



**Non-viral DNA delivery associated to TALEN<sup>®</sup> gene editing leads to highly efficient correction of sickle cell mutation in long-term repopulating hematopoietic stem cells**

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## 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.

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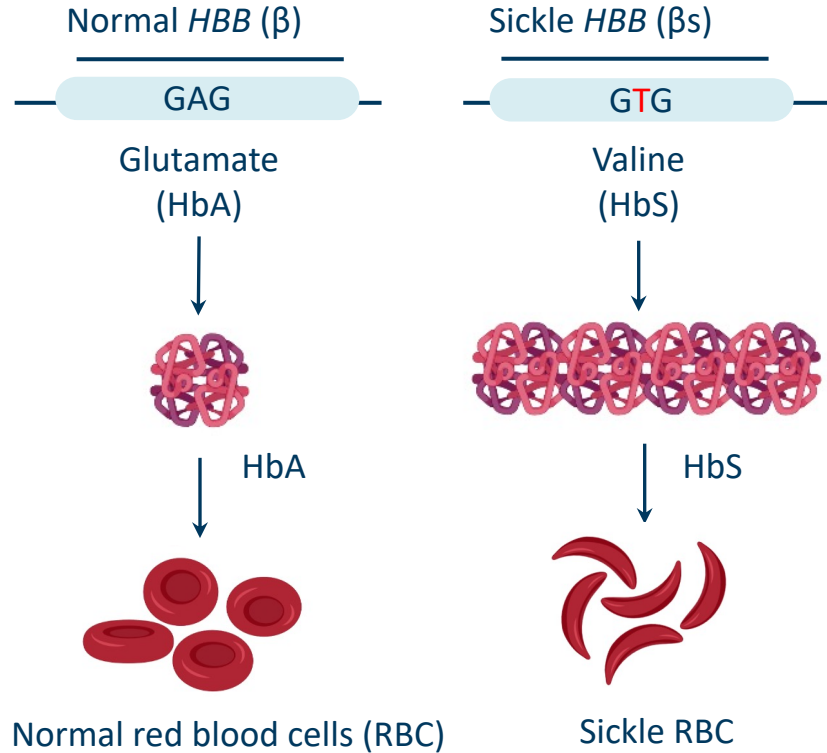
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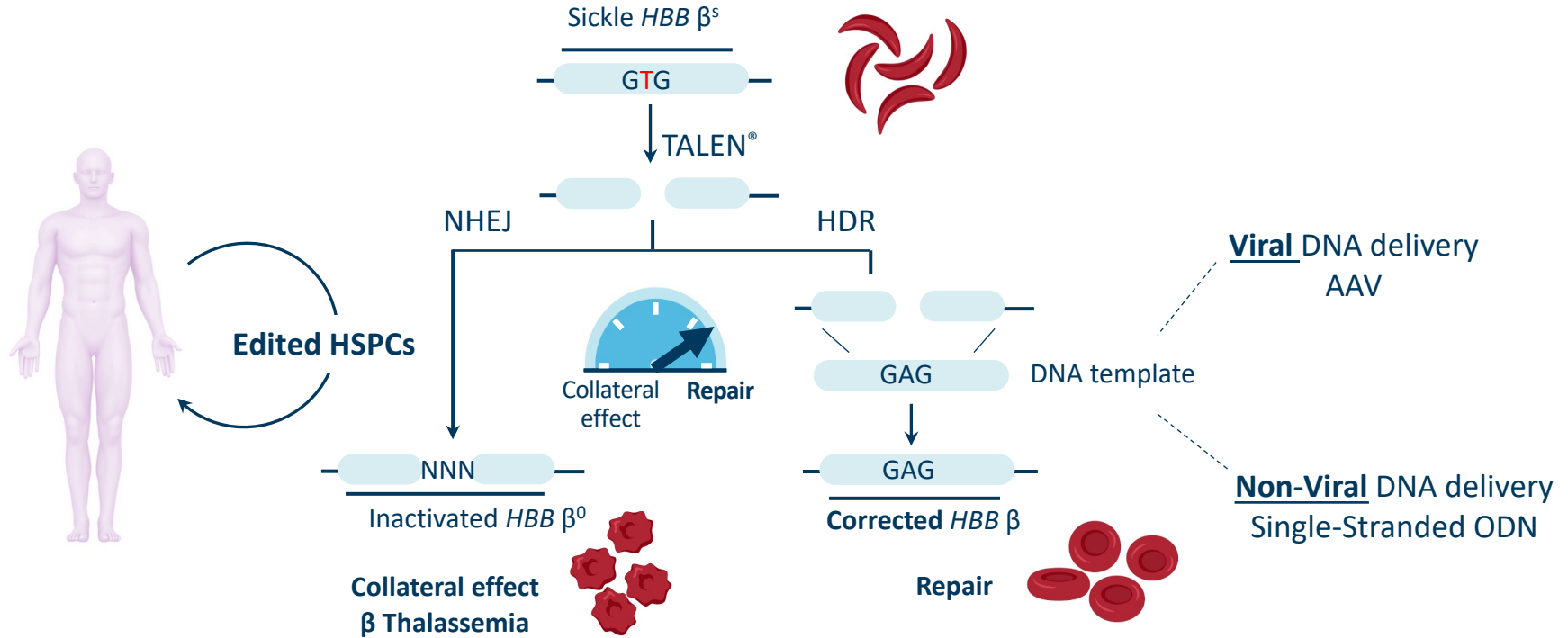


# Sickle Cell Disease



- **Sickle Cell Disease (SCD)** is caused by an A-T point mutation leading to an E6V substitution resulting in the  **$\beta$ -globin ( $\beta^s$ )** defective polypeptide (sickle hemoglobin)
- Vascular occlusion, multiorgan damage and anemia
- **Allogenic hematopoietic stem cell (HSC)** transplantation is the only curative option

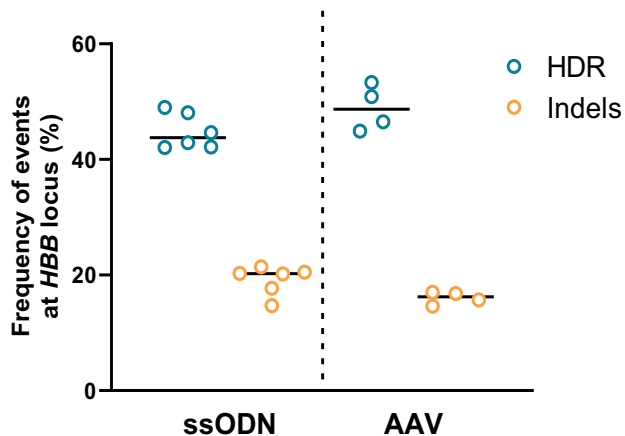
# TALEN<sup>®</sup> mediated gene correction strategy at *HBB* locus



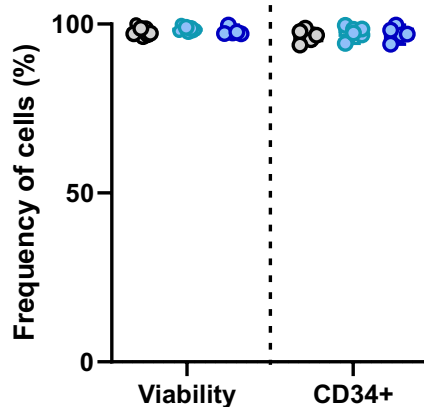
# TALEN® gene editing at *HBB* locus in mobilized healthy donors' HSPCs



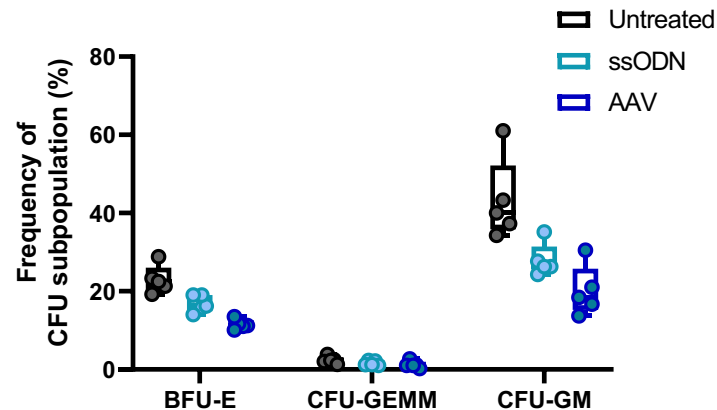
## Gene editing in HSPCs



## Viability and purity

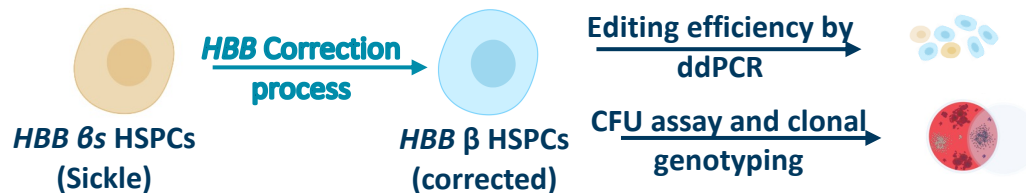


## Clonogenic potential

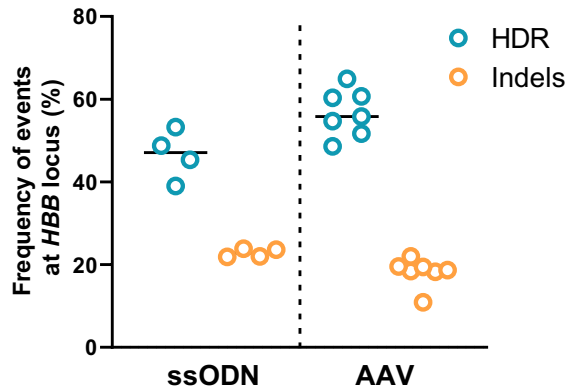


TALEN® efficiently edits *HBB* without affecting HSPCs viability, purity and clonogenic potential

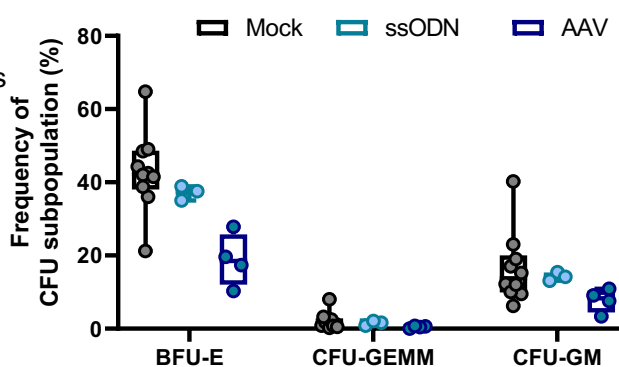
# TALEN® gene editing in SCD patients' HSPCs



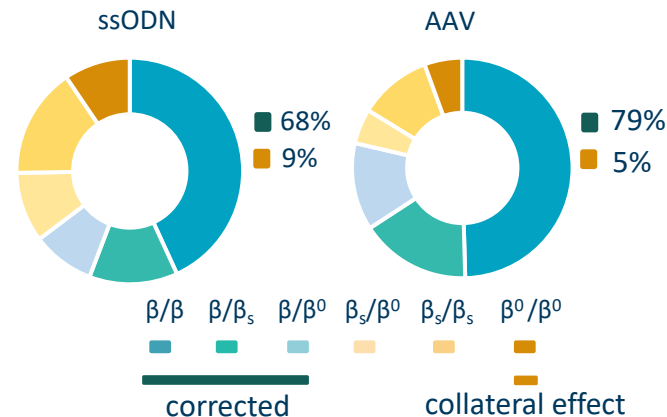
## Gene editing in HSPCs



## Clonogenic potential

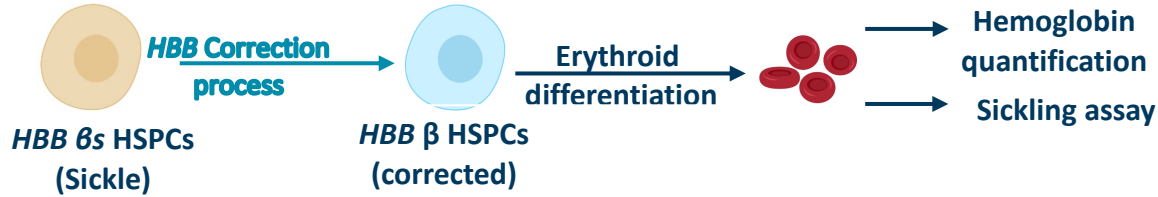


## Clonal genotyping of BFU-E

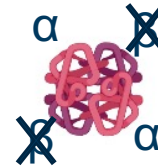
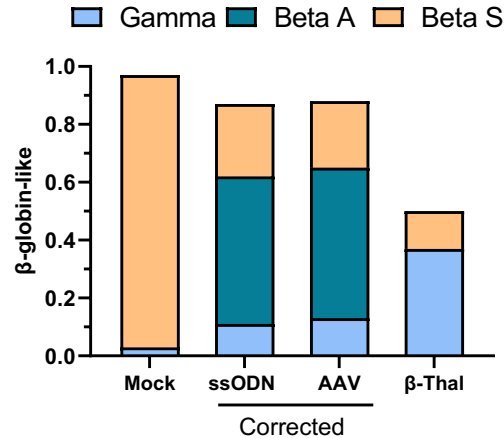


TALEN® gene editing leads to high level *HBB* gene correction and mitigates collateral effects

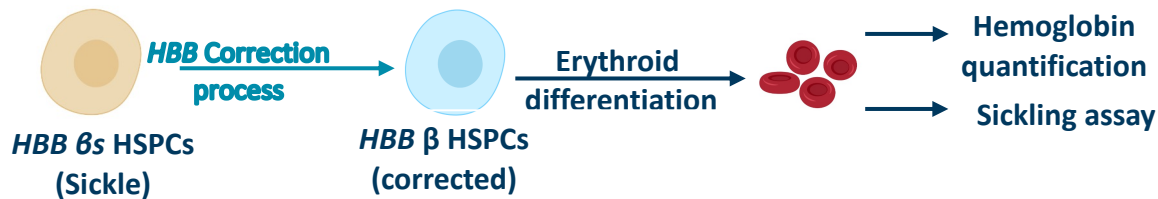
# HBB correction in fully differentiated RBCs



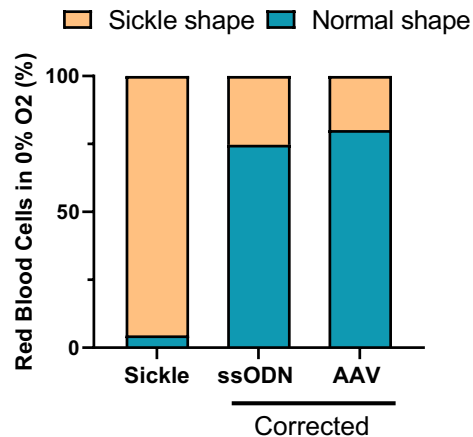
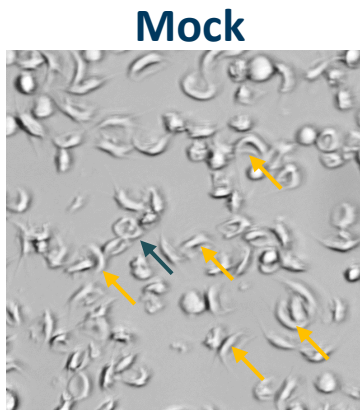
## HPLC-RP in differentiated RBCs



# HBB correction in fully differentiated RBCs



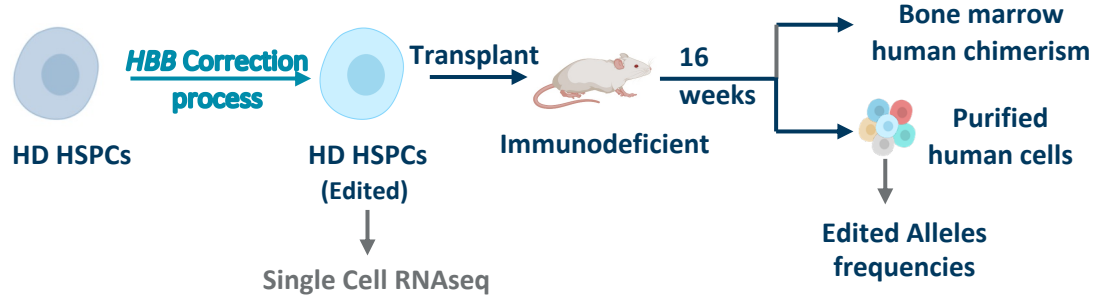
Sickling properties of patient's edited HSPCs-derived RBCs



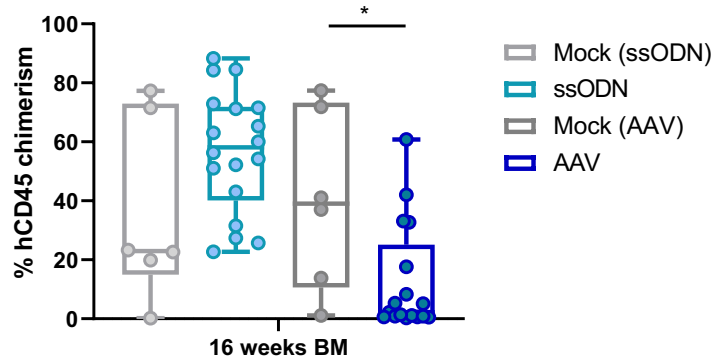
TALEN<sup>®</sup> mediated *HBB* gene correction using viral or non-viral DNA delivery efficiently rescues hemoglobin defect in RBCs



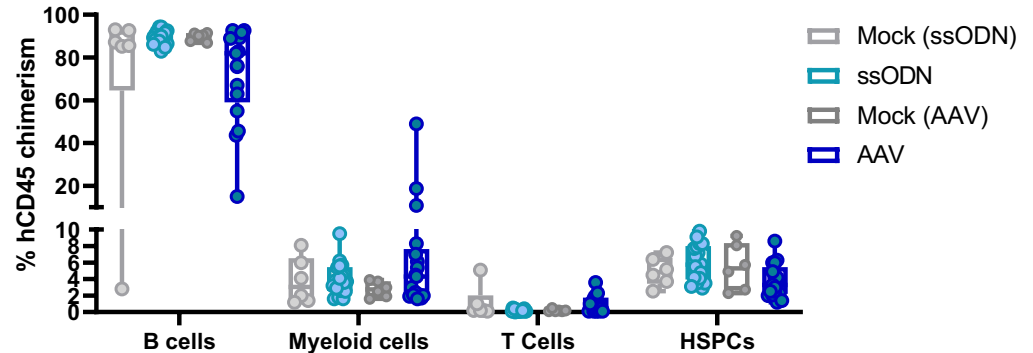
# HBB edited HSC long-term engraftment *in vivo*



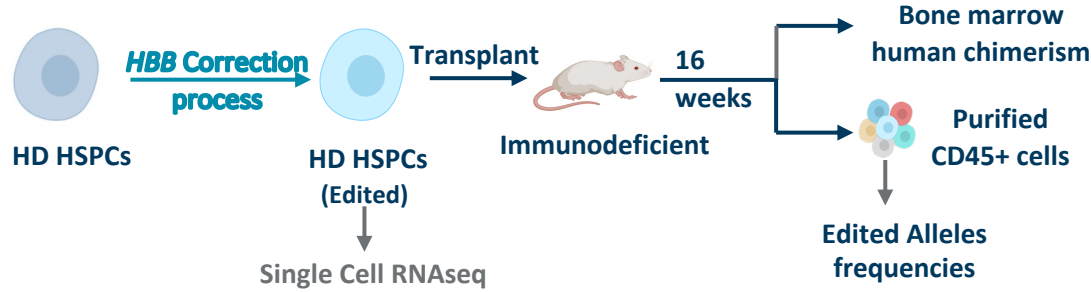
## Bone marrow engraftment



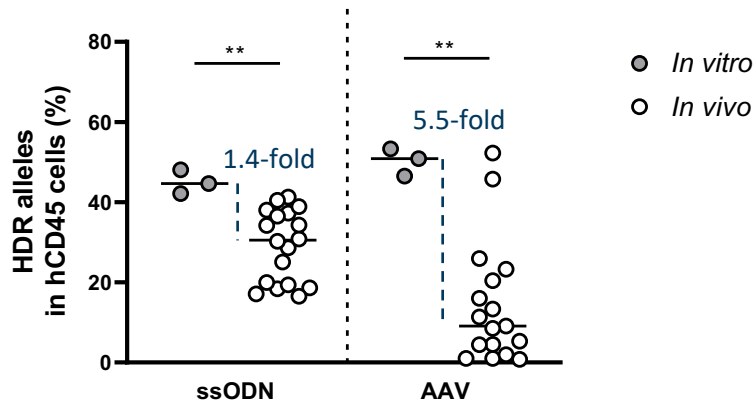
## Bone marrow multilineage differentiation



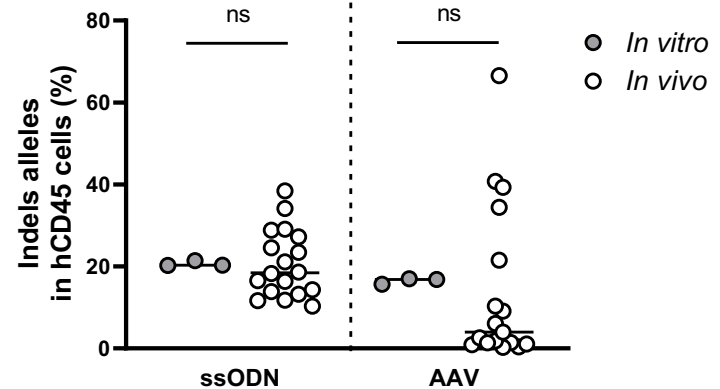
# HBB editing in bone marrow *in vivo*



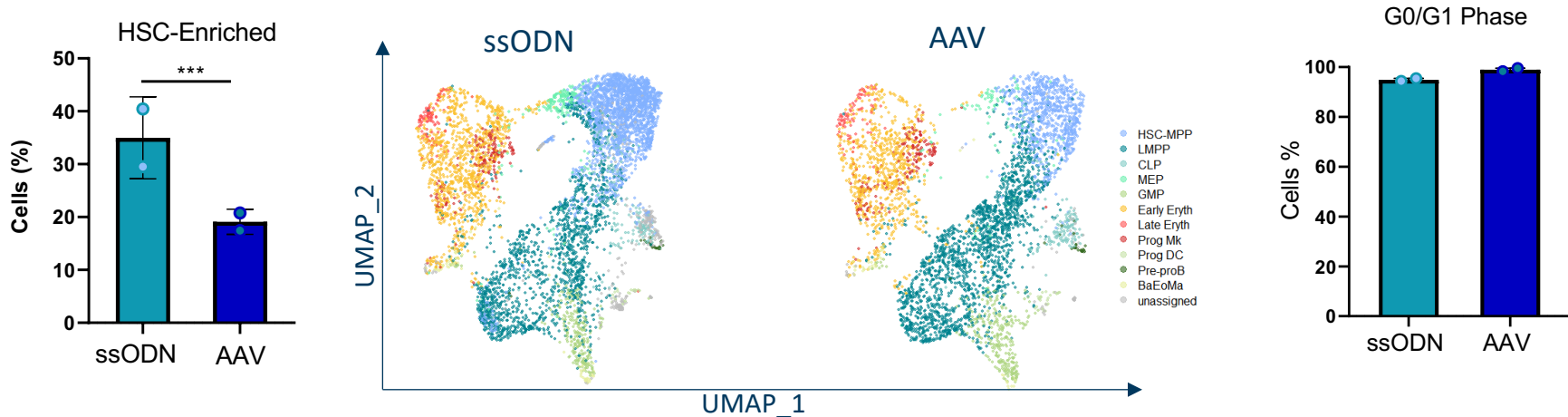
## HDR efficiency in bone marrow



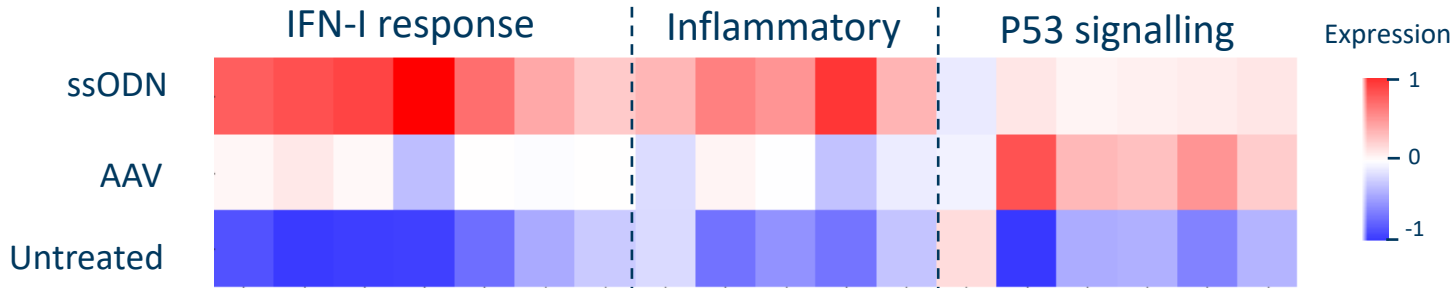
## Indels are not enriched *in vivo*



# Single-cell RNAseq analysis of TALEN<sup>®</sup> edited HSPCs injected *in vivo*

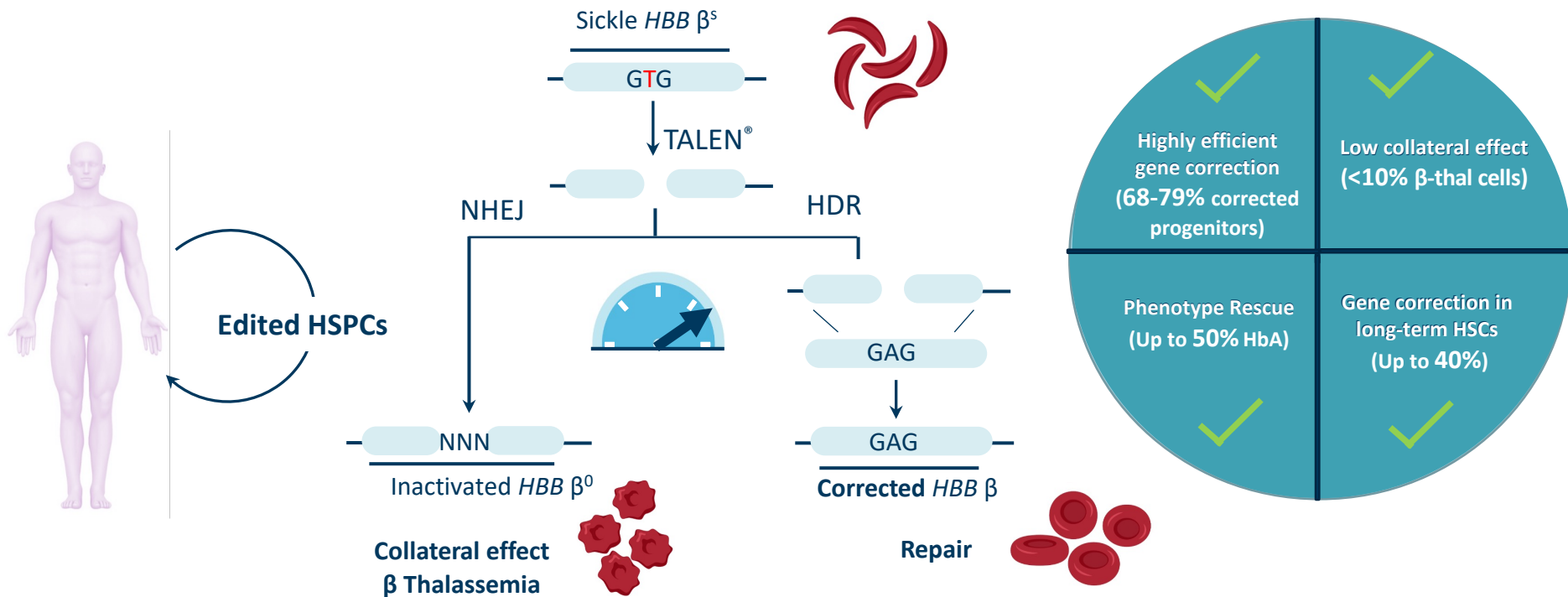


## HSC transcriptomic signature at the time of engraftment



Non-viral mediated repair preserves LT-HSCs frequency and fitness

# Conclusions



# Aknowledgements

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## Bioinformatics

Aymeric Duclert



Anne Chalumeau  
Tristan Felix  
Annarita Miccio

...More TALEN® Gene  
Therapy applications at  
Poster #556

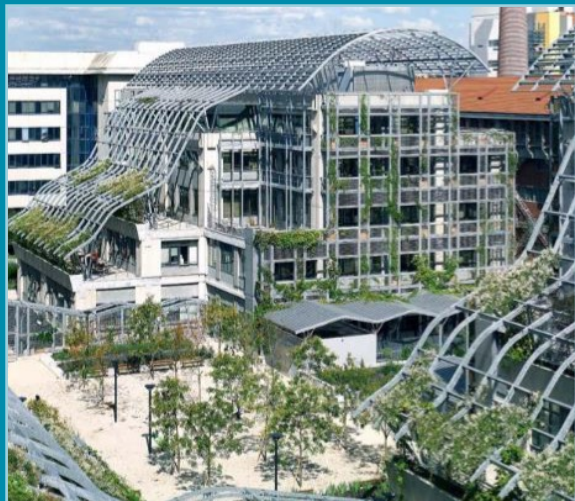


\* Previous employees at Collectis

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