Gene Therapy for SCD: Webinar program for patients

webinar

PATIENTS

Session 4: Genome Editing: CRISPR/Cas9 Advanced Tools and SCD – using new methods

Marcello Maresca & Annarita Miccio
AstraZeneca / Imagine Institute

15 April 2026

ERN | EuroBloodNet

Disclosure for conflict of interest

Marcello Maresca: AstraZeneca employee

Annarita Miccio: No conflict of interest

What we'll talk about today

1

Recap of the previous webinars

An overview on gene therapy and gene editing for SCD.

2

Gene editing limitations and alternatives.

Drawbacks of CRISPR/Cas9-based gene editing and base editing as an alternative

3

Base editing - precision gene editing

How the technology works and how it can be used to treat SCD.

4

Base editing for SCD

Beam-101 as a therapy for SCD. Comparison to Casgevy and current status.

5

Challenges of base editing

We'll introduce the main drawbacks of base editing technology and the topic of the next webinar in this 7-part series.

01

RECAP OF THE PREVIOUS WEBINARS

An overview on gene therapy and gene editing for SCD.

Annarita Miccio
Imagine Institute

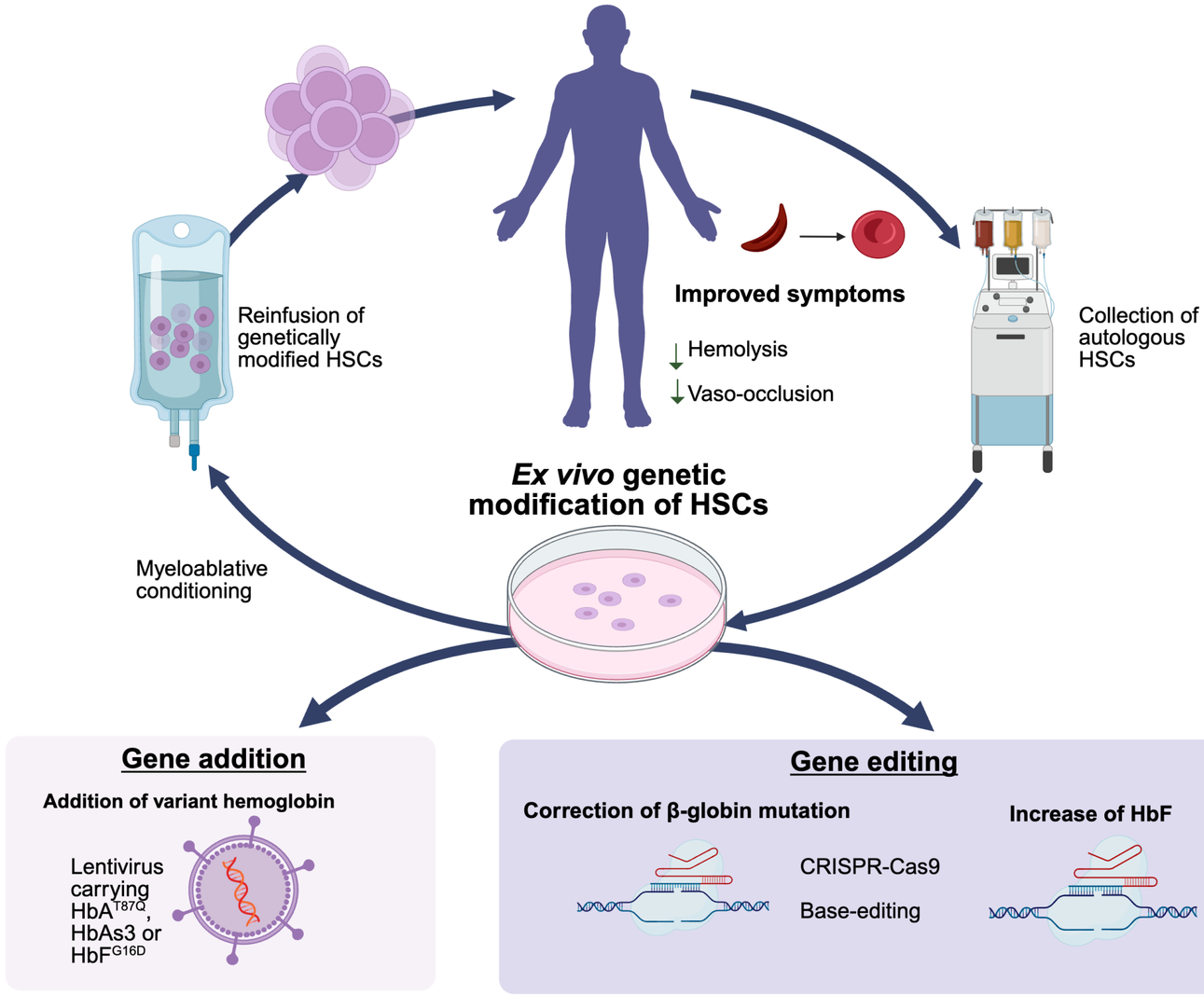
Gene Therapy for Sickle Cell Disease

Ex vivo gene therapy modifies HSCs outside the body

Scientists can modify HSCs extracted from the patient and correct them. Corrected HSCs give rise to red blood cells producing different types of hemoglobin depending on the therapeutic strategy.

Ex vivo gene therapy requires collecting and culturing the HSCs, as well as using chemotherapy to remove all remaining mutant HSCs before reinfusion.

Despite the potential risks associated, the approach has managed to dramatically improve symptoms like hemolysis and vaso-occlusions in SCD patients.



From: https://onlinelibrary.wiley.com/doi/10.1111/vox.13612

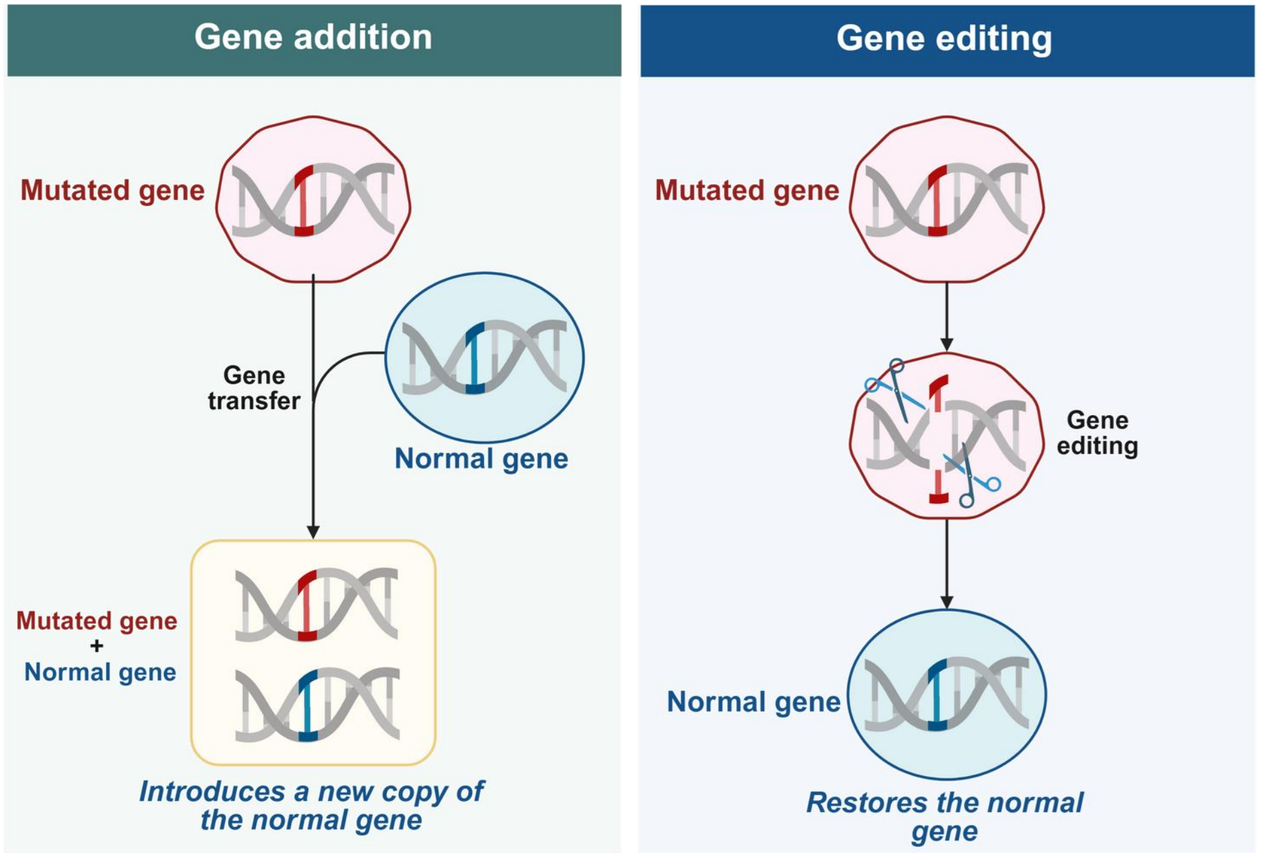
Gene Addition vs Gene Editing

Gene editing addresses the genetic mutations directly in the cell's DNA

While gene addition provides a correct copy of the faulty gene, it doesn't correct the root problem. Gene editing addresses the genetic cause of the disease, trying to correct or cirvumvent a genetic mutation.

Gene addition introduces a new, correct copy of the faulty gene, giving the cell a new set of instructions to use.

Gene editing seeks to repair the mutated gene, fixing the "typo" to correct the incorrect instructions or to circumvent the genetic mutation, modifying a gene to increasing the production of the fetal hemoglobin.



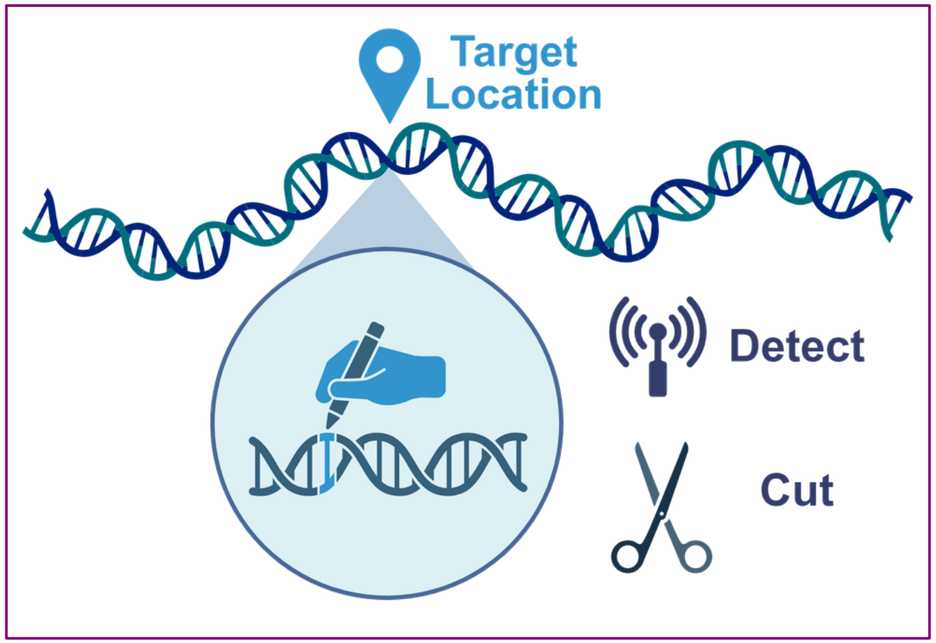
Gene Editing

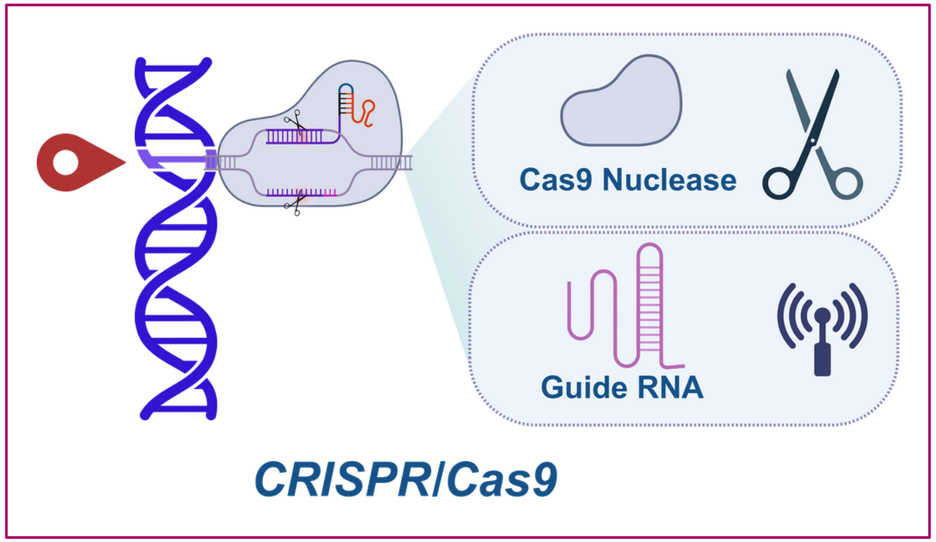
Gene editing is a highly targeted genetic surgery

It uses “molecular scissors” to cut the DNA and modify the information it contains.

Molecular scissors are guided to a specific sequence of the DNA

A “guiding system” directs the molecular scissors to cut the DNA in a specific location in the DNA.





02

GENE EDITING
LIMITATIONS AND ALTERNATIVES

Drawbacks of CRISPR/Cas9-based gene editing and base editing as an alternative.

Marcello Maresca
AstraZeneca

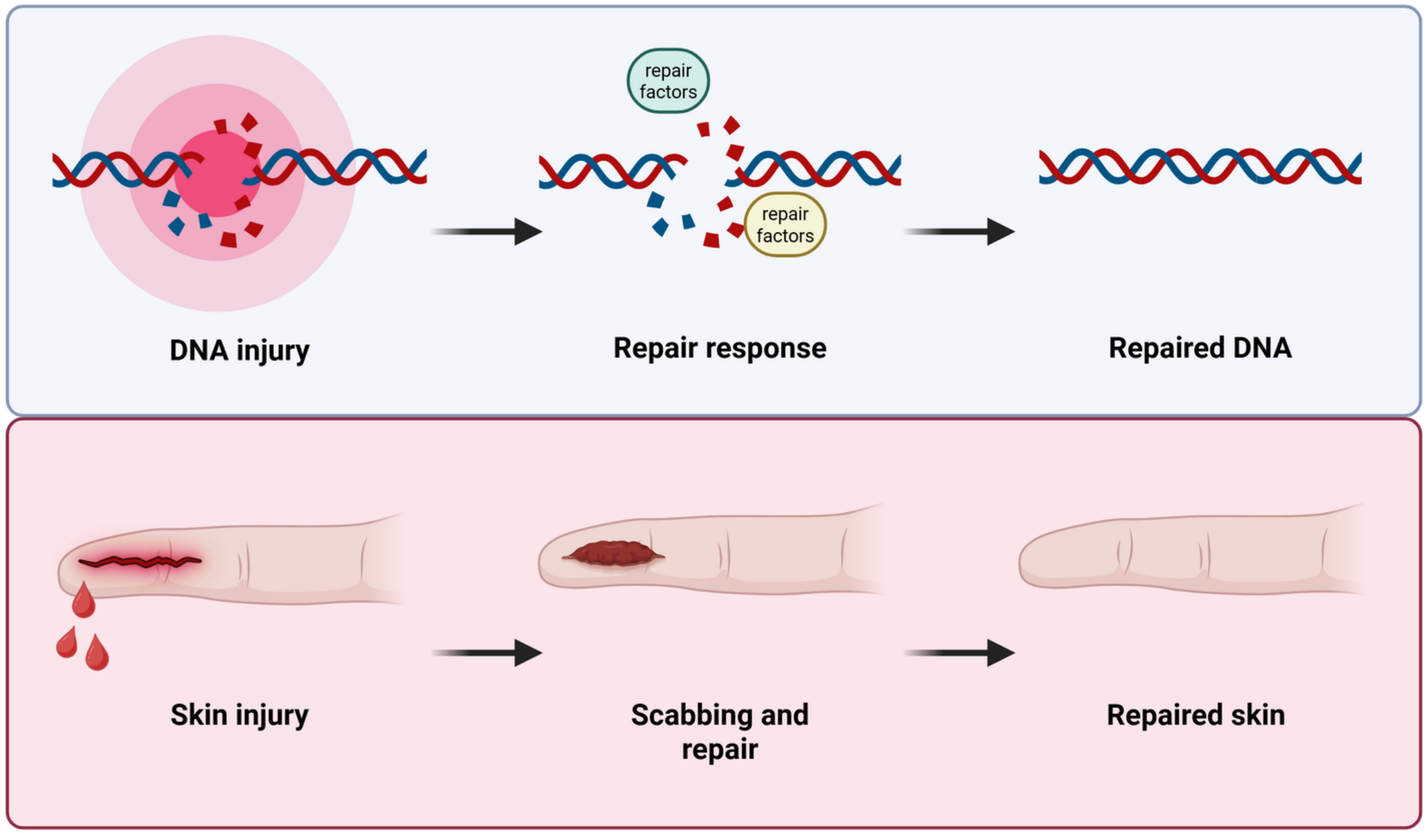
CRISPR-Cas9 breaks the DNA

Double-strand breaks (DSB) are injuries in the DNA

Just like any injury in our body, DNA lesions must be repaired quickly and effectively.

When a double-strand break (DSB) occurs in the DNA, the cell activates a repair response aimed at minimizing and correcting damage.

The broken DNA ends are evened out and glued back together, similar to how a skin injury scabs before the skin can heal.



DNA breaks must be repaired

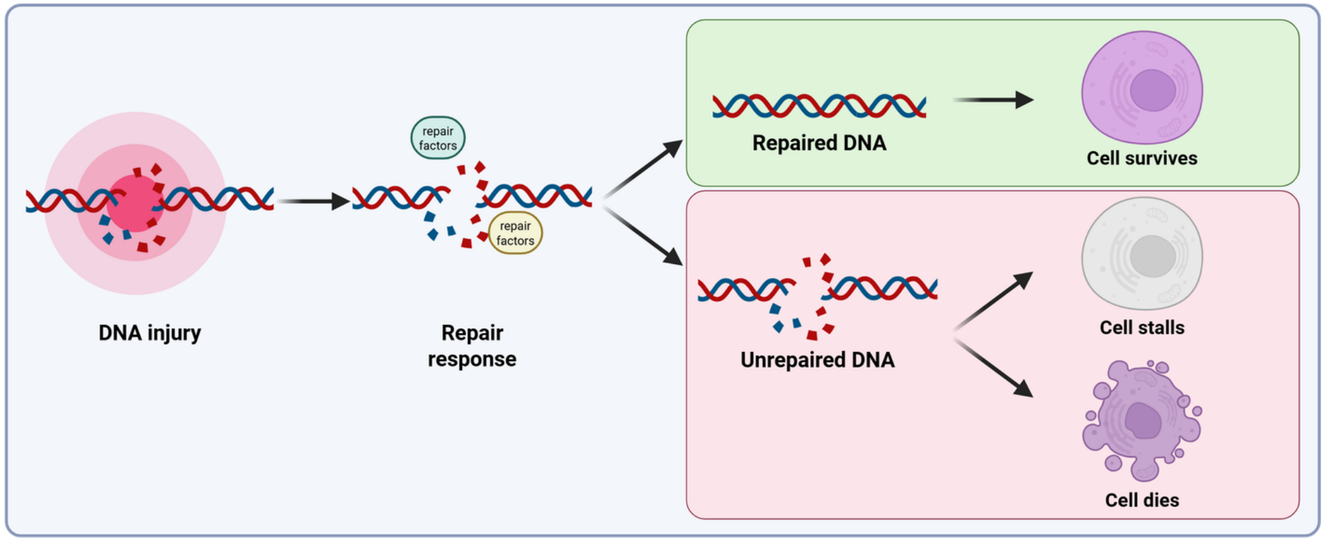
If it can’t, the cell either dies or gets “stalled”

Like with an unstable building after an earthquake, it is often better to either evacuate and abandon the building or to demolish it completely.

Even when the DNA can be put together, sometimes this repair can be wrong and introduce even worse problems.

Especially when various DSBs happen simultaneously, the wrong DNA fragments can be glued together creating chromosomal rearrangements and new, potentially dangerous genetic sequences.

However, DSB repair is very efficient and works properly in most cases.



03

BASE EDITING
PRECISION GENE EDITING

How the technology works and how it can be used to treat SCD.

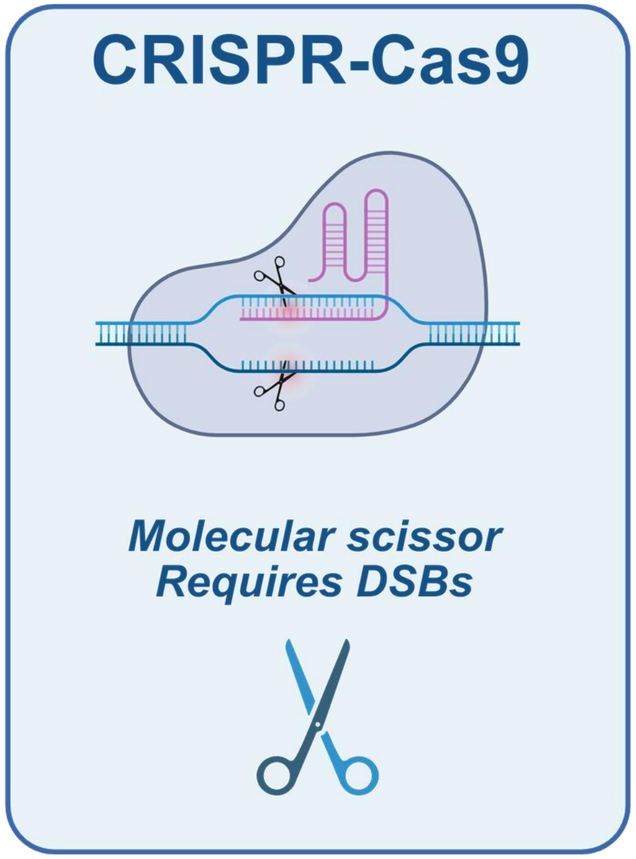
Marcello Maresca
AstraZeneca

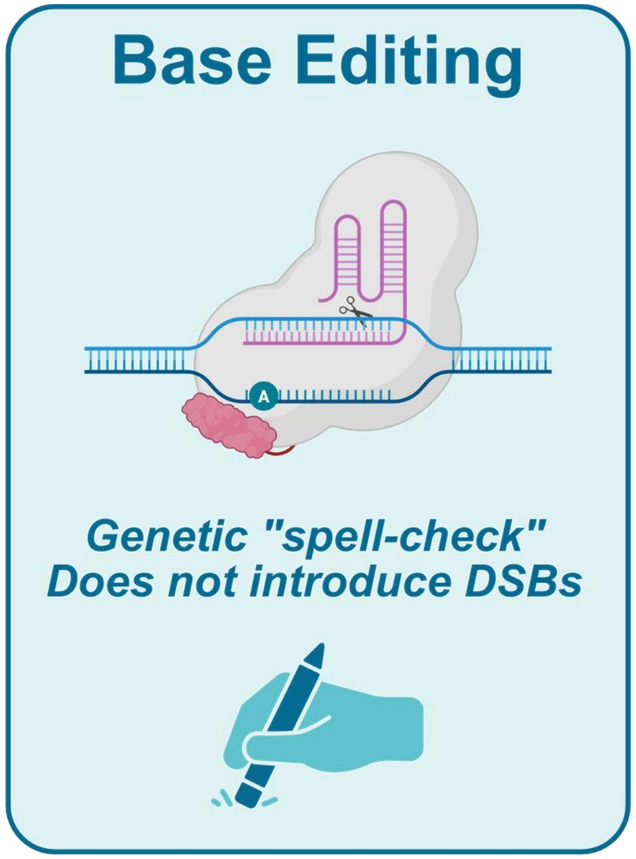
Base Editing - what it is

Base editing works like a genetic spell check

Base editing is the first real “evolution” of CRISPR-Cas9, aimed to address its drawbacks.

Base editing allows scientists to edit the DNA while introducing only very few DSBs.





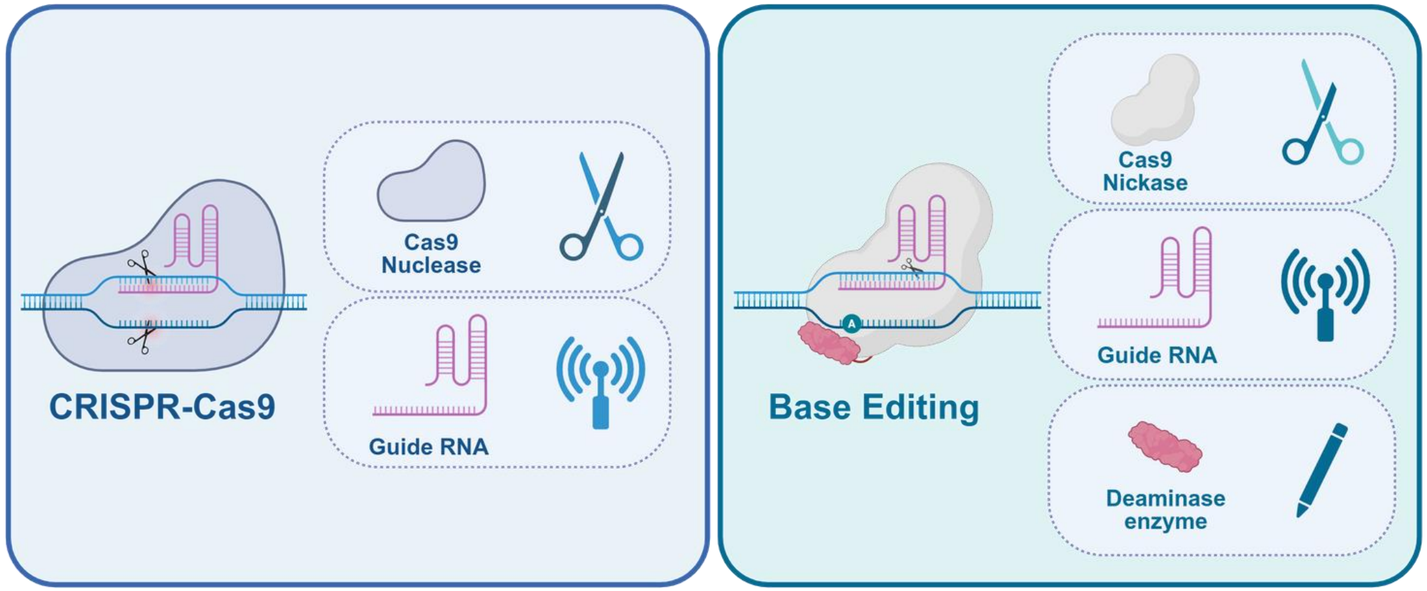
Base Editing - how it works

Base editing maintains the key CRISPR-Cas9 elements

However, a base editor uses a version of Cas9 that cannot cut both DNA strands, but only one. n addition, it carries an enzyme called deaminase.

The system still uses a guide RNA to find its target in the DNA. However, the Cas9 nickase has been modified so that it cannot cut the DNA, as its “blades” have gone dull.

Instead, the deaminase enzyme attached to the nickase acts chemically on the DNA to introduce an edit, working very similarly to a pencil with eraser.

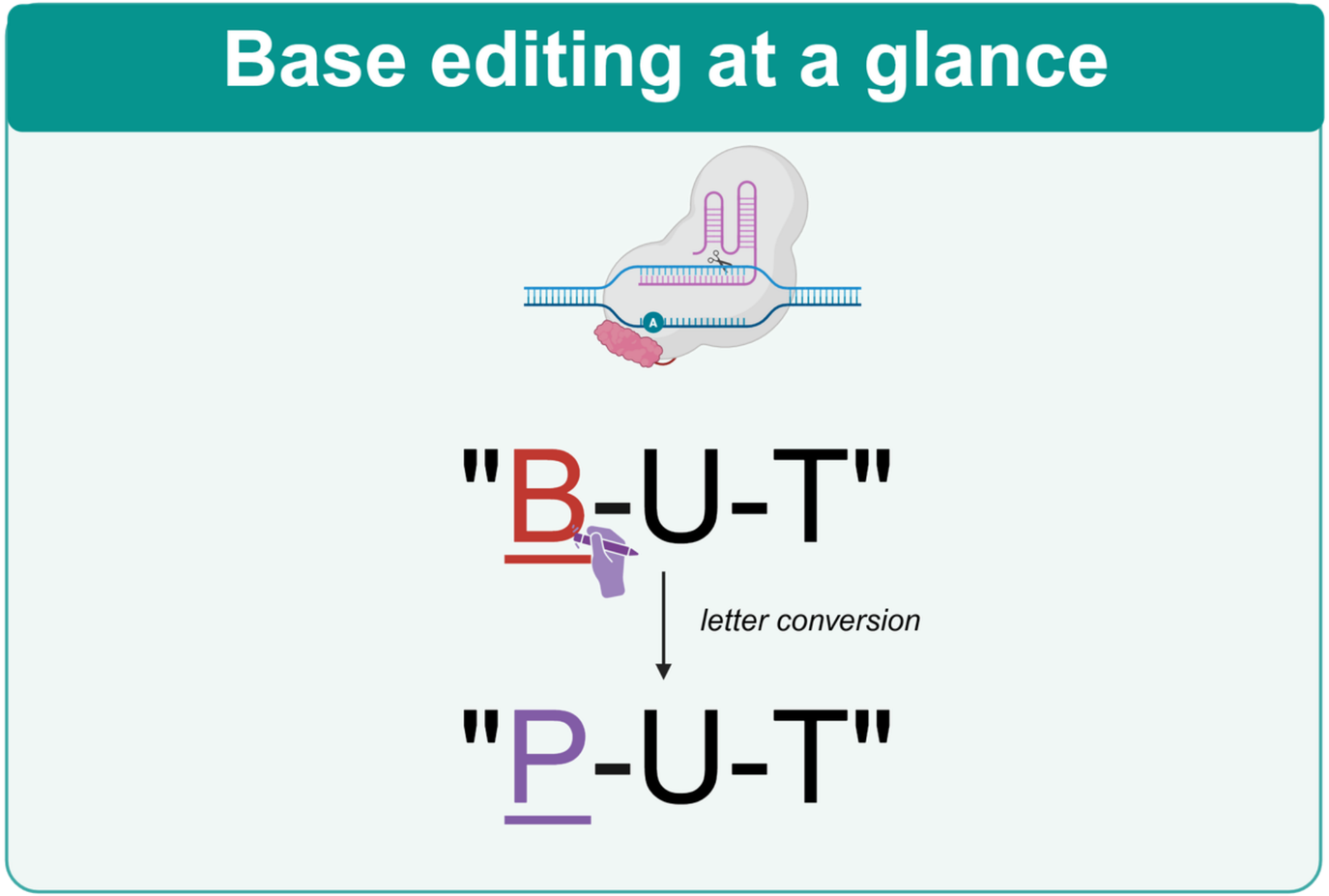


Base Editing - how it works

Base editing chemically modifies the DNA

Every “letter” on the DNA code has a chemical structure. The deaminase on a base editor changes this structure to replace one letter with another.

The deaminase removes a small chemical structure called an amino group. This tricks the cell into “reading” a different letter.

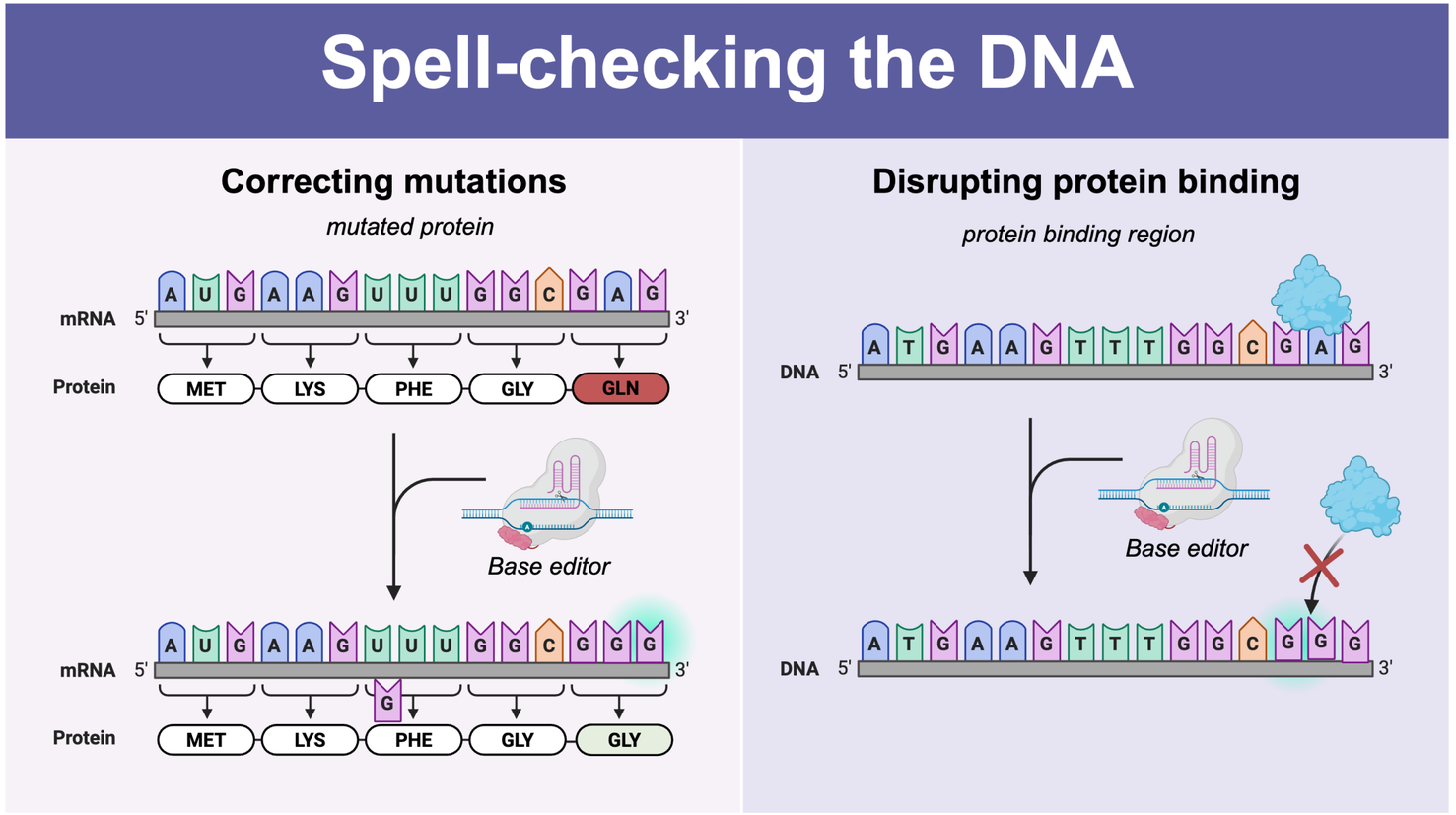


Base Editing - how it works

One base, multiple outcomes

Base editors enable targeted nucleotide conversions (A→G, C→T) without inducing double-strand breaks.

These precise edits can introduce premature stop codons, correct pathogenic mutations, or modify regulatory elements, demonstrating how single-base changes can profoundly impact gene expression and protein function.



04

THE BEAM-101 JOURNEY

BEAM-101, the clinical trial journey, limitations and comparison to other therapies for SCD.

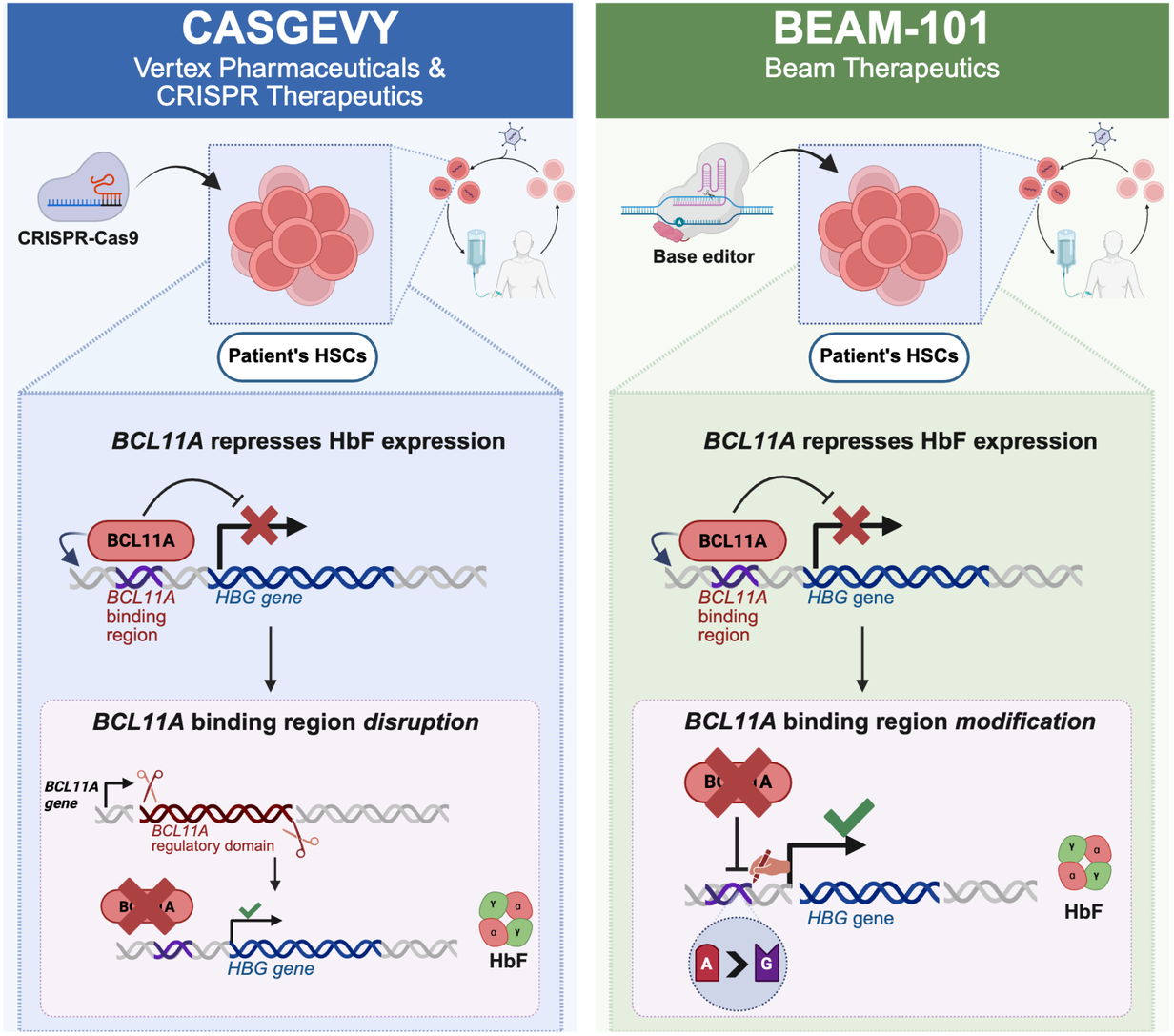
Annarita Miccio
Imagine Institute

Base Editing - CASGEVY vs BEAM-101

Two paths to reactivate fetal hemoglobin

Casgevy turns off BCL11A, the switch that silences fetal hemoglobin.

BEAM-101, instead, rewires the system by editing a single DNA letter in *HBG*, preventing BCL11A from binding and allowing fetal hemoglobin to be produced again.

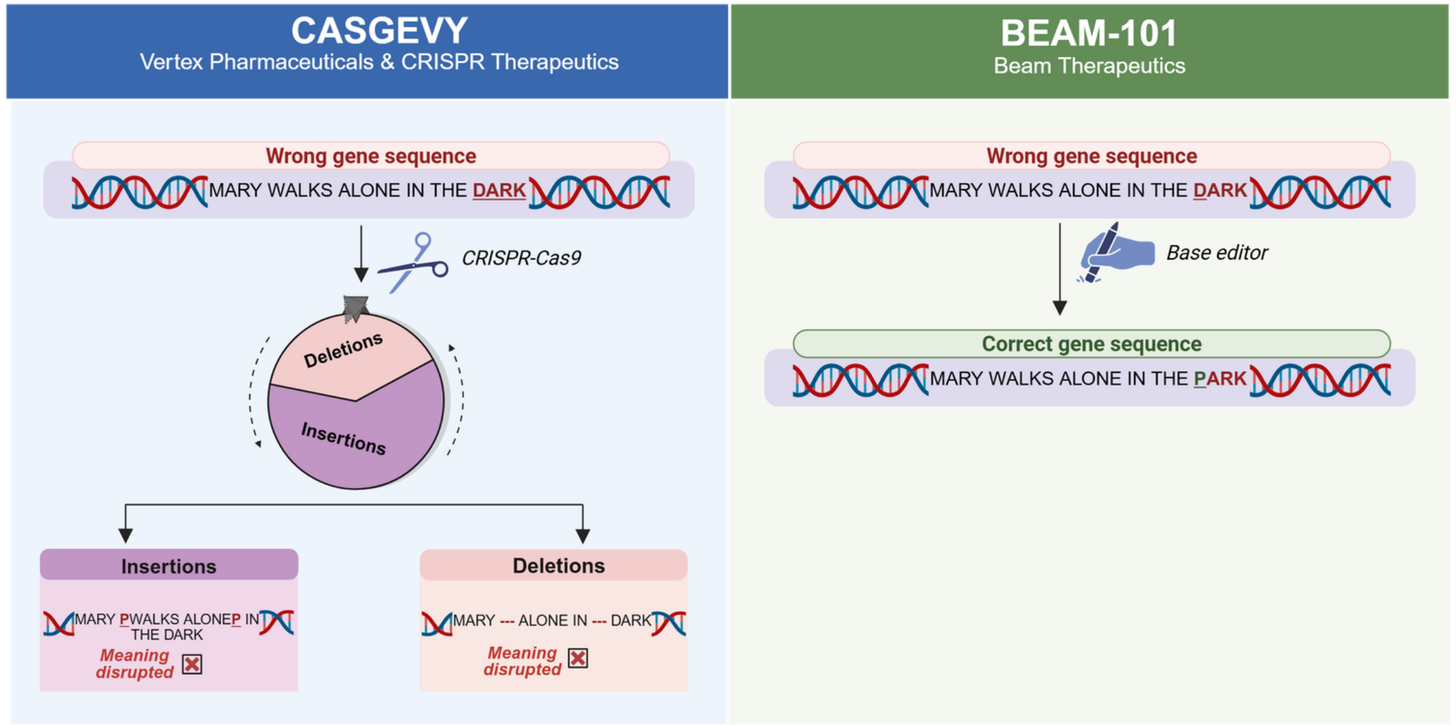


Base Editing - CASGEVY vs BEAM-101

Editing modality shapes the outcome

Both Casgevy and BEAM-101 aim to restore fetal hemoglobin, but they work very differently. CRISPR creates a DNA break that is repaired unpredictably, leading to insertions or deletions.

Base editing, instead, directly converts one base into another, reducing DNA DSBs and producing more precise and consistent outcomes.



Base Editing - CASGEVY vs BEAM-101

A gentler approach to editing stem cells

Cutting the DNA can place a higher burden on stem cells, requiring large numbers to ensure successful treatment.

Base editing avoids these cuts, preserving cell health and allowing treatment starting with far fewer cells.

Compared to Casgevy, BEAM-101 enables quicker recovery of neutrophils and platelets.
Hemoglobin levels rise rapidly, helping resolve anemia and improving red blood cell function and oxygen delivery.

	CASGEVY Vertex Pharmaceuticals & CRISPR Therapeutics	BEAM-101 Beam Therapeutics
HSCs needed:	30 million/kg + 2 million/kg for rescue	3 million/kg
DSB introduction	High	Low
Cell toxicity	High	Low
Immune recovery	Up to a month	2-3 weeks
Hemoglobin levels	Good	Higher

BEAM-101 clinical trial: what we know so far

BEAM-101 is currently in clinical testing

The study has enrolled patients with severe SCD who continue to experience frequent crises despite treatment.

Careful inclusion and exclusion criteria ensure the therapy is evaluated in patients with unmet medical need.

Inclusion criteria

- Age **≥12 years** and **≤35 years**
- **Diagnosed with SCD** with βS/βS, βS/β0, or βS/β+ genotypes
- **Severe SCD** with at least 4 severe VOCs in the 24 months prior to screening despite receiving supportive care measures
- Able to undergo **stem-cell mobilization and collection**
- Able to undergo **high-dose busulfan conditioning**

Exclusion criteria

- **HbF levels >20%**, obtained at the time of screening on or off hydroxyurea therapy
- **Previous** receipt of an **autologous or allogeneic HSCT** or **solid organ transplantation**
- **Available** and willing **matched sibling donor**
- Definitive diagnosis of **moyamoya syndrome**
- History of **overt stroke**

BEAM-101: early clinical outcomes

Promising efficacy and safety signals

BEAM-101 shows encouraging early results, with successful engraftment and high levels of fetal hemoglobin (>60%).

Protocol improvements have enhanced the quality and number of edited HSCs.

Safety data also remains favorable, with no major adverse events reported to date.

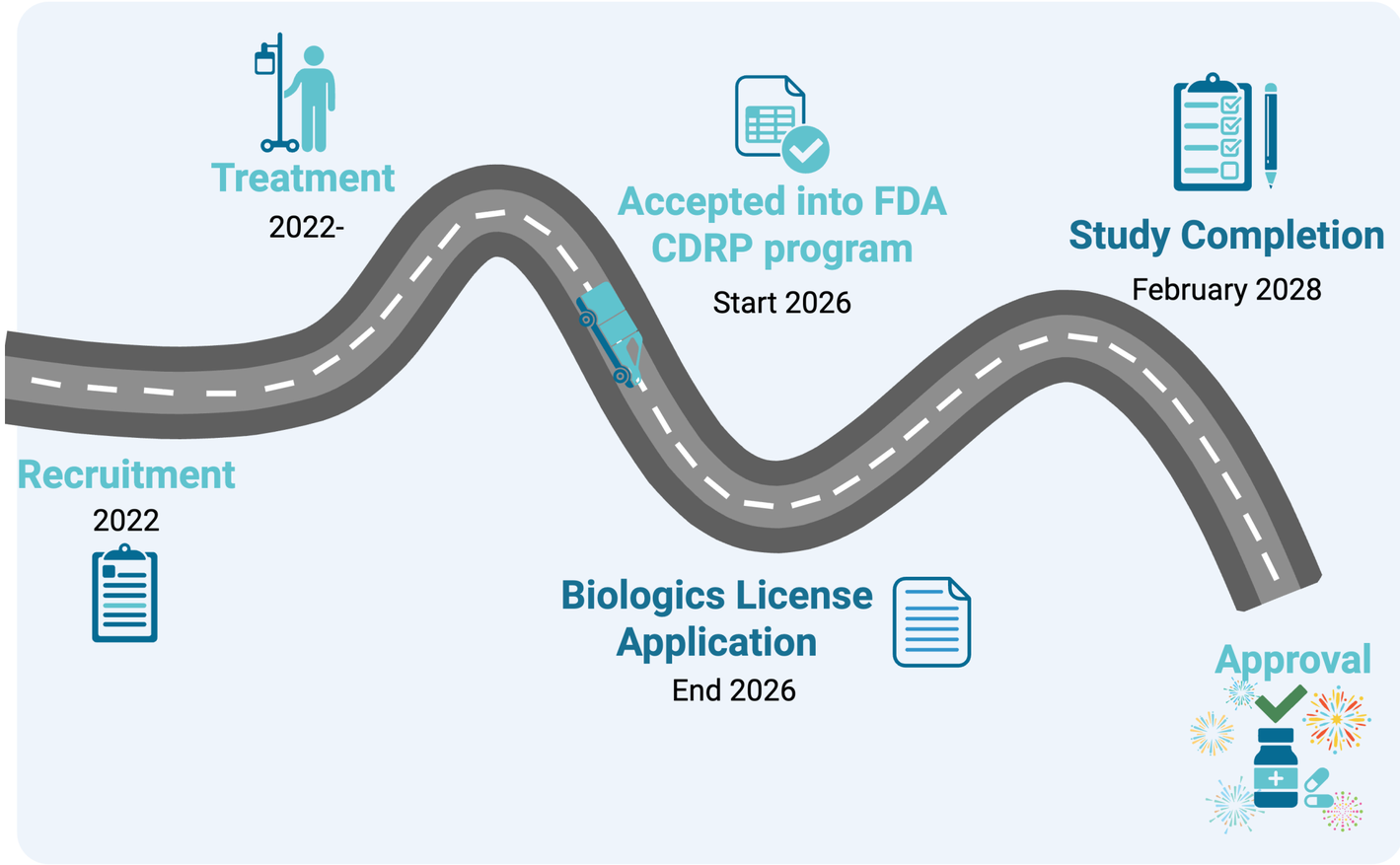
The Good	The Bad
31 patients treated	Common adverse events: stomatitis, febrile neutropenia, anemia
Higher HSC collection and survival	One reported death associated with HSC transplantation conditioning
>60% fetal hemoglobin expression	Longer follow-up needed for both efficacy and safety
Reduction in sickle hemoglobin	
No vaso-occlusive crises (VOC)	

BEAM-101: path toward clinical approval

With encouraging early results, BEAM-101 is progressing through clinical development

The focus now shifts to confirming long-term safety and durability.

Regulatory processes are underway bringing this one-time base editing therapy closer to potential approval.



05

CHALLENGES OF BASE EDITING

We will introduce the main drawbacks of base editing technology and the topic of the next webinar in this 7-part series.

Marcello Maresca
AstraZeneca

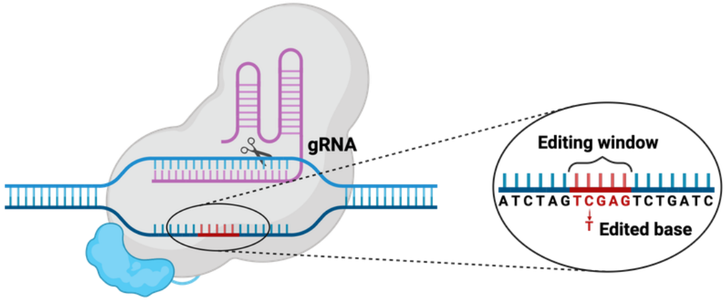
Challenges of base editing

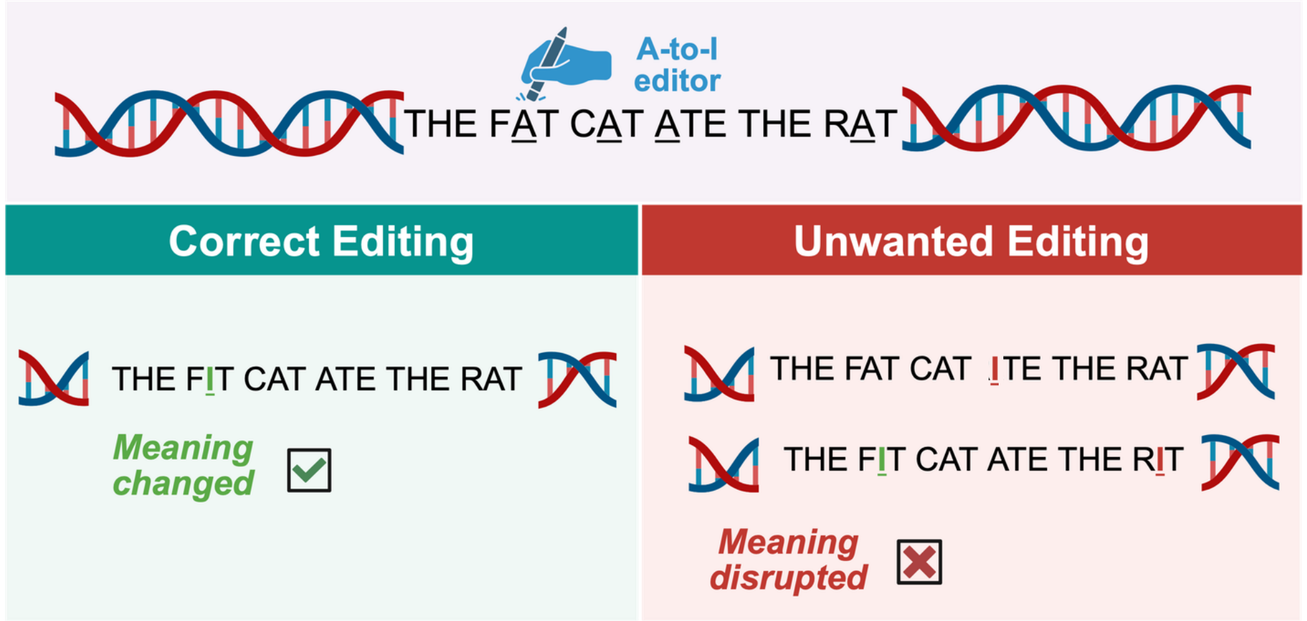
Base editing carries some important challenges

Although it can be an extremely powerful tool for precise, targeted therapies, base editing carries inherent risks and limitations that need to be considered.

Base editors do not change just one exact letter, they act within a small “editing window.”

If multiple identical bases are present in that region, unintended edits can occur, potentially altering the final outcome in unexpected ways.





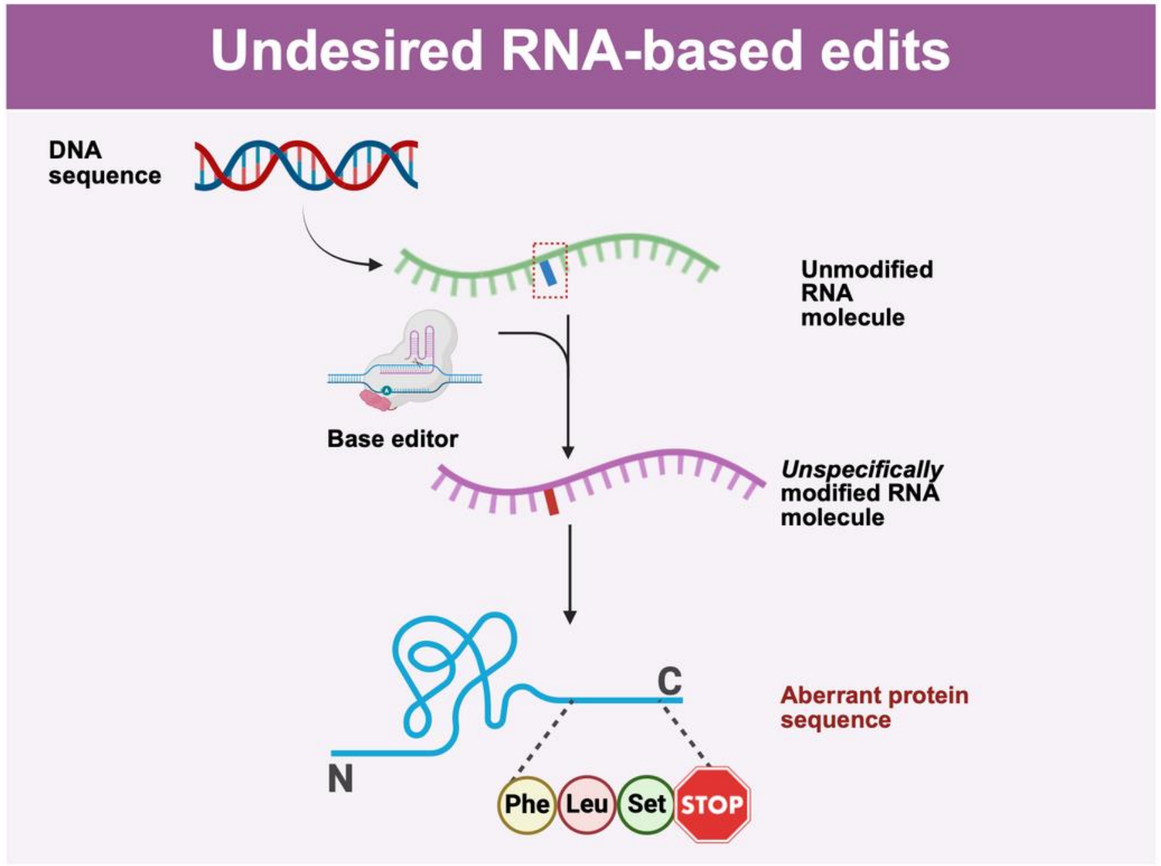
Challenges of base editing

Off-targets beyond the DNA

Although they are designed to edit the DNA, base editors can sometimes modify the RNA instead.

This kind of editing is not sequence-specific, but rather an effect of the deaminase enzyme being too “promiscuous”.

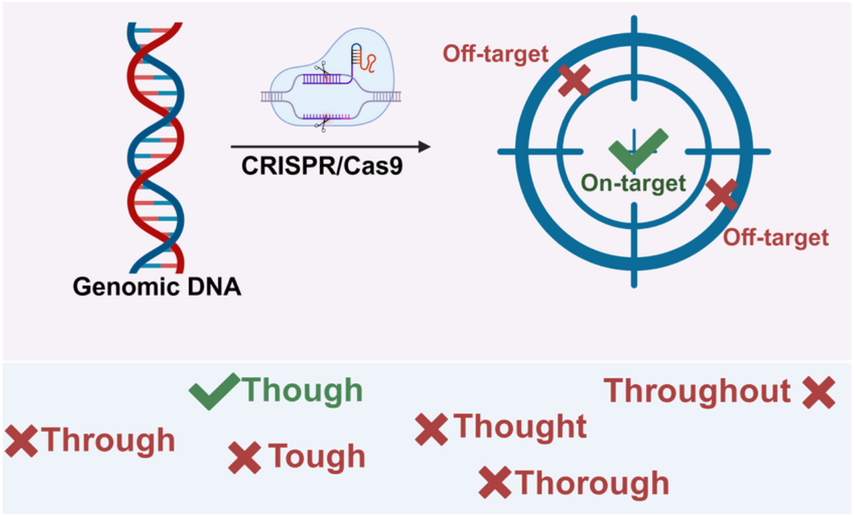
In some cases, it can unintentionally edit the temporary instructions used to make proteins, potentially leading to incorrect protein production even when the DNA remains unchanged.



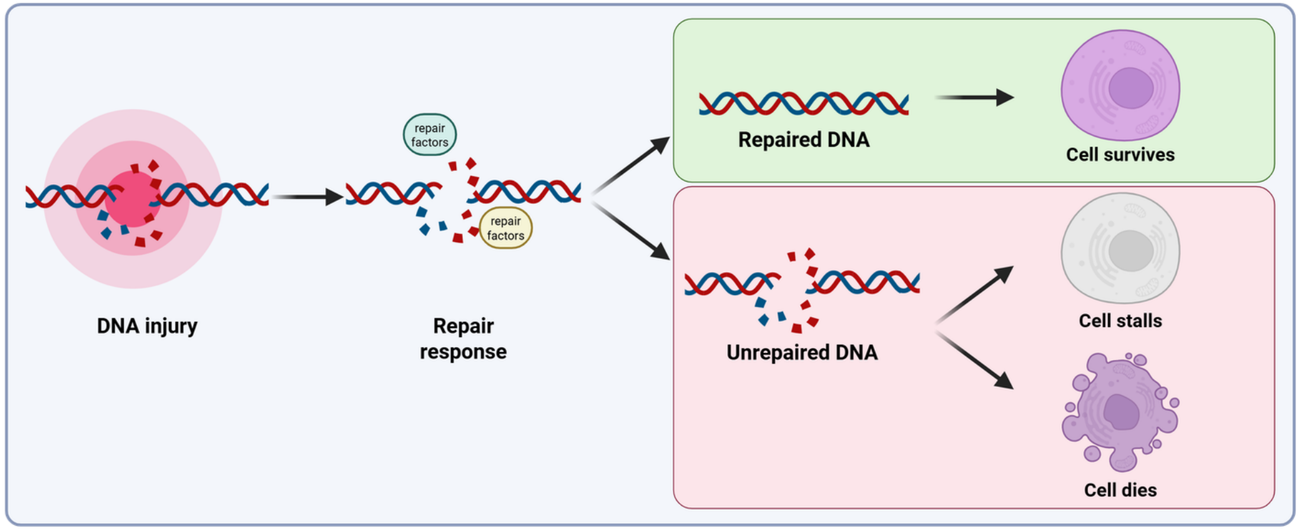
Next webinar: Safety of CRISPR/Cas9

How scientists measure and address safety issues in gene editing

Undesired DNA edits



Genotoxicity



Future Webinars

Session 5: Safety of CRISPR/Cas9
Ayal Hendel and Toni Cathomen
June 2026

Session 6: Future Developments and CRISPR/Cas9 for SCD
Annarita Miccio
July 2026

Session 7: Regulatory path to the clinic
David Morrow
September 2026

ED T SCD ACKNOWLEDGMENT

Marcello Maresca
Annarita Miccio
Michaela Semeraro
Laure Joseph
Giuliana Ferrari
Claudio Mussolino
Mario Amendola
Ayal Hendel
Toni Cathomen

EDITSCD

Conceptualization, design, and content curation of slides and graphics:
Martina Franchini • Antonio Carusillo • Manel Llado Santaeularia

WE DO CRISPR

webinar

www.eurobloodnet.eu

@ERNEuroBloodNet

eurobloodnet-european-reference-network-on-rare-hematological-diseases

Eurobloodnet - European Reference Network on Rare Hematological Diseases

ERN-EuroBloodNet's EDUcational Youtube channel

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

Funded by the European Union

THANK YOU

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

Funded by
the European Union