Gene Therapy for SCD: Webinar program for patients

webinar

PATIENTS

Session 3: Genome Editing: CRISPR/Cas9 and SCD – how it works and its uses

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Institute for Transfusion Medicine and Gene Therapy - University Medical Center Freiburg / Genethon / Imagine Institute

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Disclosure for conflict of interest

Claudio Mussolino: No conflict of interest

Mario Amendola: No conflict of interest

Annarita Miccio: No conflict of interest

What we'll talk about today

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Recap of the previous webinar

An overview on SCD gene therapy.

2

Gene editing and how it works

What gene editing is and how it can be used to correct genetic diseases.

3

Gene editing of SCD

How scientists can use gene editing to modify HSCs and treat SCD.

4

The Casgevy journey

The Casgevy, the treatment journey, limitations and comparison to other therapies for SCD.

5

Challenges of gene editing

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

01

RECAP OF THE PREVIOUS WEBINAR

An overview on SCD gene therapy.

Annarita Miccio
Imagine Institute

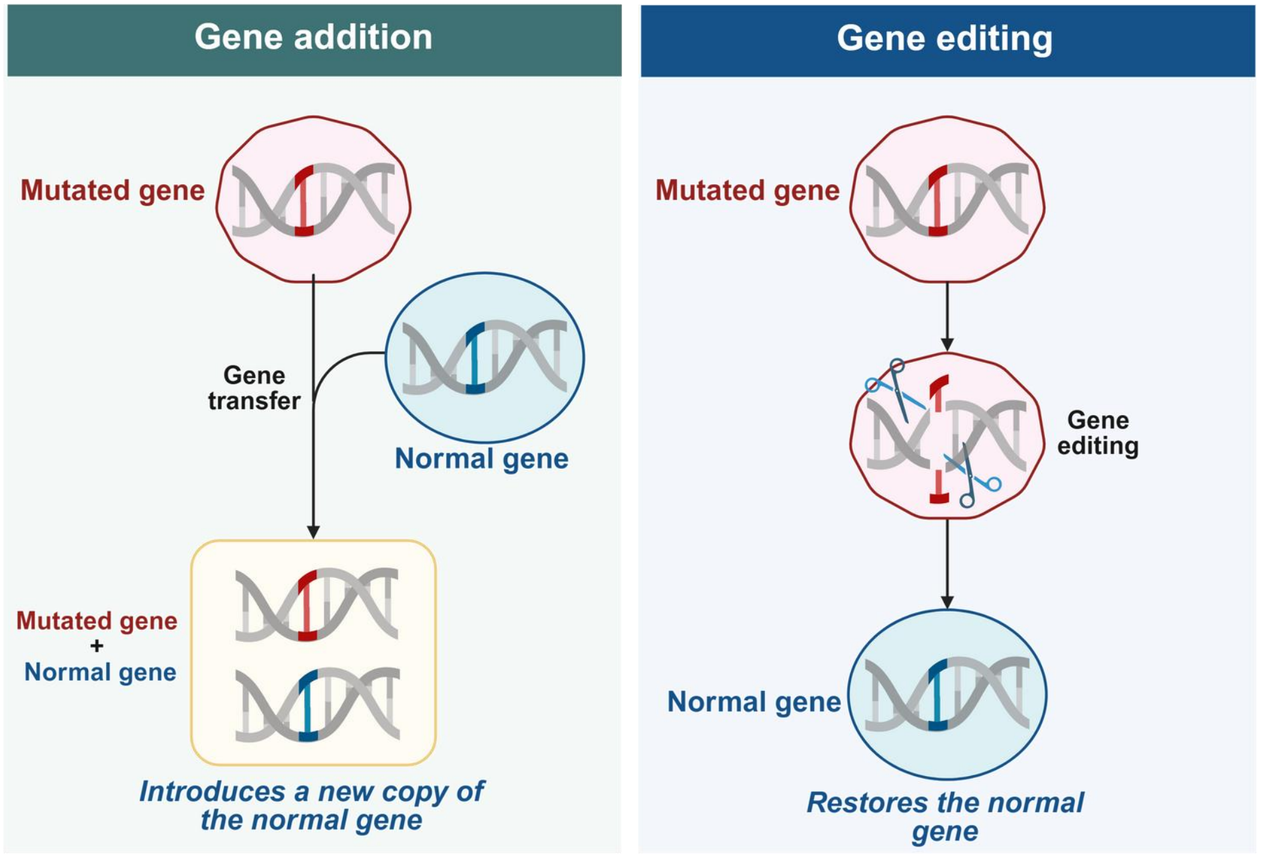
Gene Addition vs Gene Editing

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.



02

GENE EDITING
AND HOW IT WORKS

What gene editing is and how it can be used to correct genetic diseases.

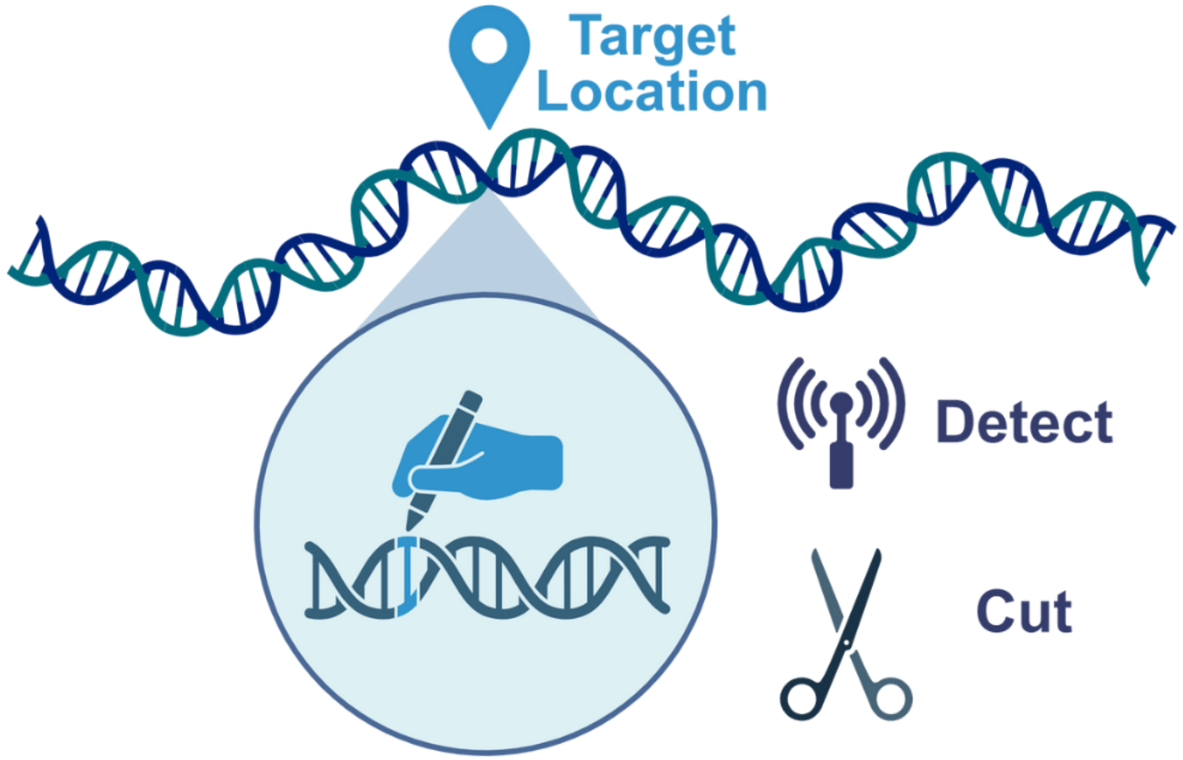
Claudio Mussolino
Institute for Transfusion Medicine and Gene Therapy

Gene Editing - how it works

Gene editing is a highly targeted genetic surgery

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

The DNA holds the instructions to make all proteins in a cell. Typos in these instructions cause genetic diseaes. Molecular scissors allow us to correct these typos and restore the correct instructions.



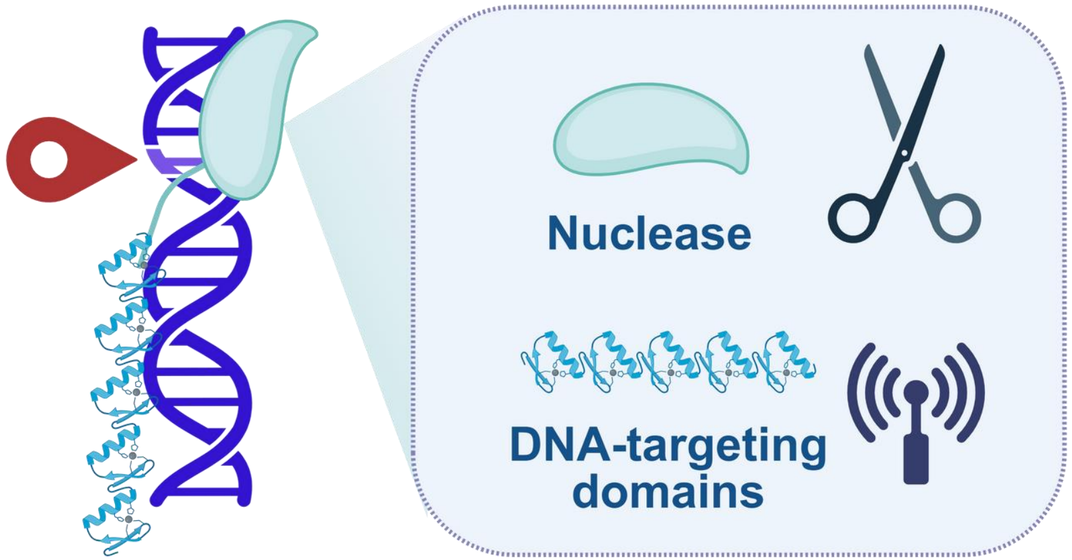
Gene Editing - how it works

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.

Early gene-editing tools were hard to use because changing the DNA target meant rebuilding the whole tool, which was slow and expensive.

CRISPR-Cas9 changed this by making gene editing much easier, faster, and cheaper.



Old molecular scissors

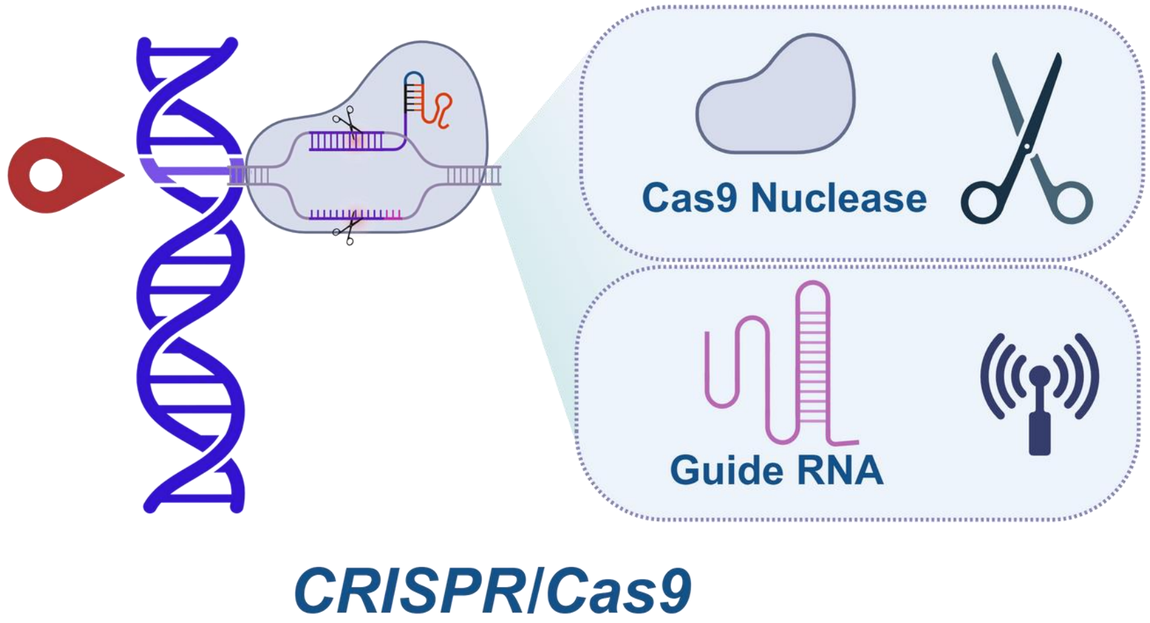
The CRISPR-Cas9 system

CRISPR/Cas9 can easily be targeted to any DNA location

CRISPR/Cas9's guiding system is not part of a protein, but an RNA sequence called a guide RNA (gRNA).

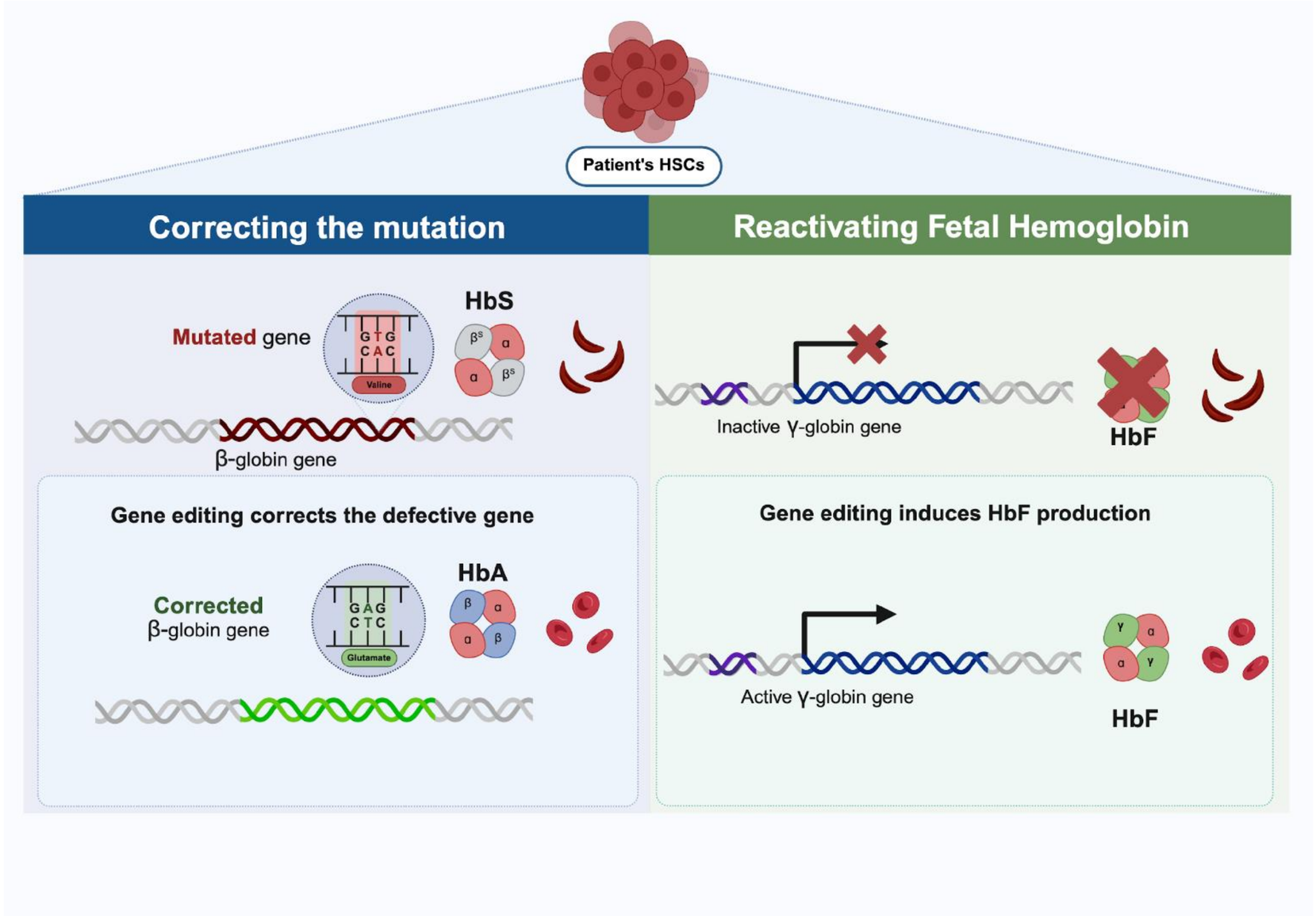
CRISPR works like a modular tool. To target a new gene, scientists don't need to rebuild the whole system, they just change a small guide.

This means new gene-editing tools can be designed in days instead of months.



CRISPR/Cas9

Gene Editing Approaches to Treat Sickle Cell Disease



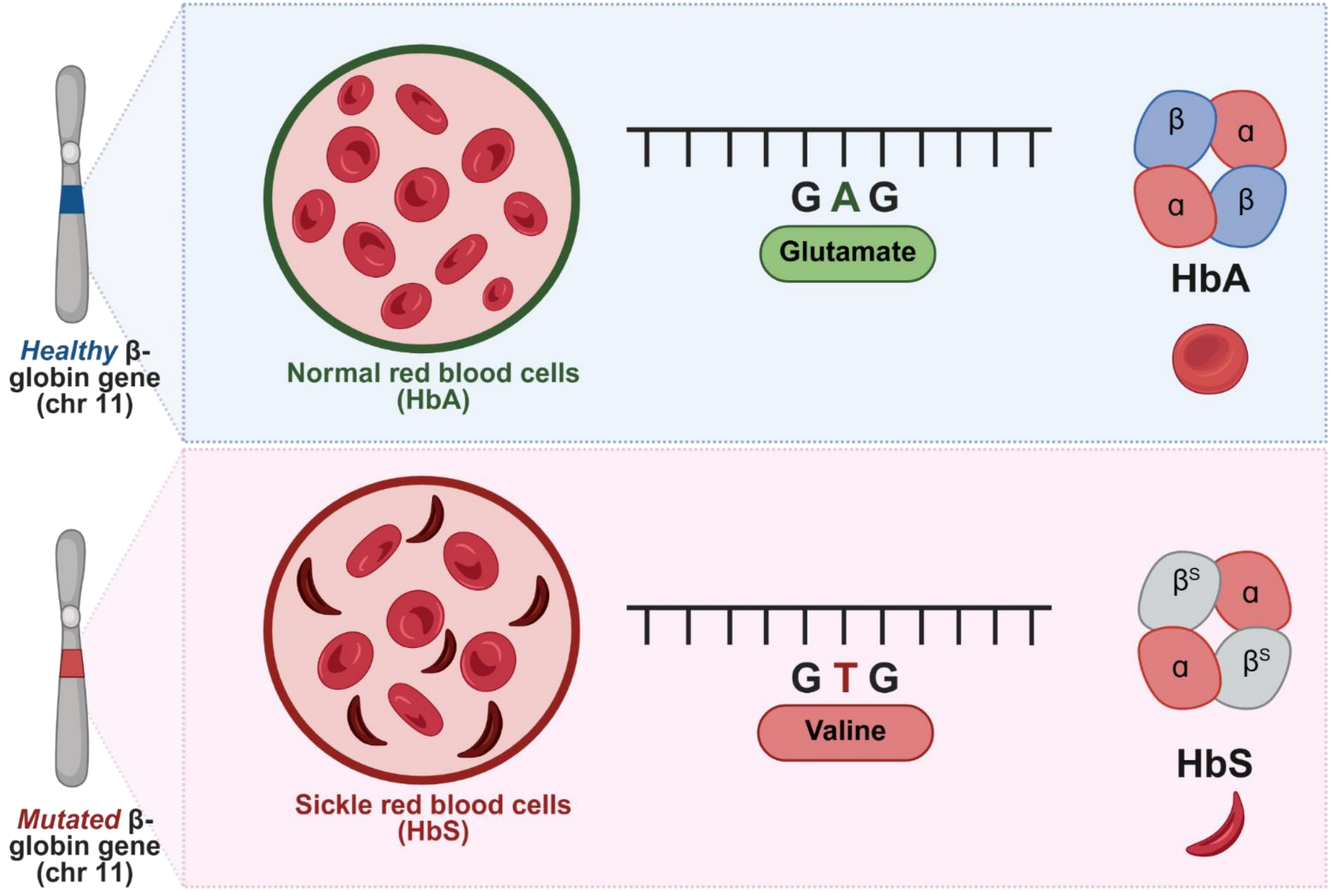
From Gene to Disease: The Mutation Behind Sickle Cell

Mutations in the gene encoding the β-chain of hemoglobin cause Sickle Cell Disease

Mutations are a change in a single letter of the cell's "instruction manual", the DNA.

Mutations can alter the meaning of these instructions. Mutations in the gene encoding the beta-globin chain cause the production of a mutant sickle beta-globin (beta S) that forms HbS instead of HbA. HbS is a different hemoglobin protein that gives red blood cells their sickled shape.

THE FAT CAT ATE THE RAT	Original meaning
THE HAT CAT ATE THE RAT	Wrong meaning



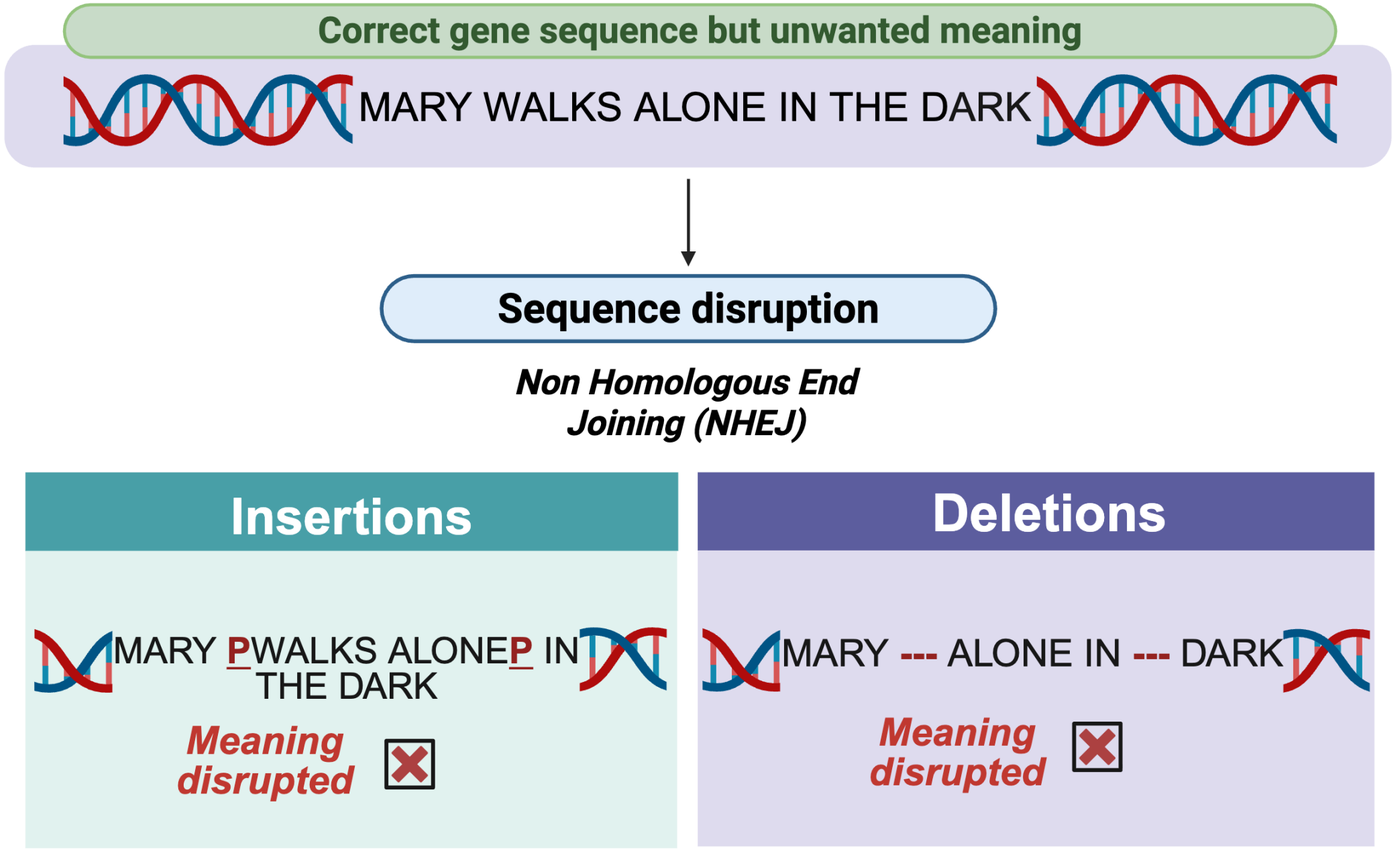
Genetic Surgery - Cutting the DNA

Cas9 cuts the DNA at the appropriate coordinates

Cutting the DNA activates the cells "fire brigades" which try to repair the DNA as quickly as possible.

DNA repair favors quickness over precision, and often introduces changes (mutations). Scientists can exploit this to introduce the desired changes into the DNA.

In most cases, repair introduces (insertions) or removes (deletions) small pieces of DNA, which can greatly alter the instructions encoded within.

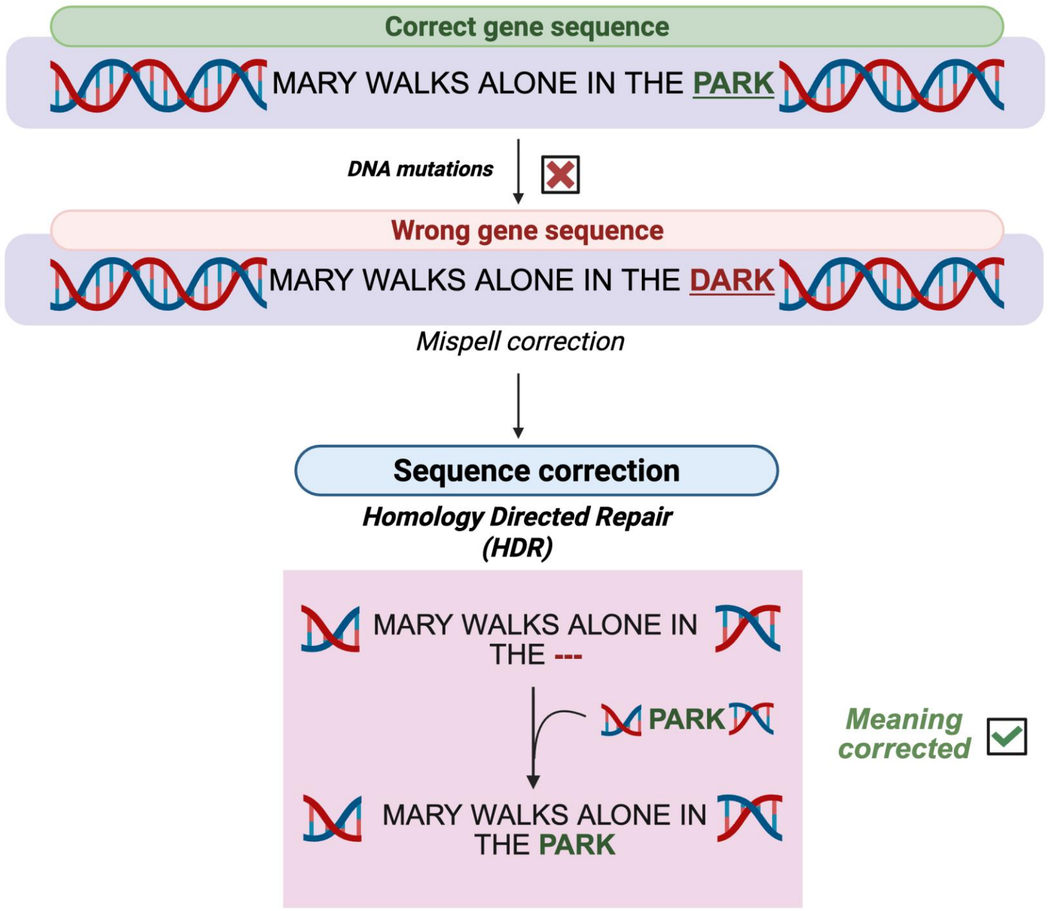


Altering the cell's instructions

Gene editing can purposefully alter the information stored in the DNA

The same way a genetic mutation disrupts the information (*the gene*) on how to make a protein, gene editing can by used to restore a gene and the associated protein's function.

To achieve this, scientists cut the DNA at the site of the mutation using CRISPR/Cas9, and then rely on the cell's own DNA repair mechanisms to introduce a repair template that corrects the mutation.



03

GENE EDITING
OF SICKLE CELL DISEASE

How scientists can use gene editing to modify patient's HSCs and treat SCD.

Annarita Miccio
Imagine Institute

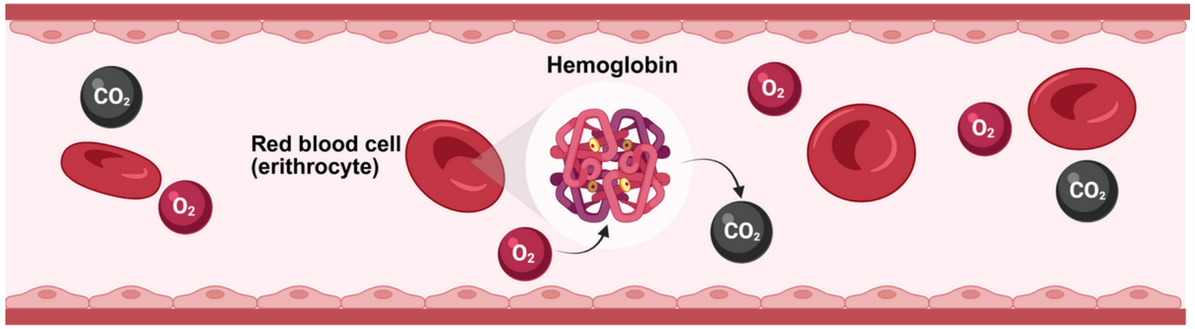
CASGEVY - Gene Editing for SCD

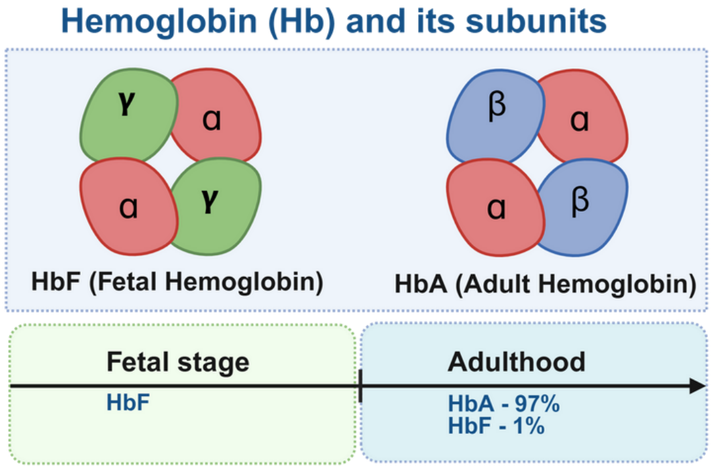
CASGEVY uses CRISPR/Cas9 to reactivate fetal hemoglobin

Fetal hemoglobin is “turned off” after birth and replaced by adult hemoglobin. In SCD patients, fetal hemoglobin production can replace sickle hemoglobin.

CASGEVY achieves this goal by using CRISPR to disrupt BCL11A, a “molecular switch” that normally “turns off” fetal hemoglobin.

This allows the modified hematopoietic stem cells (HSCs) to make new red blood cells able to produce fetal hemoglobin.





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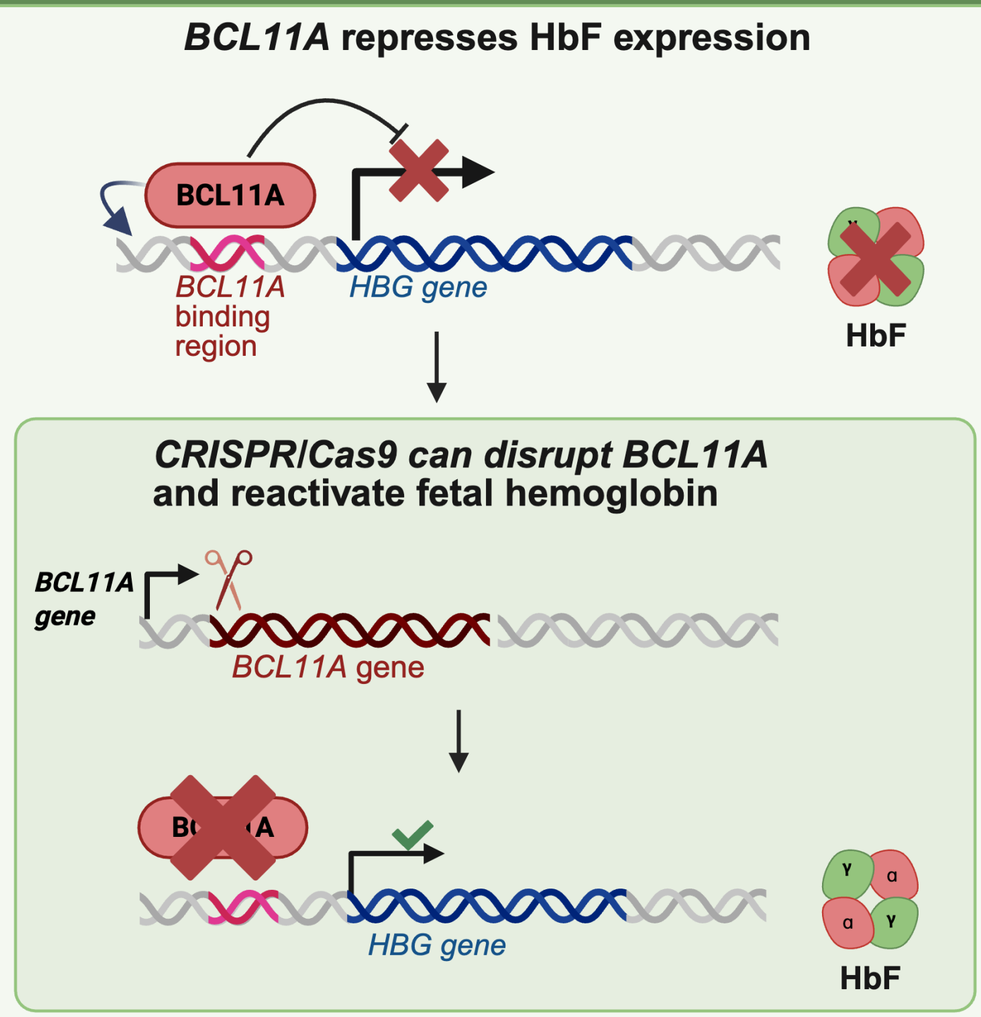
Reactivating fetal Hemoglobin



Casgevy - Gene Editing for SCD

Casgevy disrupts BCL11A only in red blood cells

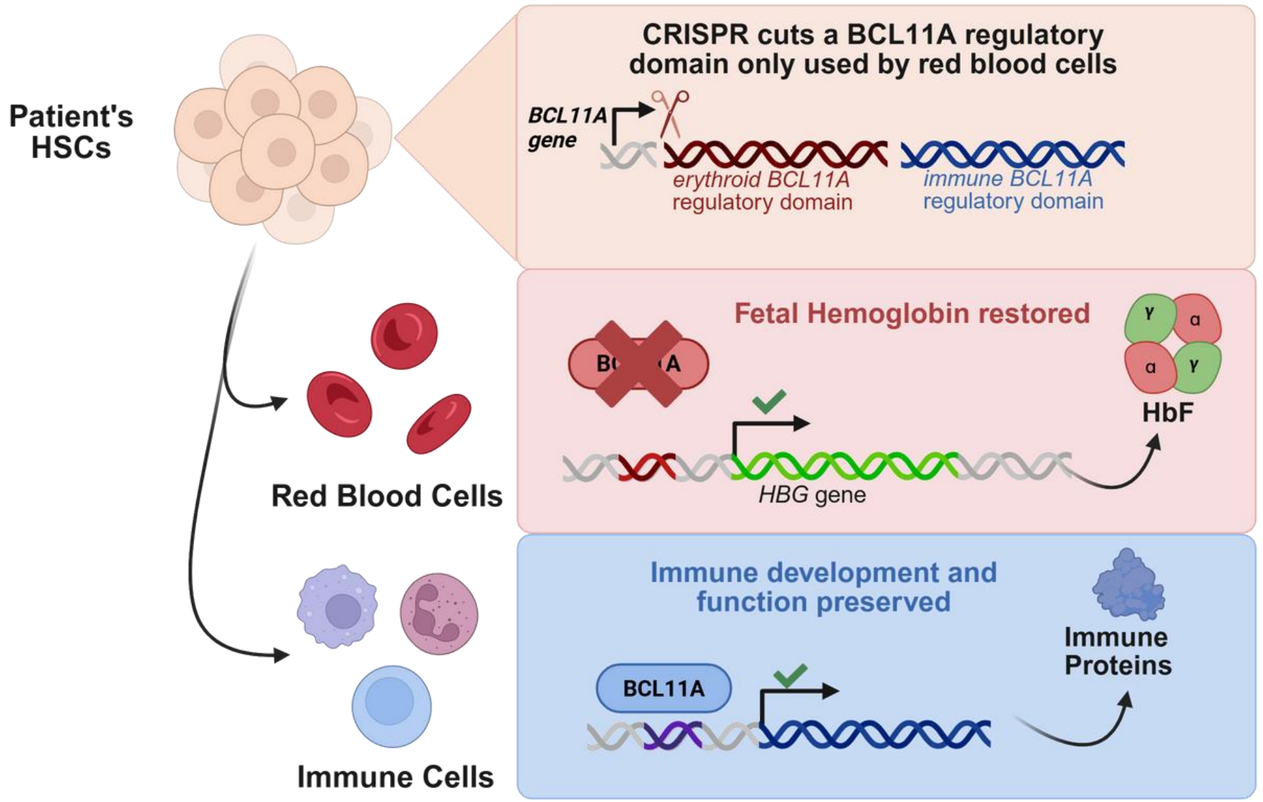
The molecular switch BCL11A is essential in other blood cells.

For this reason, CASGEVY was designed to disrupt BCL11A only in those progenitor cells that will produce red blood cells.

CASGEVY blocks BCL11A by introducing insertions or deletions into the erythroid BCL11A regulatory sequence.

CRISPR/Cas9 is introduced and active in all cells, but its effect is present only in red blood cells.

This ensures the safety of the approach by keeping BCL11A expression intact in all other blood cell types.



04

THE CASGEVY JOURNEY

The Casgevy, the treatment journey, limitations and comparison to other therapies for SCD.

Annarita Miccio
Imagine Institute

The Casgevy Journey

HSCs are mobilized, collected, edited in the lab and reinfused

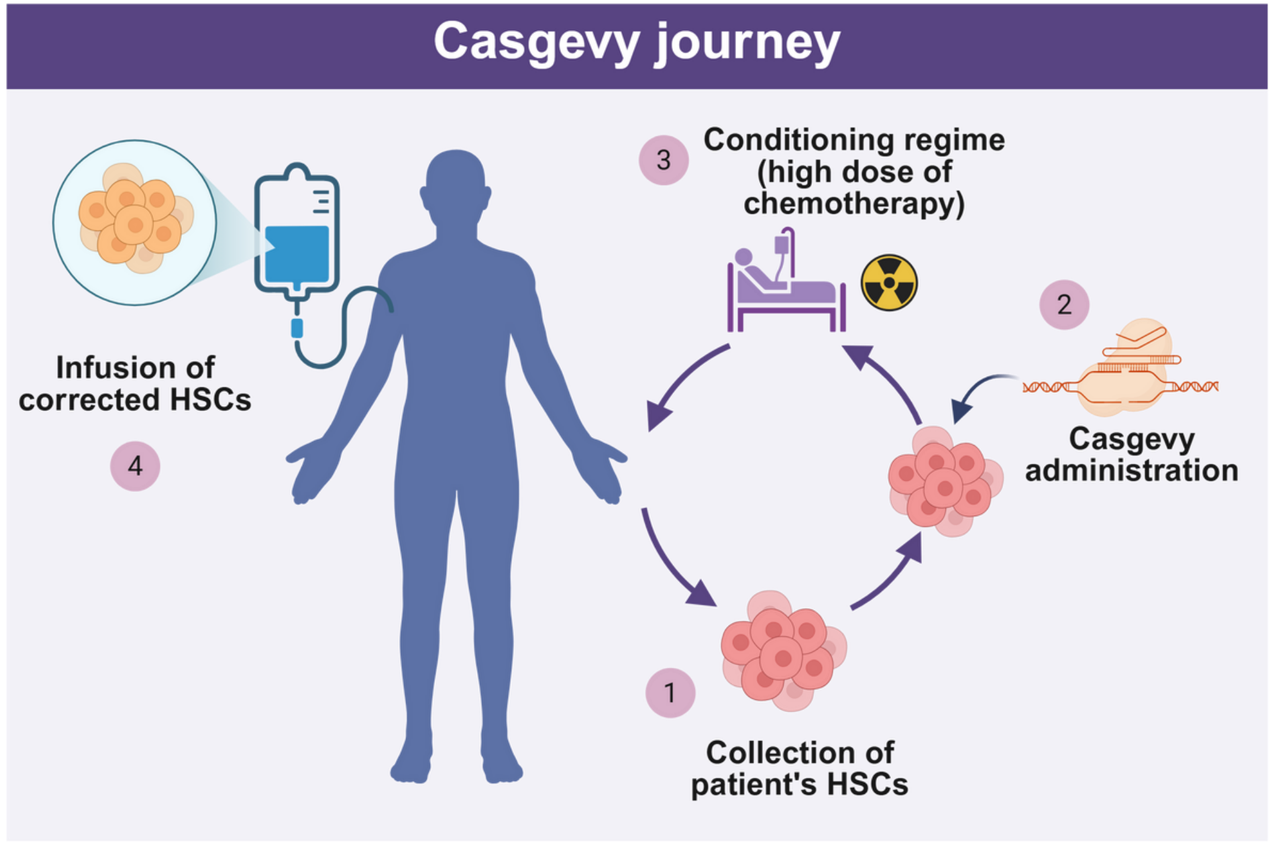
The treatment is indicated for patients 12 years old and older with sickle cell disease or transfusion-dependent β-thalassemia.

Collecting the patient's stem cells takes a few days but multiple collections might be required (up to 5).

Editing, growing, and carefully testing these cells in the lab can take some months.

Once the cells are ready, the patient receives chemotherapy to make room for the edited cells. These cells are then given back through a simple IV infusion.

After treatment, patients stay under close medical monitoring for a few weeks while their immune system recovers.



Conditioning is still required but immunosuppression is not necessary

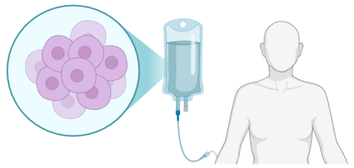
Risks and mitigations of Casgevy treatment

Most risks arise from the HSC transplantation, not the gene editing process

The procedure entails substantial risks that can be managed by medical professionals.

Prognosis after HSC transplantation is usually good.

Positive patient management and general health further improve gene therapy safety and success rates.



Inclusion/exclusion criteria to receive Casgevy

Inclusion/exclusion criteria are essential to ensure the treatment is safe

Patients who fulfill all inclusion criteria participate in a clinical study.

Patients who can't receive Casgevy can still opt for other therapeutic options.

Inclusion criteria

- Age **≥12 years**
- Diagnosed with **SCD with recurrent VOCs** or **transfusion-dependent β-thalassemia.**
- Able to undergo stem-cell mobilization and collection
- Able to undergo **high-dose busulfan conditioning**
- **Negative pregnancy test**. Accepts contraception requirements

Exclusion criteria

- **Active infections** (HIV-1/2, HBV, HCV)
- **Hemodynamic instability** or **medical conditions** making procedures unsafe
- **Inability to collect** enough stem cells
- **Pregnant** or **breastfeeding**
- Contraindications to **busulfan** or required procedures
- **Concomitant** diseases

Gene Addition vs Gene Editing for SCD

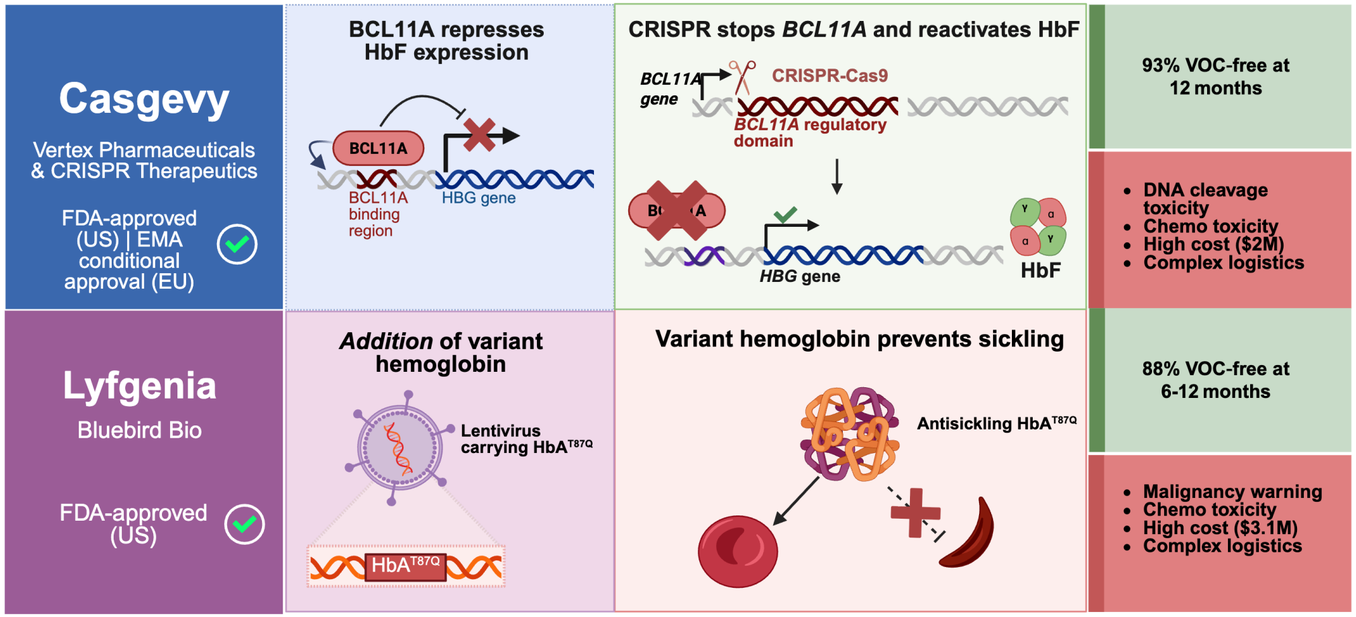
Both Lyfgenia and Casgevy have advantages and limitations

Lyfgenia can induce insertional mutagenesis, Casgevy's DNA cutting can cause toxicity in the edited cells

In both cases, cost and logistics remain important limitations for widespread application.

Both FDA-approved therapies have, so far, only benefitted a limited number of patients. Reducing costs and simplifying logistics could be essential for larger clinical success.

In addition, other, novel approaches that aim to address Casgevy's limitations are being developed.



05

CHALLENGES OF GENE EDITING

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

Mario Amendola
Genethon

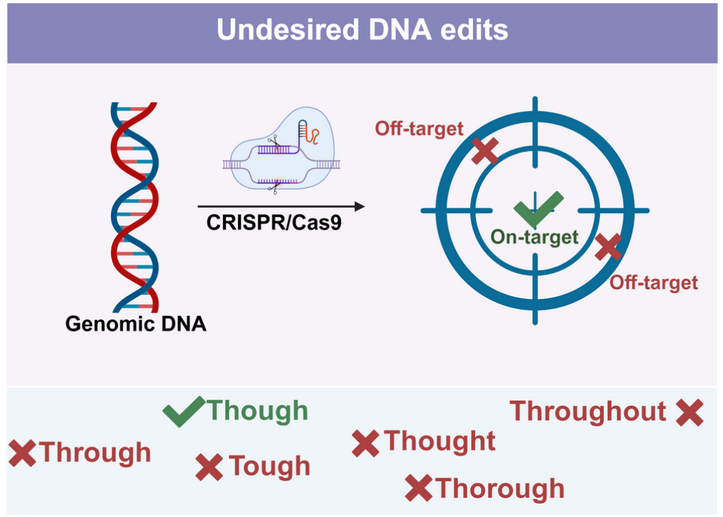
Challenges of gene editing

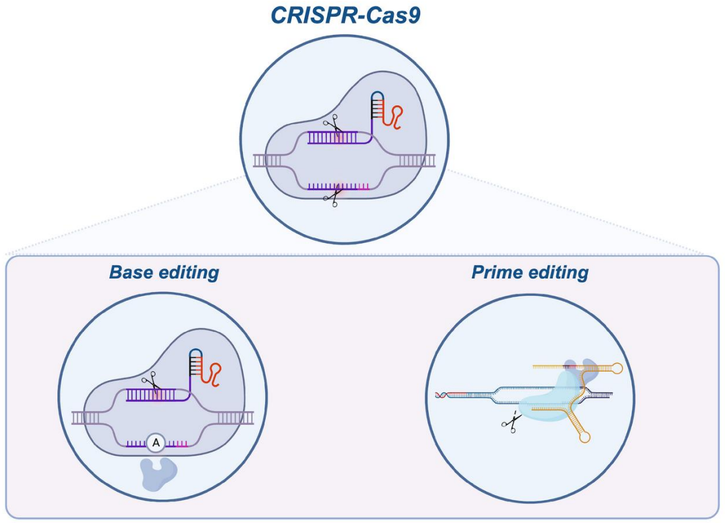
Gene editing carries some important challenges

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

Overcoming such challenges will be essential to ensure that gene editing therapies for SCD become safer and more effective.

New technologies that build upon CRISPR/Cas9 have solved some of these issues, but ongoing research aims to address any potential concerns to make gene editing safe to all.





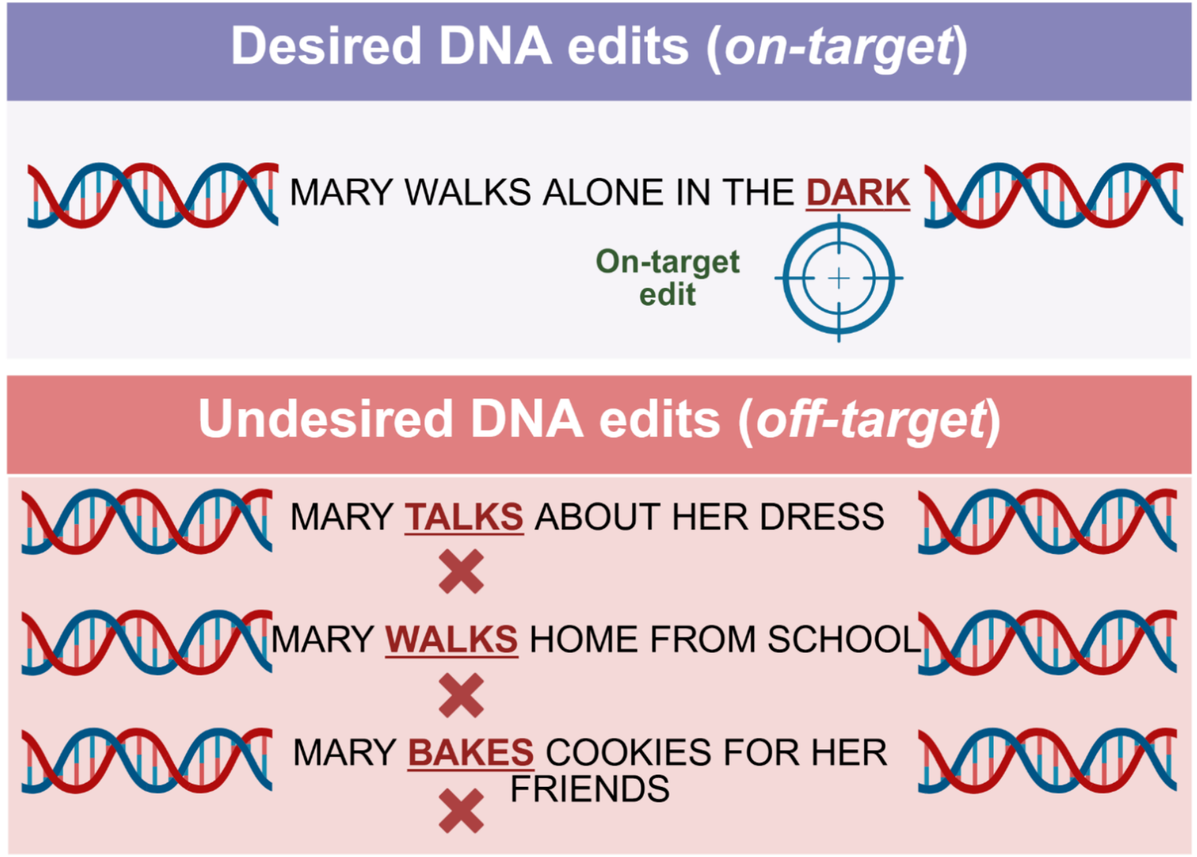
Challenges of gene editing - undesired edits

CRISPR/Cas9 can recognize DNA sequences similar to its target

This can lead to Cas9 cutting the DNA in other undesired locations, known as off-target editing.

While good design can reduce the number and frequency of off-targets, rare, unexpected off-targets could have detrimental effects.

New CRISPR variants have reduced off-targets and can be used more safely. However, the risk still exists and needs to be monitored closely through deep analysis of the cell products that will be infused into patients.



Challenges of gene editing - DNA breaks

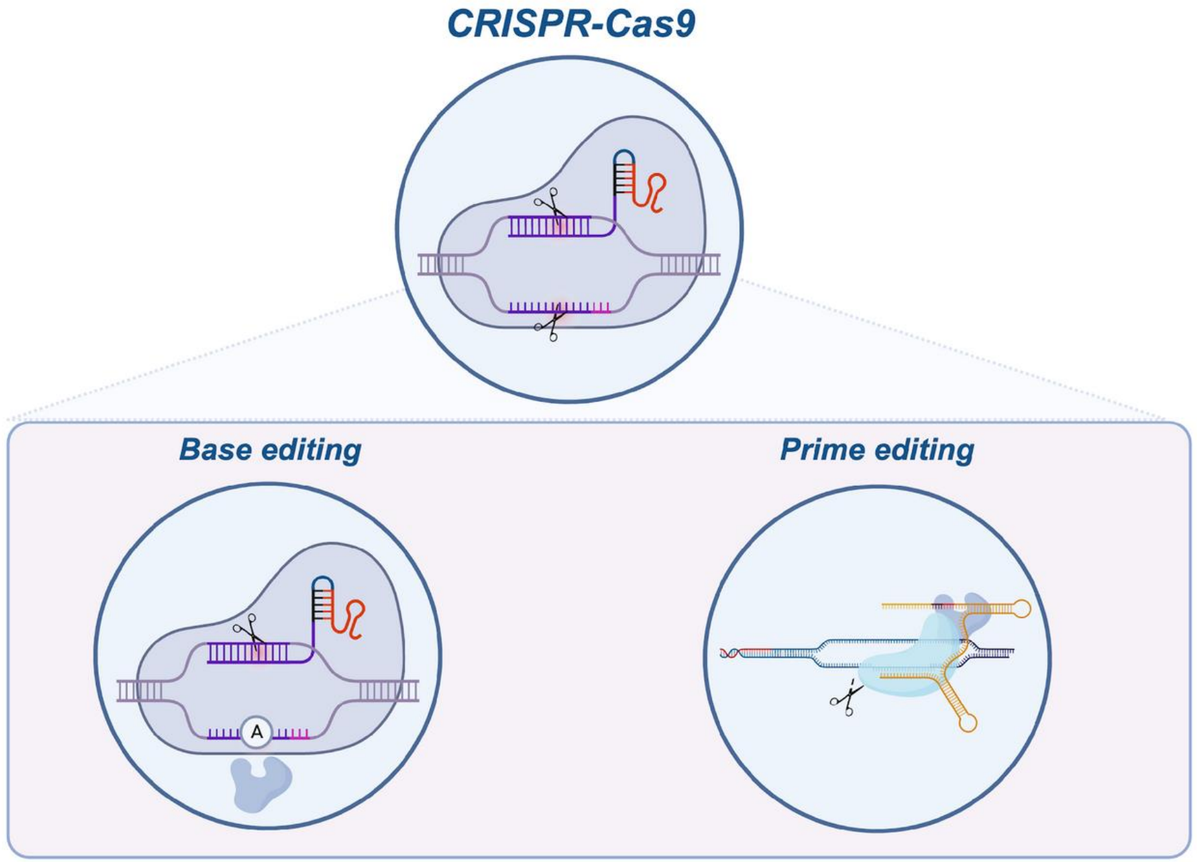
Breaking the DNA can lead to undesired effects

Cells can react badly to their DNA being cut, leading to cell death and reducing the effectiveness of gene editing.

Cells can also have worse health and thus fail to implant after being infused.

Cells such as HSCs are sensitive and hard to obtain, so ensuring their survival and engraftment is essential for successful gene editing approaches for SCD.

New CRISPR-based technologies that can introduce genetic changes with minimal DNA cutting represent a significant improvement in this field.

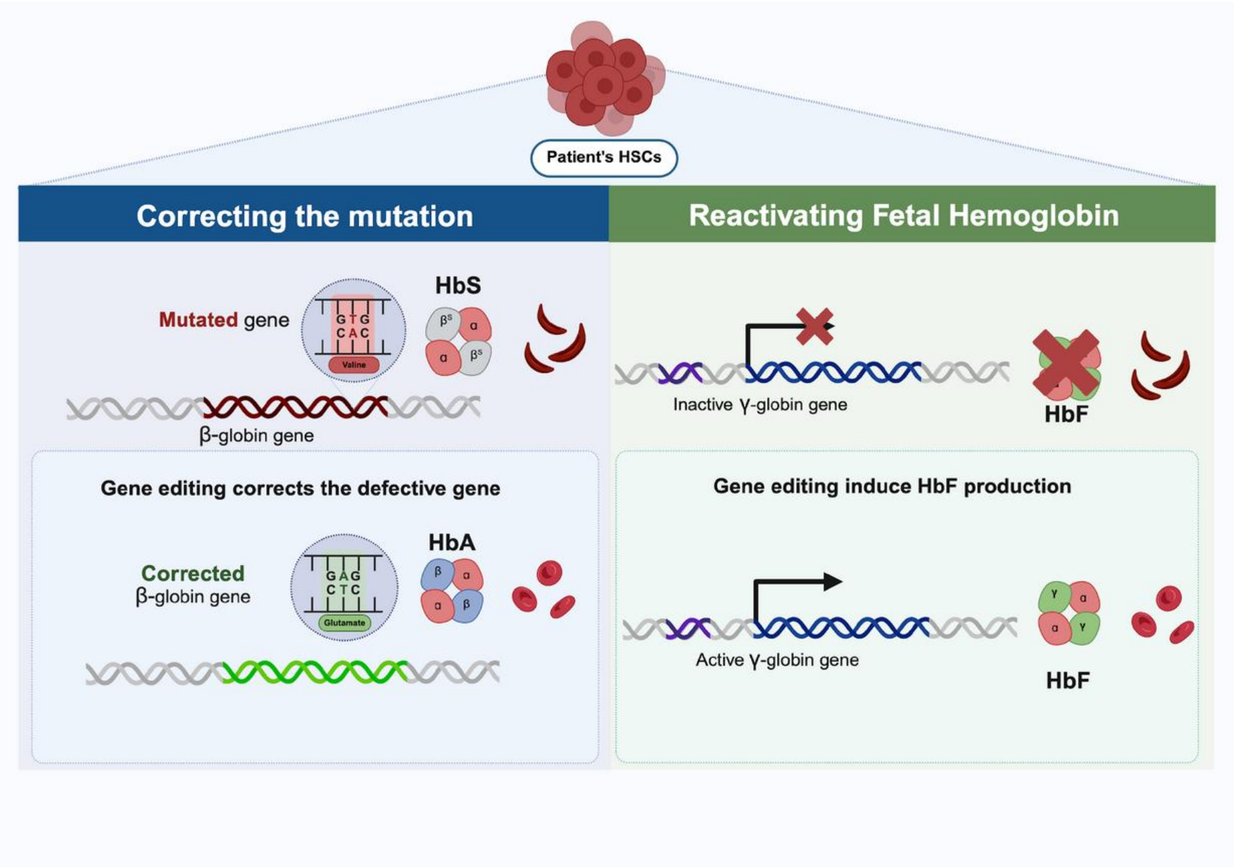


Challenges of gene editing - HDR efficiency

Correcting SCD-causing genetic mutations is feasible but has, so far, not been effective enough.

Homology-based approaches have widely been used to correct genetic mutations. They use a homologous template to guide the cell's repair machinery to introduce the desired corrections.

Unfortunately, HDR approaches to correct SCD have generally been unsuccessful due to a combination of low efficiency in HSCs and high toxicity caused by the homologous template



Future Webinars

Session 4: Genome Editing: CRISPR/Cas9 Advanced Tools and SCD – using new methods
Marcello Maresca and Annarita Miccio
April 2026

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

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

Session 7: Regulatory path to the clinic
Annarita Miccio
September 2026

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