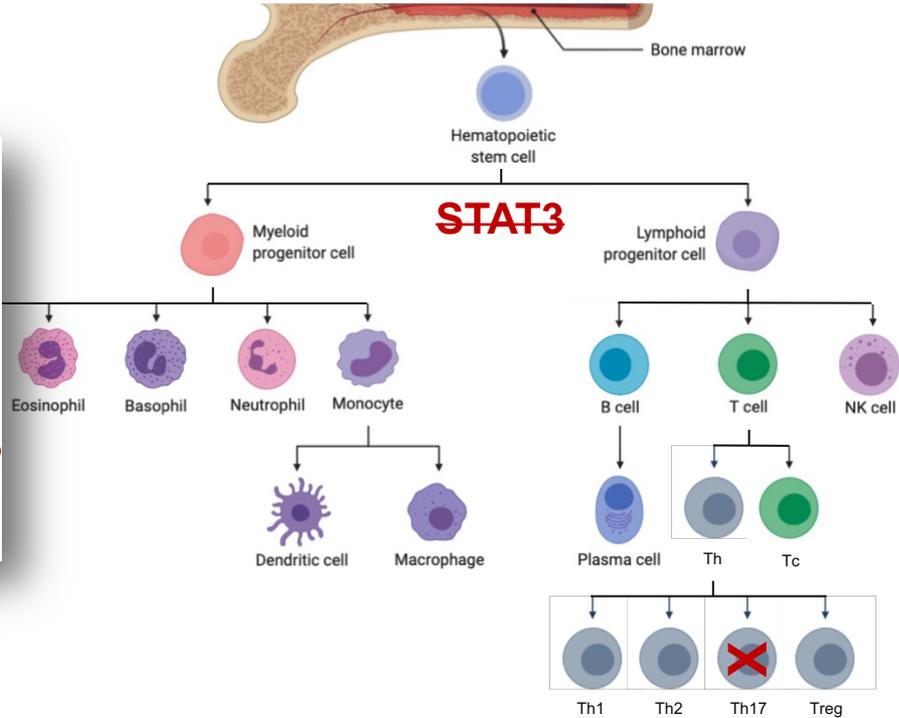
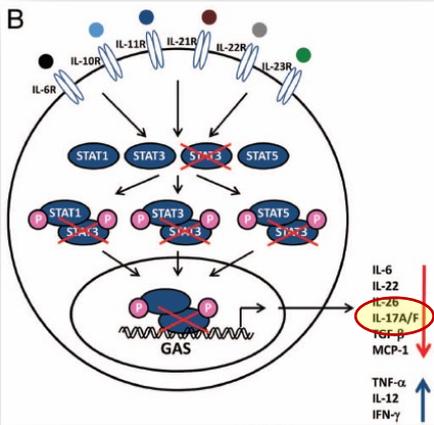
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT OF HYPER IGE SYNDROME



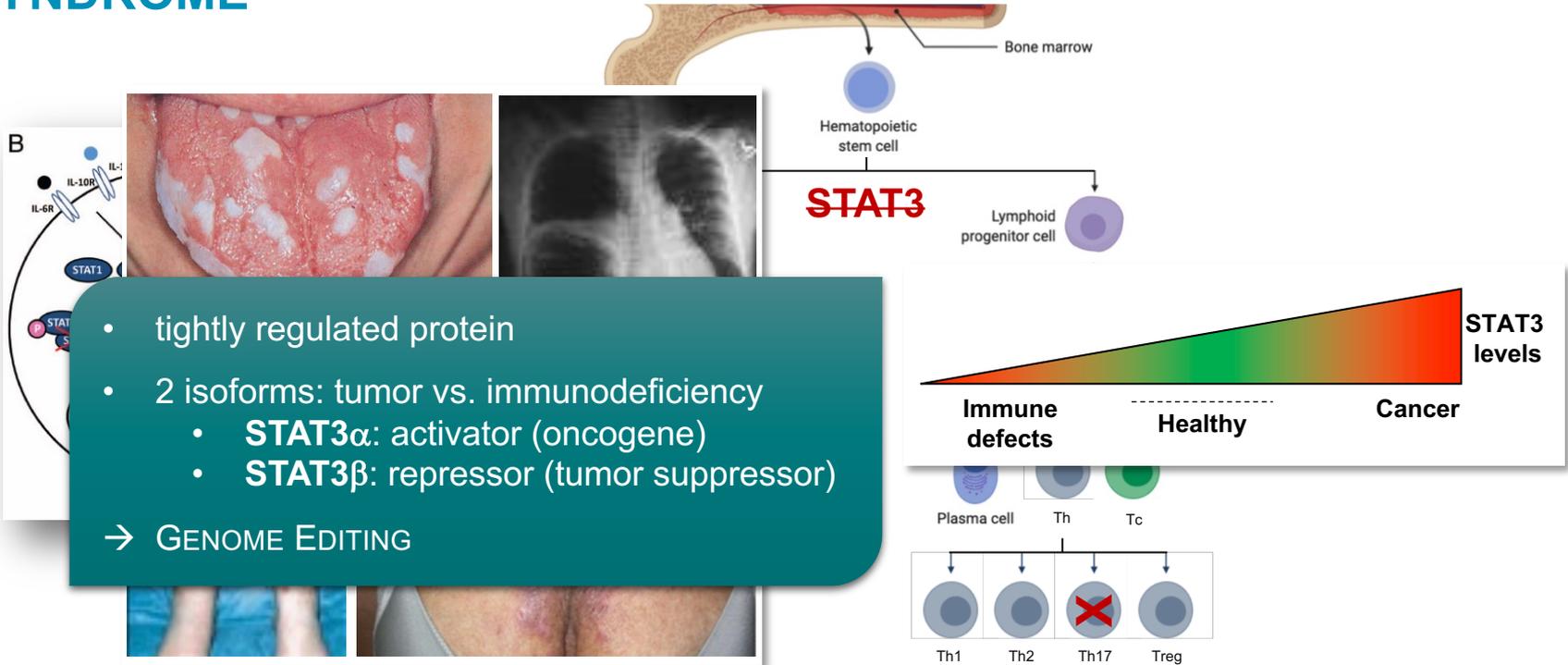
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT OF HYPER IGE SYNDROME



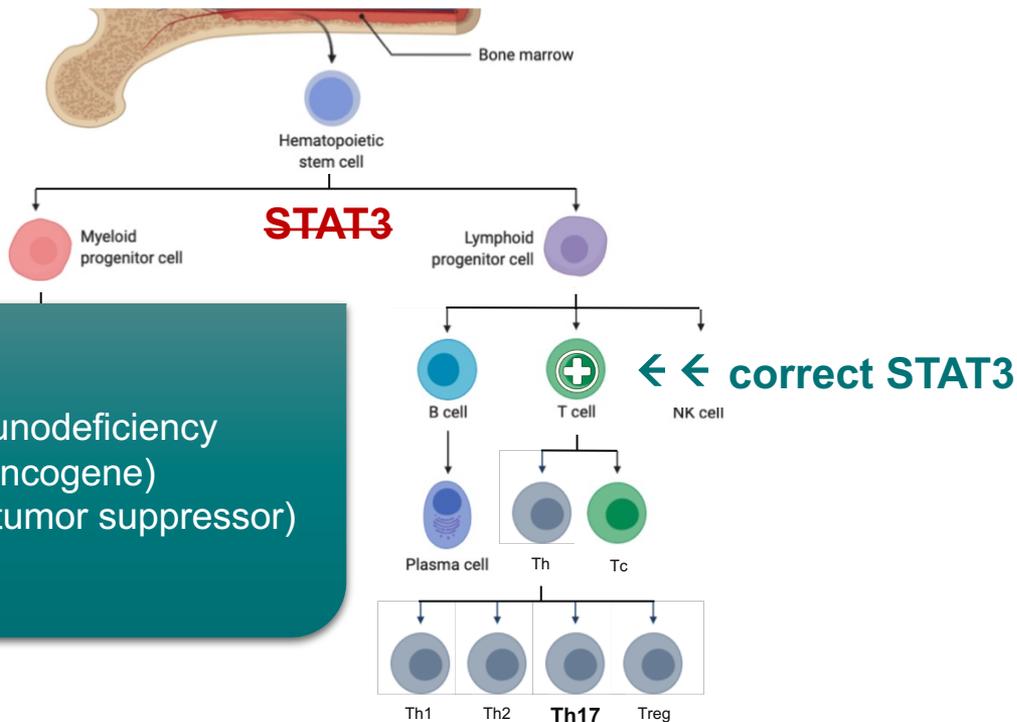
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT OF HYPER IGE SYNDROME



# OUR BLOOD & IMMUNE SYSTEM

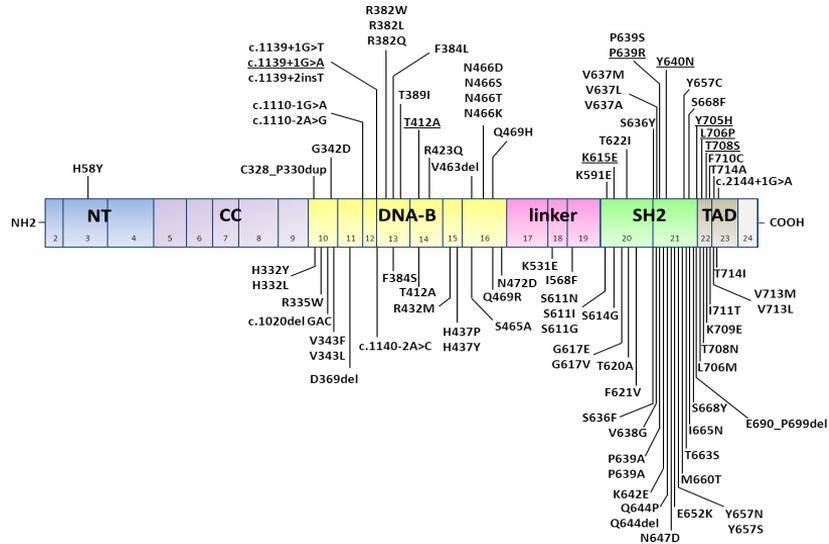
## EDITING THE IMMUNE SYSTEM – TREATMENT OF HYPER IGE SYNDROME



- tightly regulated protein
  - 2 isoforms: tumor vs. immunodeficiency
    - **STAT3 $\alpha$** : activator (oncogene)
    - **STAT3 $\beta$** : repressor (tumor suppressor)
- GENOME EDITING

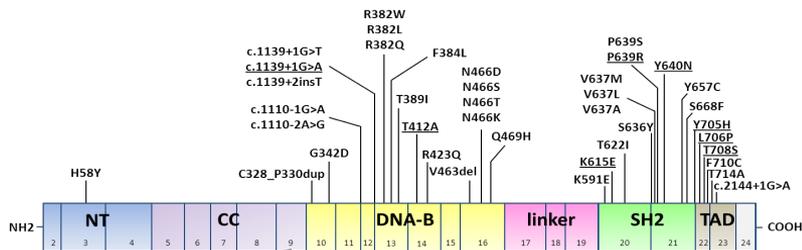
# STAT3 MUTATIONS IN HIES PATIENTS

## POSITION OF THE MUTATIONS



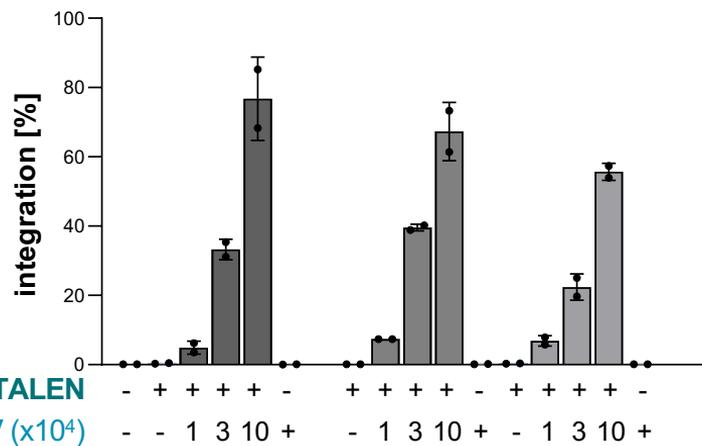
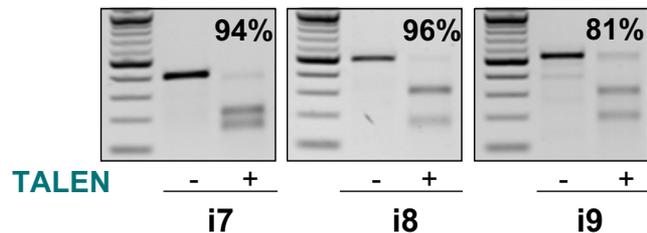
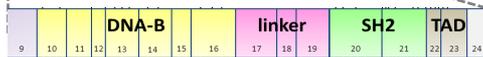
# STAT3 MUTATIONS IN HIES PATIENTS

## PROOF-OF-CONCEPT: *EX VIVO* IN NORMAL T-CELLS



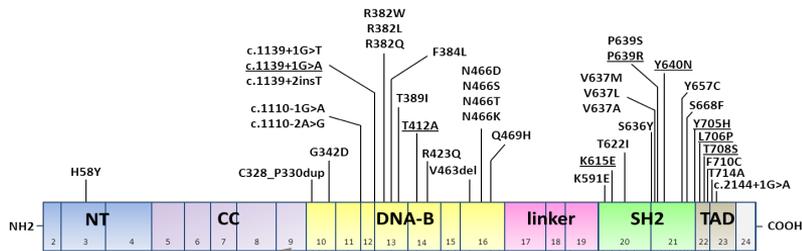
**TALEN** 

**SMART AAV DONOR**



# STAT3 MUTATIONS IN HIES PATIENTS

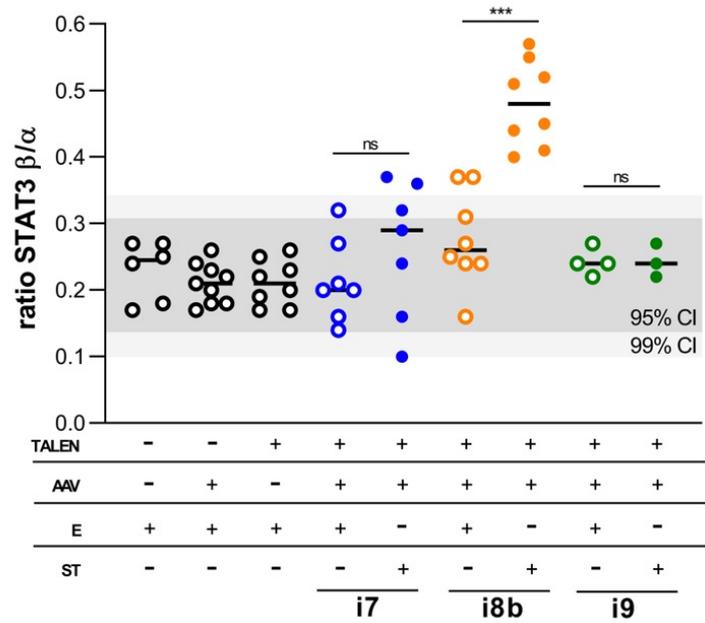
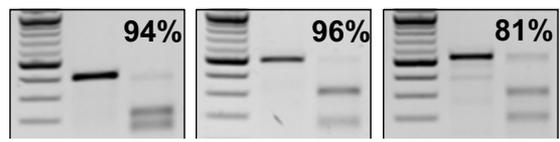
## PROOF-OF-CONCEPT: *EX VIVO* IN NORMAL T-CELLS



**TALEN**   
**SMART AAV DONOR**

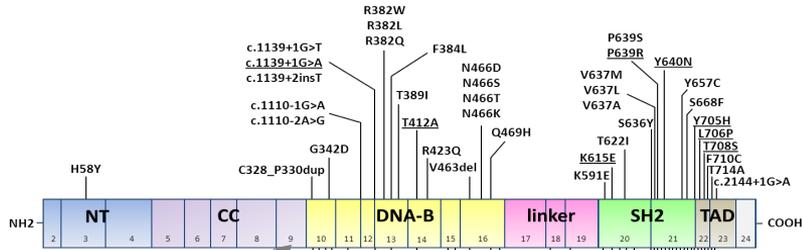
**STAT3 $\alpha$**   
**STAT3 $\beta$**

- ✓ Highly effective TALENs
- ✓ Targeted integration frequency (40-70%)
- ✓ Correct ratio of STAT3 $\alpha$  : STAT3 $\beta$  for i7 and i9



# STAT3 MUTATIONS IN HIES PATIENTS

## PROOF-OF-CONCEPT: *EX VIVO* IN PATENT-DERIVED T-CELLS

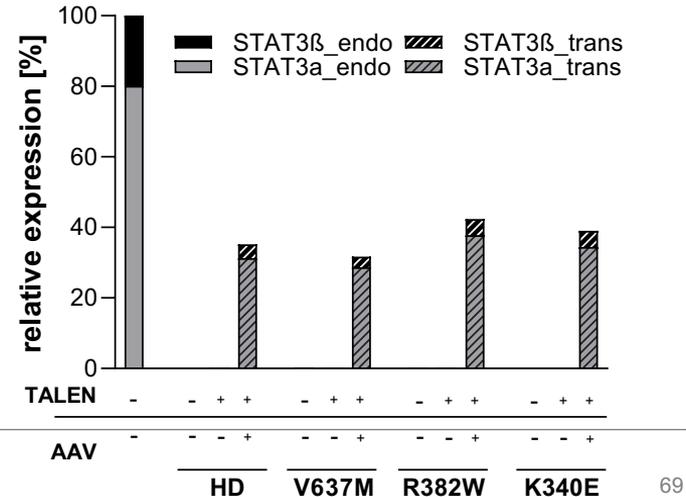
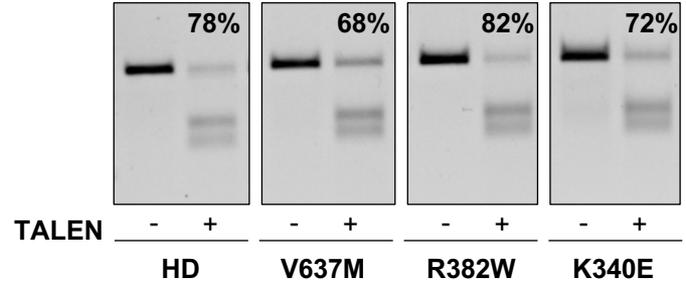


TALEN  
SMART AAV DONOR



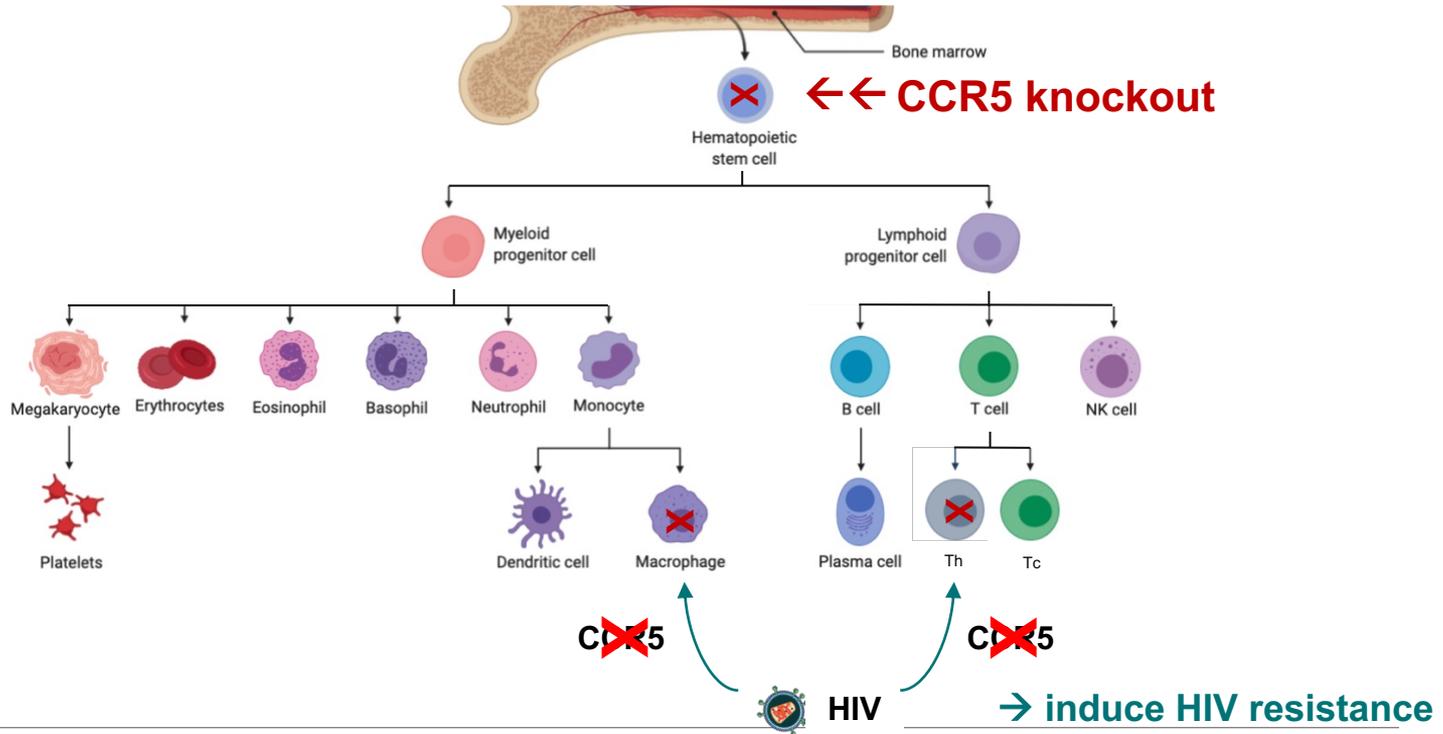
STAT3 $\alpha$   
STAT3 $\beta$

- ✓ Highly effective TALENs
- ✓ Targeted integration frequency (40-60%)
- ✓ Correct ratio of STAT3 $\alpha$  : STAT3 $\beta$   
→ ready for clinical development



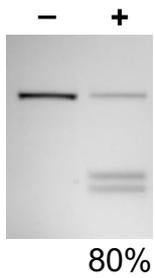
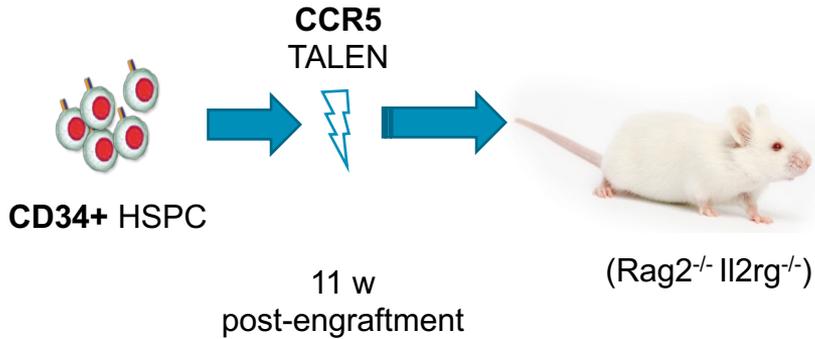
# OUR BLOOD & IMMUNE SYSTEM

## EDITING THE IMMUNE SYSTEM – TREATMENT FOR HIV



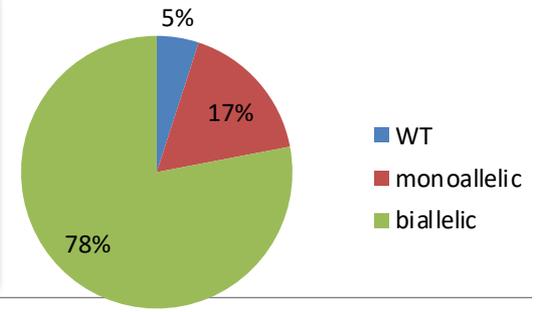
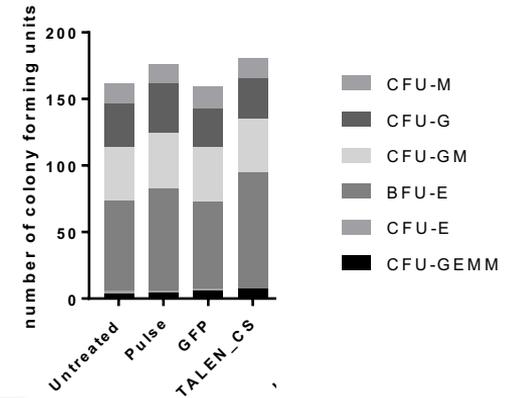
# ENGINEERING RESISTANCE TO HIV INFECTION

## PROOF-OF-CONCEPT: *EX VIVO* AND *IN VIVO*



- leukocytes
- ✓ CCR5 editing
  - ✓ efficient KO
  - ✓ stable KO
  - ✓ safe KO
  - ✓ T cells resistant to HIV
- Ready for clinical translation

Colony forming units



# SUMMARY

## EDITING THE IMMUNE SYSTEM

**Proof-of-Concept Studies** demonstrate feasibility to edit the immune system for the treatment of

- primary immunodeficiencies (*RAG1* in HSC, *STAT3* in T-cells)
- HIV infection (*CCR5* KO to induce resistance)

### Foundation

- highly active and highly specific TALENs (~90% editing)
- smart donor design (regulated transgene expression)
- optimized culturing systems (TI in 20-30% in HSC, 40-70% in T-cells)

**Opportunity** to treat unmet clinical need