Gene Therapy for SCD: Webinar program for patients

webinar

PATIENTS

Session 2: Basics of Gene Therapy with Lentiviral Vectors

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Imagine Institute / San Raffaele University and SR-Tiget

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EDITSCD

ERN | EuroBloodNet

Disclosure for conflict of interest

Annarita Miccio: No conflict of interest

Giuliana Ferrari: No conflict of interest

What we'll talk about today

1

Recap of the previous webinar
An introduction to gene therapy.

2

HSC transplantation in SCD therapy
What HSCs are and how they can be used to treat SCD. Overview of the transplantation process, risks and mitigations.

3

HSCs for gene therapy of SCD
How scientists can use viral vectors to modify HSCs and treat SCD.

4

Current gene therapies for SCD
Gene therapy approaches to treat SCD. Advantages and limitations of new therapeutic approaches.

5

Introduction to future webinars
We'll introduce the topics of the next webinars in this 7-part series.

01

RECAP OF THE PREVIOUS WEBINAR

An introduction to gene therapy.

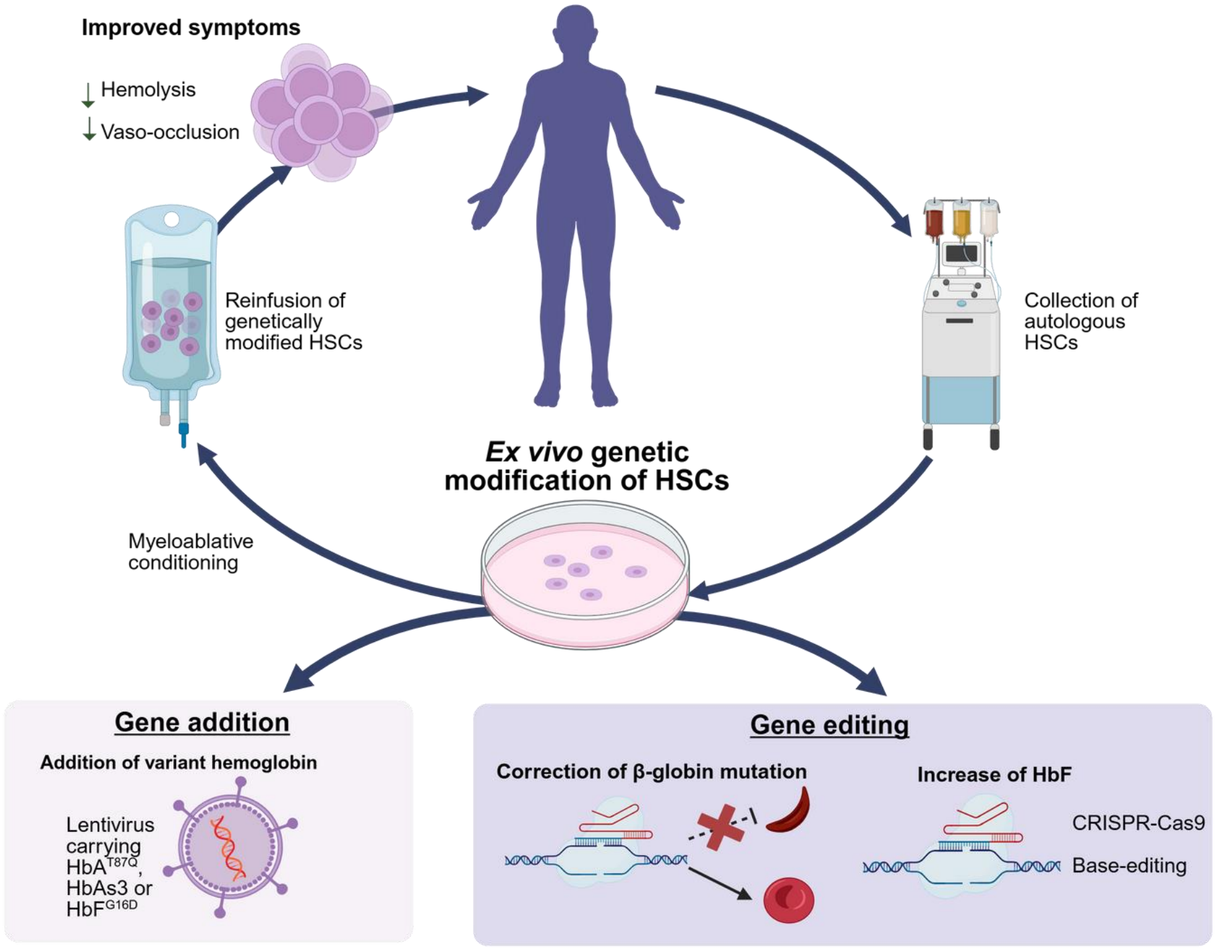
Annarita Miccio
Imagine Institute

Gene Therapy of Sickle Cell Disease

Gene therapy using Hematopoietic Stem Cells (HSCs) can provide a long-term cure for SCD

Different gene therapy approaches aim to treat Sickle Cell Disease by modifying HSCs in different ways to replace the missing hemoglobin.

- Gene Addition provides a healthy copy of the gene.
- Gene Correction repairs the mutation directly.
- Gene Reactivation awakes dormant genes.



02

HSC TRANSPLANTATION IN SCD THERAPY

What HSCs are and how they can be used to treat Sickle Cell Disease.

Overview of the transplantation process, risks and mitigations.

Annarita Miccio
Imagine Institute

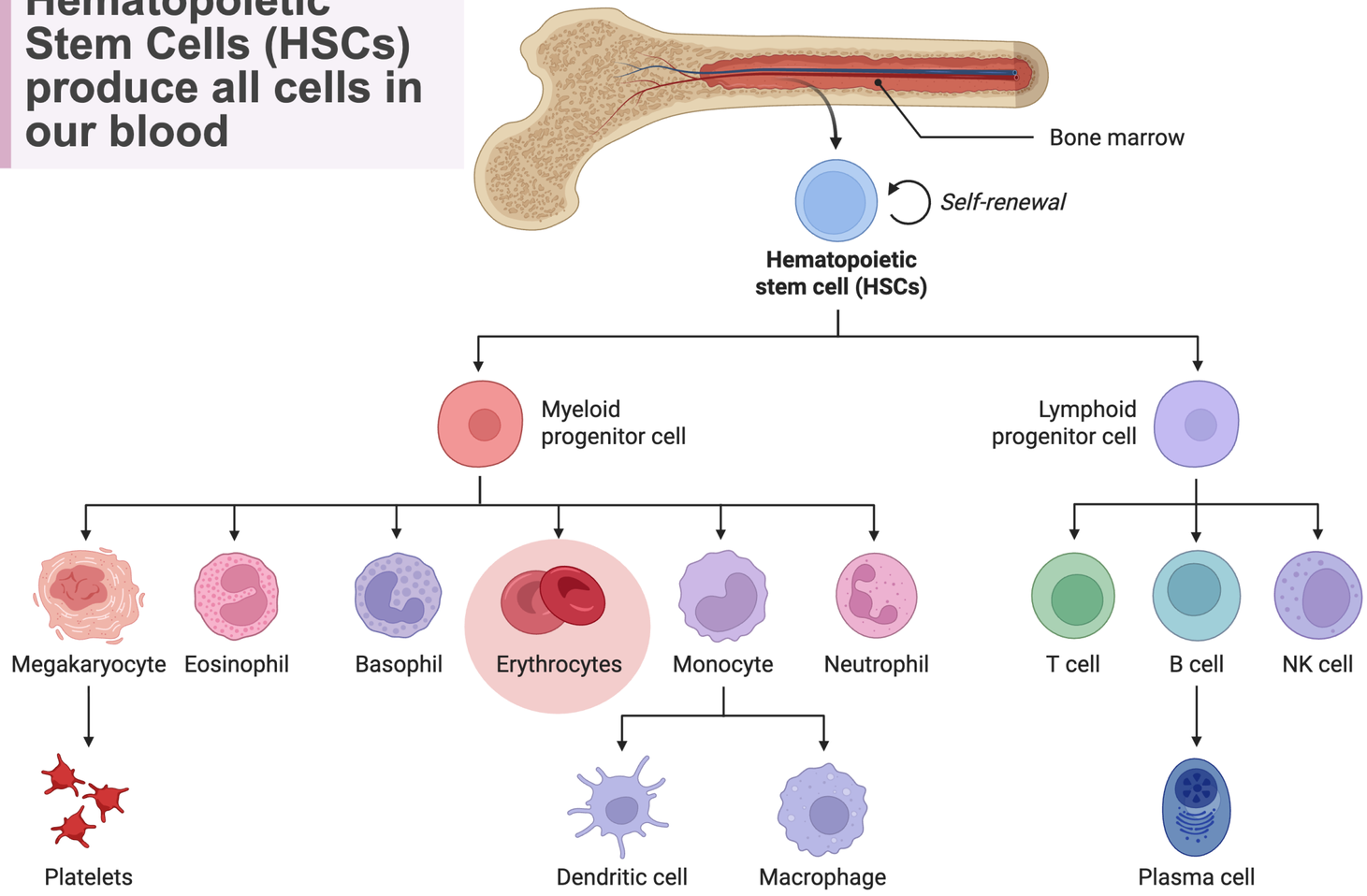
HSCs and their role in Gene Therapy

HSCs are found in the bone marrow.

HSCs can simultaneously self-renew and produce new blood cells, making them an excellent vessel for gene therapy.

The bone marrow produces and renews red blood cells, platelets and all the types of cells of our immune system.

Hematopoietic Stem Cells (HSCs) produce all cells in our blood

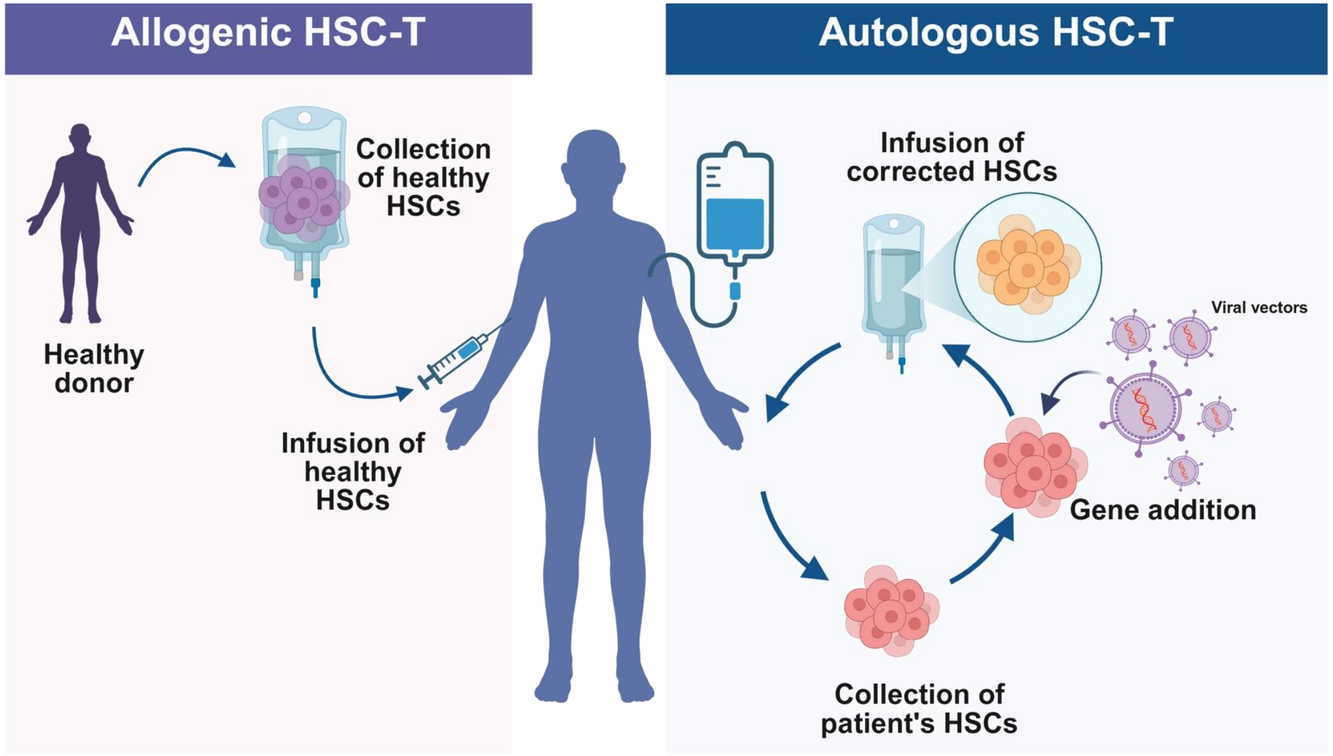


HSC Transplantation to treat blood disorders

Receiving HSCs from a healthy donor offers a long-lasting treatment

Allogeneic HSC transplantation was first proposed in the 1990s and has been used to treat several genetic blood disorders.

As an alternative, the patient's own HSCs can be modified and corrected before re-implantation, a process known as autologous transplantation.

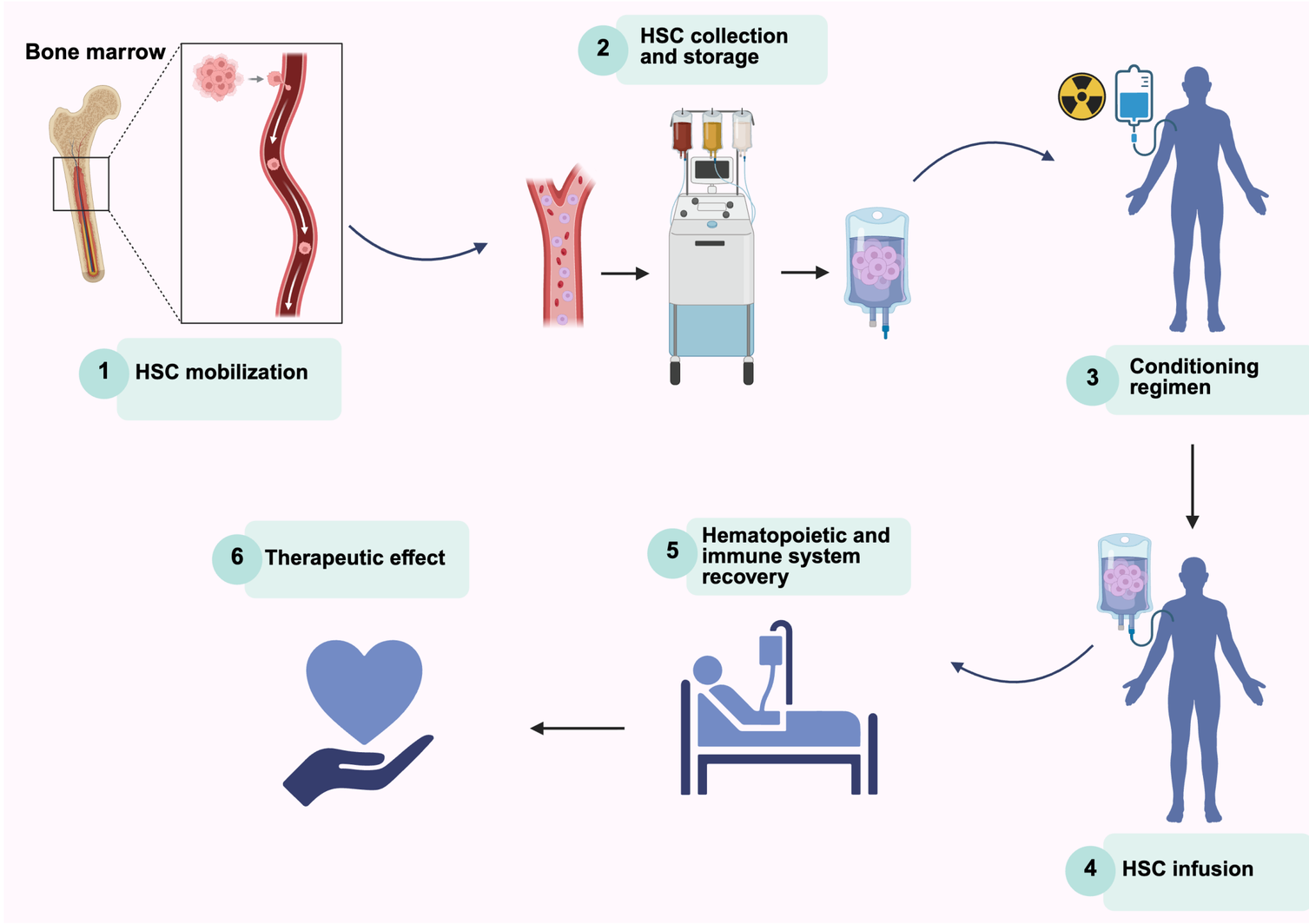


HSC Transplantation is a serious medical procedure

It requires a hospital stay and has inherent risks

Conditioning/immunosuppression and HSC infusion are physically demanding procedures. The patient and their immune system require a recovery period.

When successful, HSC transplantation is a one-time procedure providing long-term therapeutic benefits.



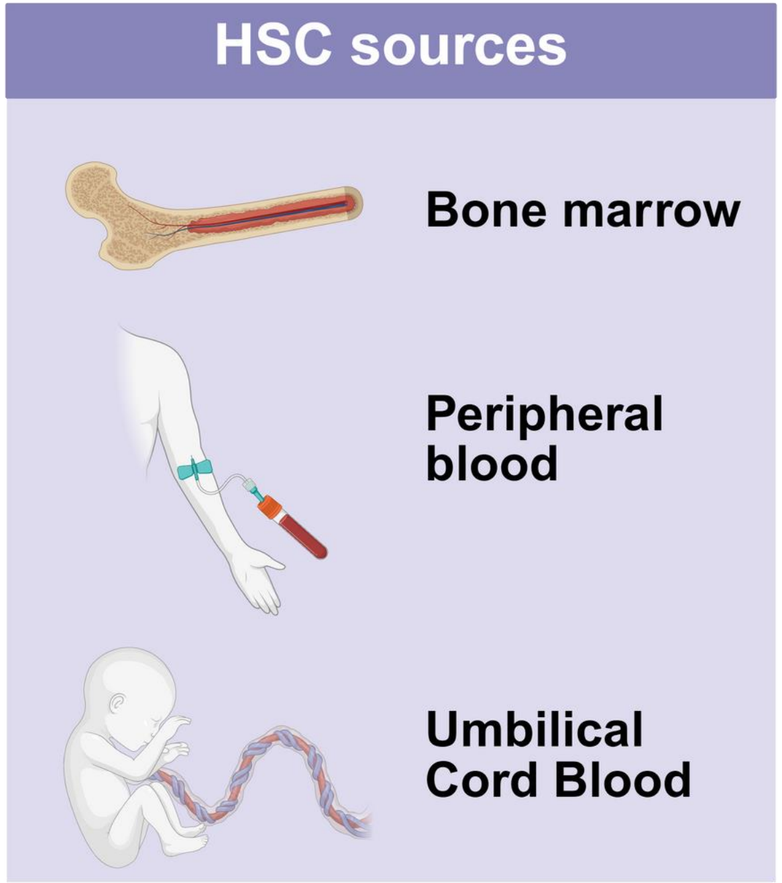
Sources of HSCs for Transplantation

HSCs can be obtained from various sources

Primary HSCs are most commonly mobilized from the bone marrow using drugs and collected from the peripheral blood.

HSCs were initially obtained from the bone marrow, but the process was invasive and painful. New drugs allow mobilization of HSCs to the bloodstream, making peripheral blood collection an easier and safer option.

Umbilical cord blood can be collected during pregnancy and stored for later use. In some cases, it has been used to treat a sick sibling.



Conditioning for HSC Transplantation

Conditioning makes space for transplanted HSCs in the bone marrow

It removes disease-carrying HSCs from the bone marrow so they can be replaced by therapeutic HSCs.

MAC is used in children or young adults.

RIC, and NMA are less strong treatment s(e.g., using low doses of chemotherapy.

NMA can be considered in weaker or older patients.

Type	Pros	Cons
Myelo-Ablative Conditioning (MAC)	Complete ablation of the recipient's bone marrow Highly effective engraftment	High toxicity due to high dose regimens Only adept to young adults or children
Reduced Intensity Conditioning (RIC)	Lower doses reduce toxicity Adapt to patients subjected to particular treatments	Higher risk of failed engraftment
Non-Myelo-Ablative Conditioning (NMA)	Lower risks of infection and transplant-related mortality Adapt to older patients	Least intensive regimen, only partial destruction of the recipient's HSCs

Allogeneic HSC transplantation requires also immunosuppression to remove patients' immune cells that can attack the donor cells and cause graft failure

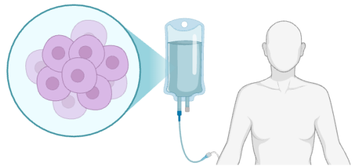
Risks and mitigations of HSC transplantation

HSC transplantation risks are well known and mitigated

The procedure entails substantial risks, but those ca managed by good medical professionals.

Prognosis after HSC transplantation is usually good.

Positive patient management and general health further improve HSCT transplantation safety and success rates.



Allogeneic HSC Transplantation

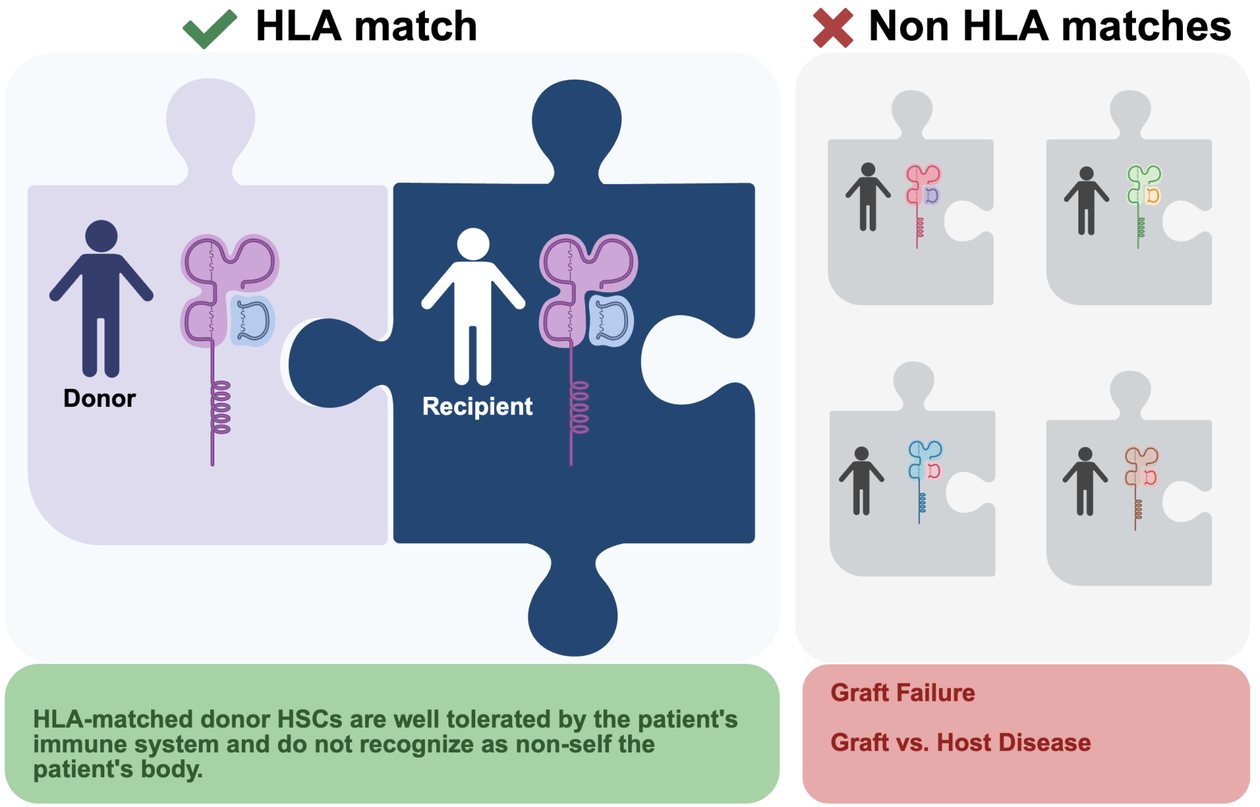
Immune compatilibity is essential for allogeneic HSC transplantation

Only cells from an HLA-matched donor (usually a relative) can be used without causing immune compatibility issues.

Human leukocyte antigens (HLA) are proteins on the surface of white blood cells that recognize foreign pathogens.

In Graft failure, the the transplanted donor cells can be recognized as non-self and rejected and eliminated by the host/patient immune system.

In Graft versus Host Disease, the transplanted donor HSCs produce a new immune system that recognizes the body as an enemy, attacking it and causing severe complications.



03

HSCs FOR GENE THERAPY OF SICKLE CELL DISEASE

How scientists can use viral vectors to modify a patient's HSCs and treat SCD.

Giuliana Ferrari
San Raffaele University and SR-Tiget

Autologous HSC Transplantation

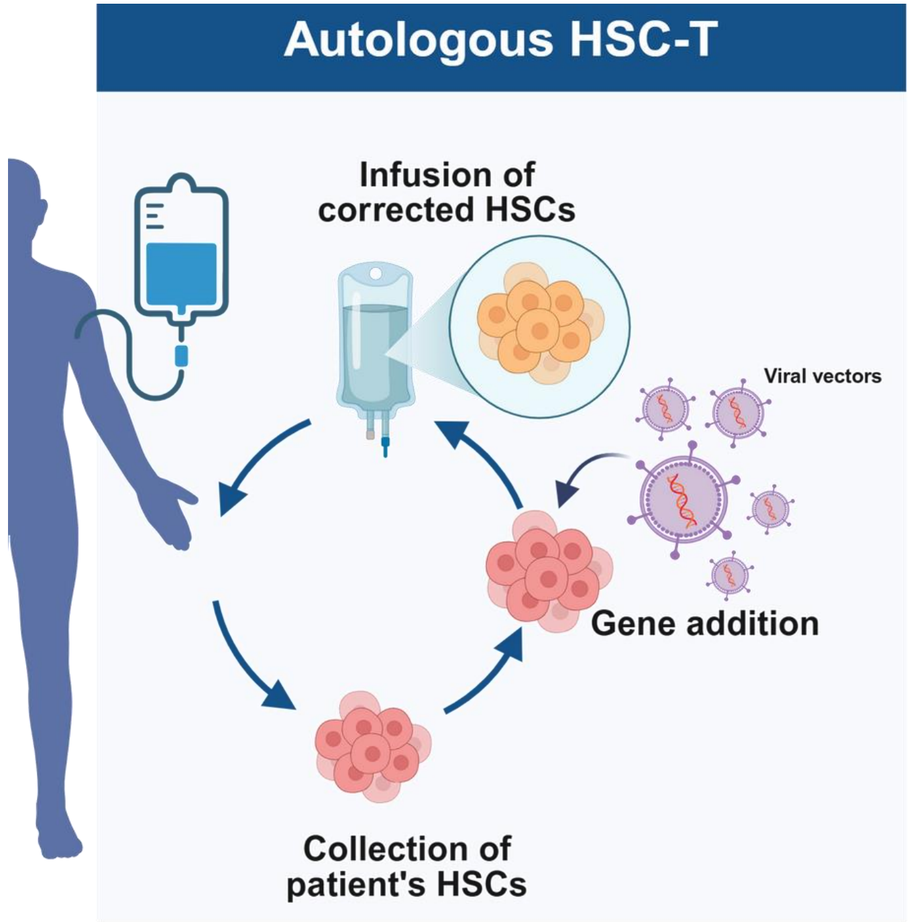
Transplanting the patient's own HSCs avoids compatibility issues

However, we first need to fix the patient's HSCs so that they can produce healthy red blood cells.

The objective is to equip the patient's HSCs with the right instructions to make the missing protein.

Different methods to modify the patient's HSCs have been explored, but lentiviral vectors are the most common.

Once corrected, the patient's HSCs can be re-implanted for a fully compatible treatment.

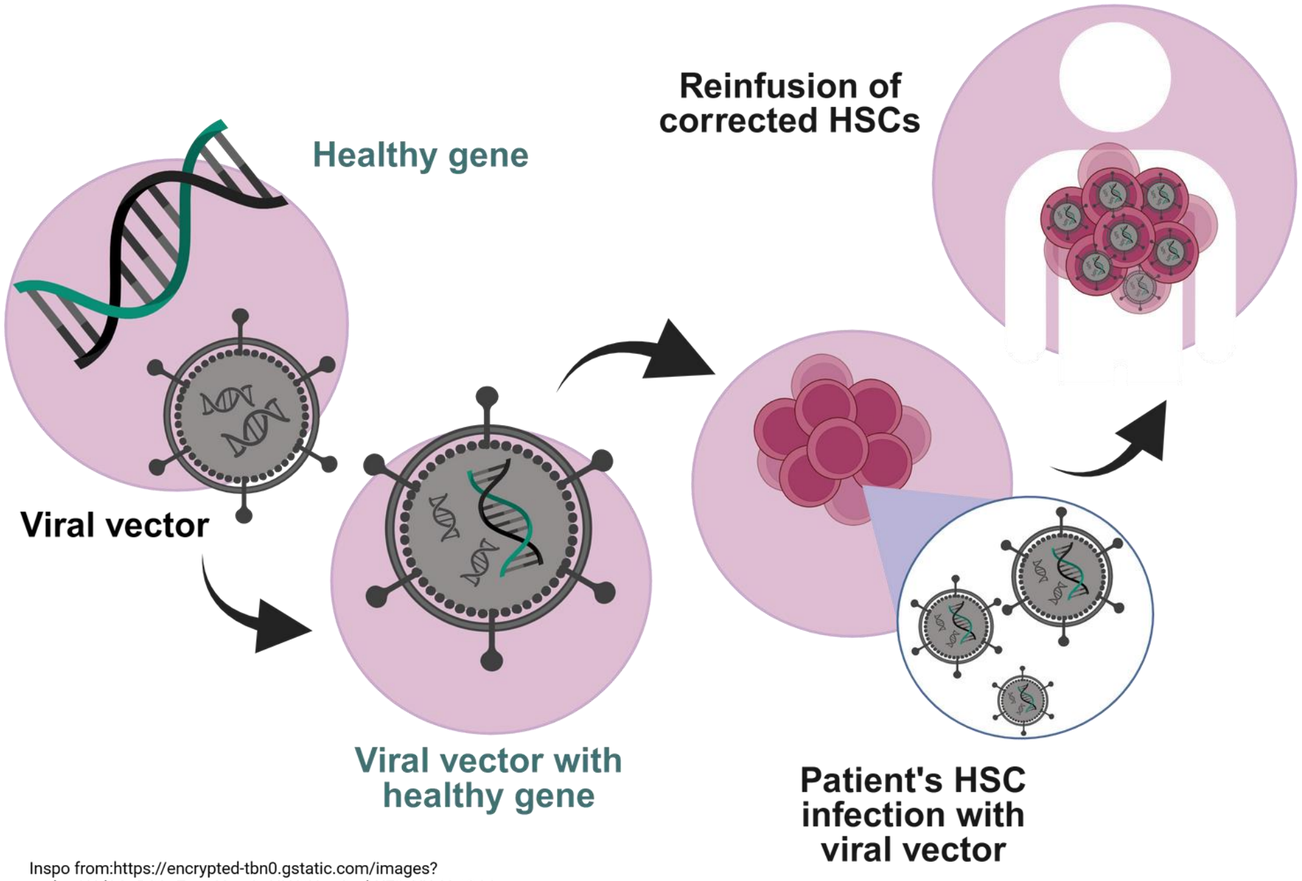


Conditioning (MAC/RIC) is still required but immunosuppression is not necessary

Modifying HSCs using viral vectors

Gene therapy allows us to modify the patient's HSCs

By providing a correct copy of the mutated gene, we can fix the patient's HSCs and re-implant them, avoiding compatibility issues.



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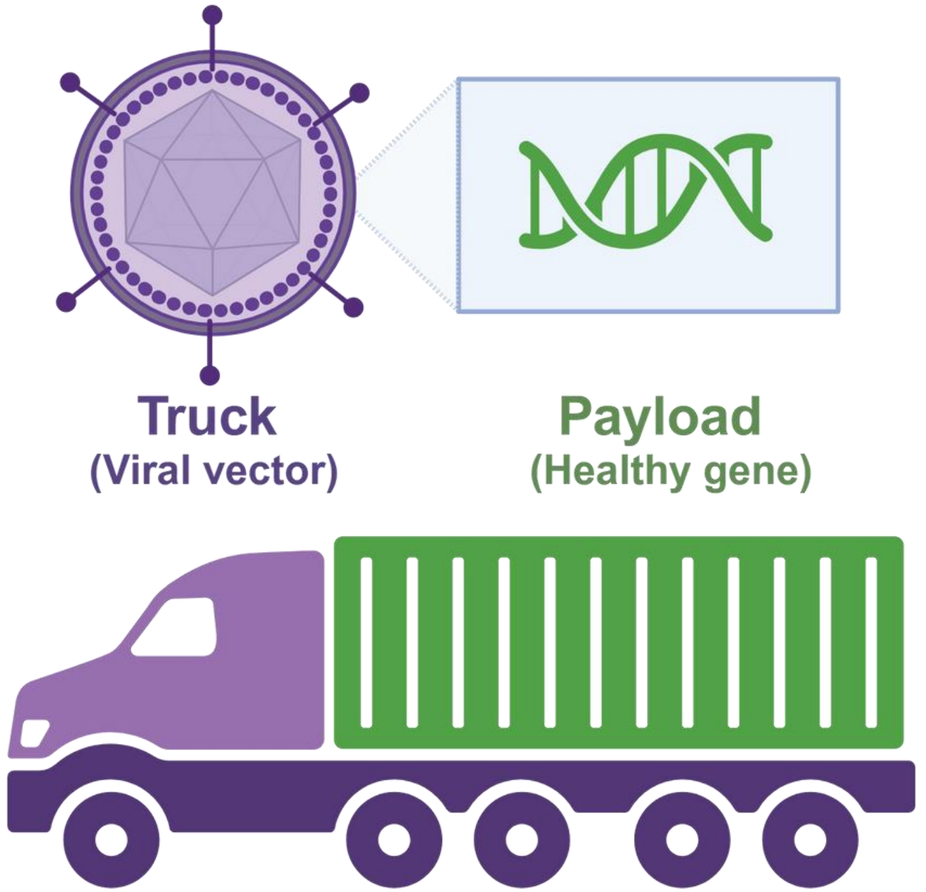
Viral vectors for gene therapy in HSCs

Viral vectors are genetic delivery trucks

Viruses evolved to deliver genetic material into our cells, a skill that scientists can harness by turning viruses into DNA delivery vectors.

Viral vectors are engineered viruses that only carry a therapeutic genetic sequence. The therapeutic gene is often a correct copy of the faulty gene, giving cells the instructions to produce the missing protein.

Using viral vectors, scientists can modify a patients HSCs before re-implanting them.

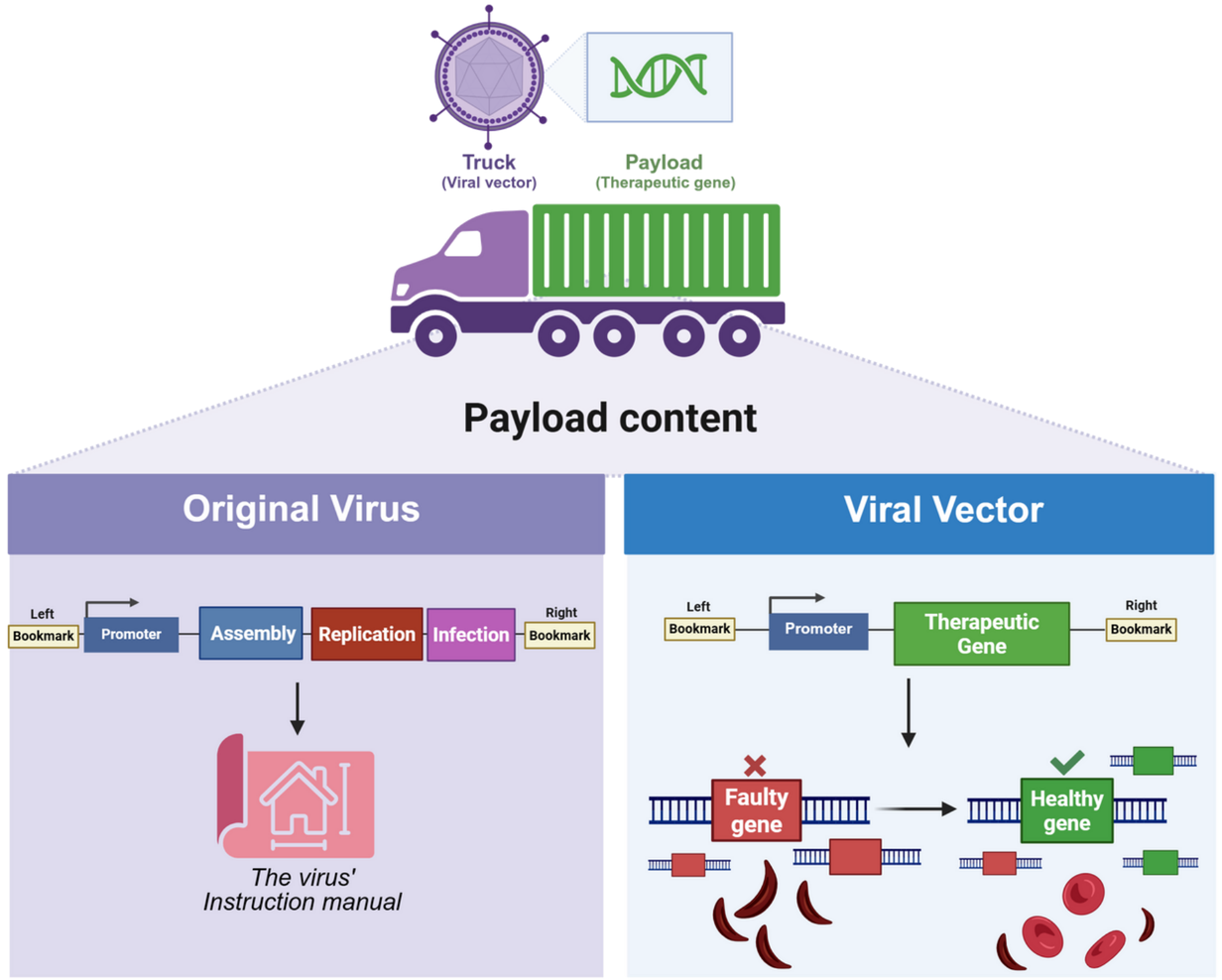


Viral vectors have complex cargoes

Viral vectors carry a therapeutic gene into the target cells

The therapeutic gene is often a correct copy of the faulty gene, giving cells the instructions to produce the missing protein.

A viral vector doesn't carry the genes necessary to produce new viruses, but instead carries a healthy copy of the faulty gene to replace the missing function.



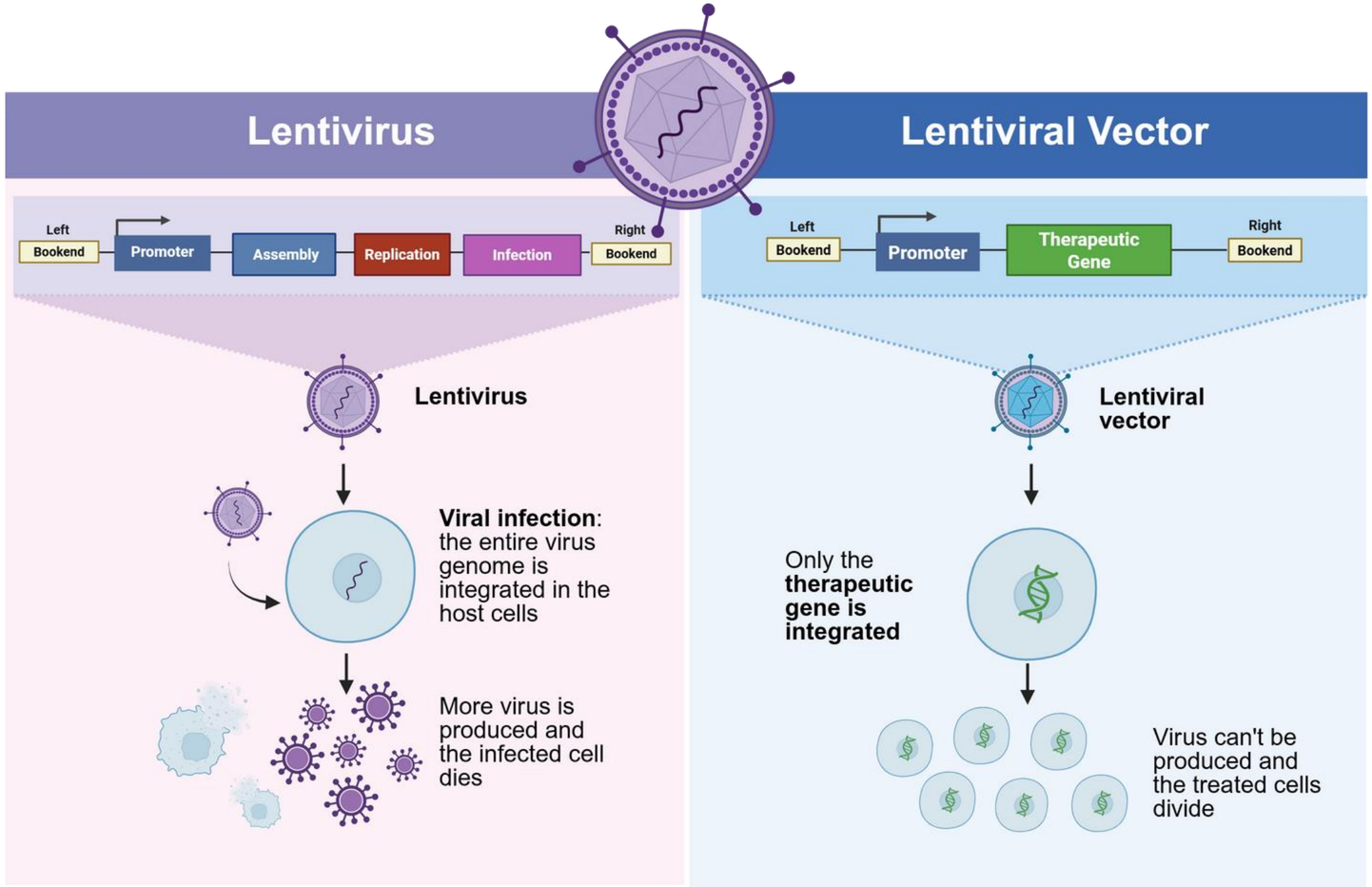
Lentiviral vectors are derived from the HIV virus

Viral vectors carry a therapeutic gene into the target cells

Lentiviruses insert their genetic information, packaged between genetic "bookends", into a cell's DNA.

Lentiviral vectors only carry the therapeutic genetic sequences between their "bookends". Extra information to produce viruses is provided during vector production, but the vector doesn't carry it.

Thus, the vector can only integrate the genetic sequences into the cells, and can't produce more viruses.



04

CURRENT GENE THERAPIES FOR SICKLE CELL DISEASE

Gene therapy by gene addition to treat SCD. Advantages and limitations of new therapeutic approaches.

Giuliana Ferrari
San Raffaele University and SR-Tiget

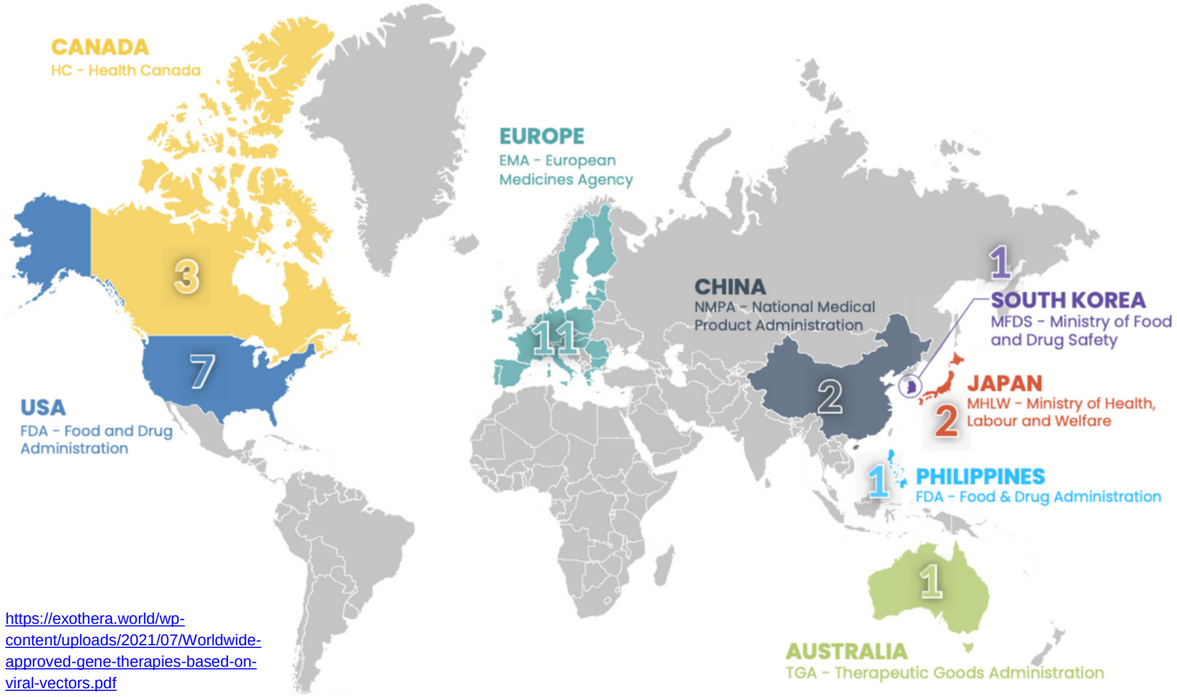
Lentivirus Gene Therapy worlwide

Lentivirus-mediated gene therapy for blood disorders is a reality

Lentiviral vector-based gene therapy has been investigated for more than two decades and, to date, a number of therapies have become available.

While not always commercially available in the EU, they can still be accessed via clinical trials. Their approval underlies the efficacy of such approaches.

It is important to note that Lentiviral vectors have also been extensively used in Cancer Immunotherapy to generate CAR-T cells, further proving that lentiviral vectors are valuable tools for gene therapy.



https://exothera.world/wp-content/uploads/2021/07/Worldwide-approved-gene-therapies-based-on-viral-vectors.pdf

Zynteglo - Bluebird Bio

Ex-vivo autologous CD34+ cells

β-thalassemia

June 3, 2019

Skysona - Elivaldogene Autotemcel

Ex-vivo autologous CD34+ cells

Cerebral adrenoleukodystrophy (CALD)

Approved in these areas

September 16, 2022

Reviewed in these areas

Libmeldy - Orchard Therapeutic

Ex-vivo autologous CD34+ cells

Early-onset Metachromatic leukodystrophy

Approved in these areas

December 22, 2020

Strimvelis - GlaxoSmithKline

Ex-vivo autologous CD34+ cells

Adenosine deaminase deficiency (ADA-SCID)

Approved in these areas

May 25, 2016

webinar

Gene Therapy for SCD - Lyfgenia

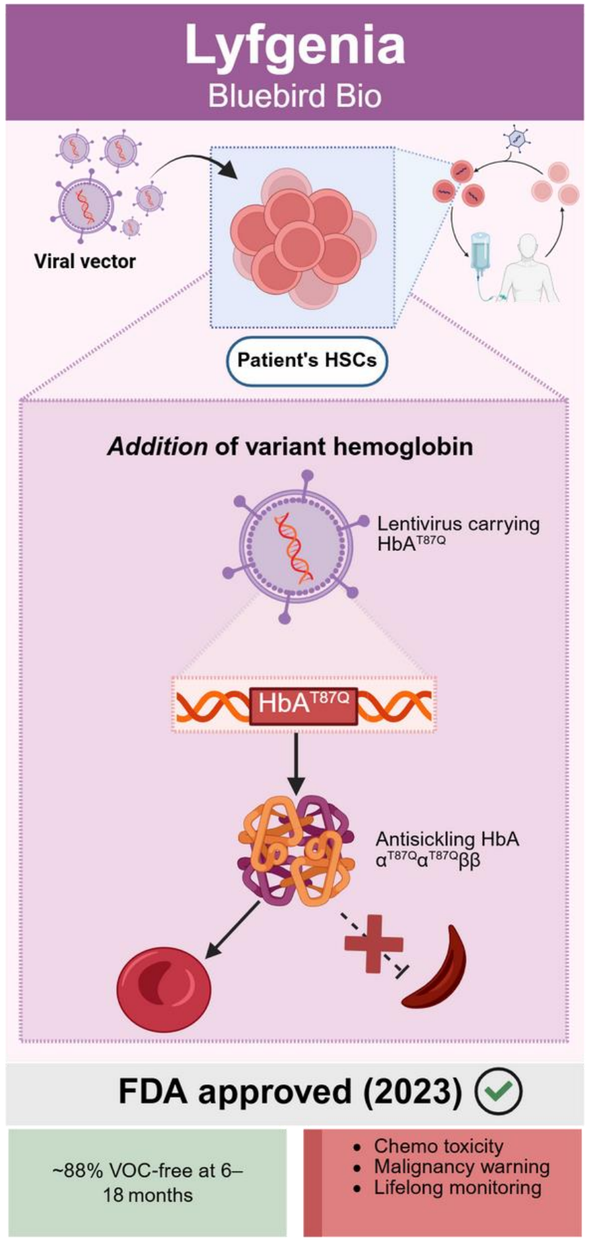
Lyfgenia is a lentiviral vector-based treatment for SCD

Lyfgenia is designed to address the root cause of SCD by enabling the patient's body to produce a form of hemoglobin that resists sickling.

The inserted gene enables HSC-derived red blood cells to produce HbAT87Q, a hemoglobin variant that mimics normal adult hemoglobin (HbA) but is specifically engineered to prevent the polymerization that causes red blood cells to sickle.

Most patients achieve durable production of HbAT87Q, with a marked reduction or complete resolution of severe vaso-occlusive events over a follow-up period of 9 years, demonstrating the potential for a long-lasting functional cure of SCD.

Lyfgenia is currently approved in the USA but not in the EU or UK.



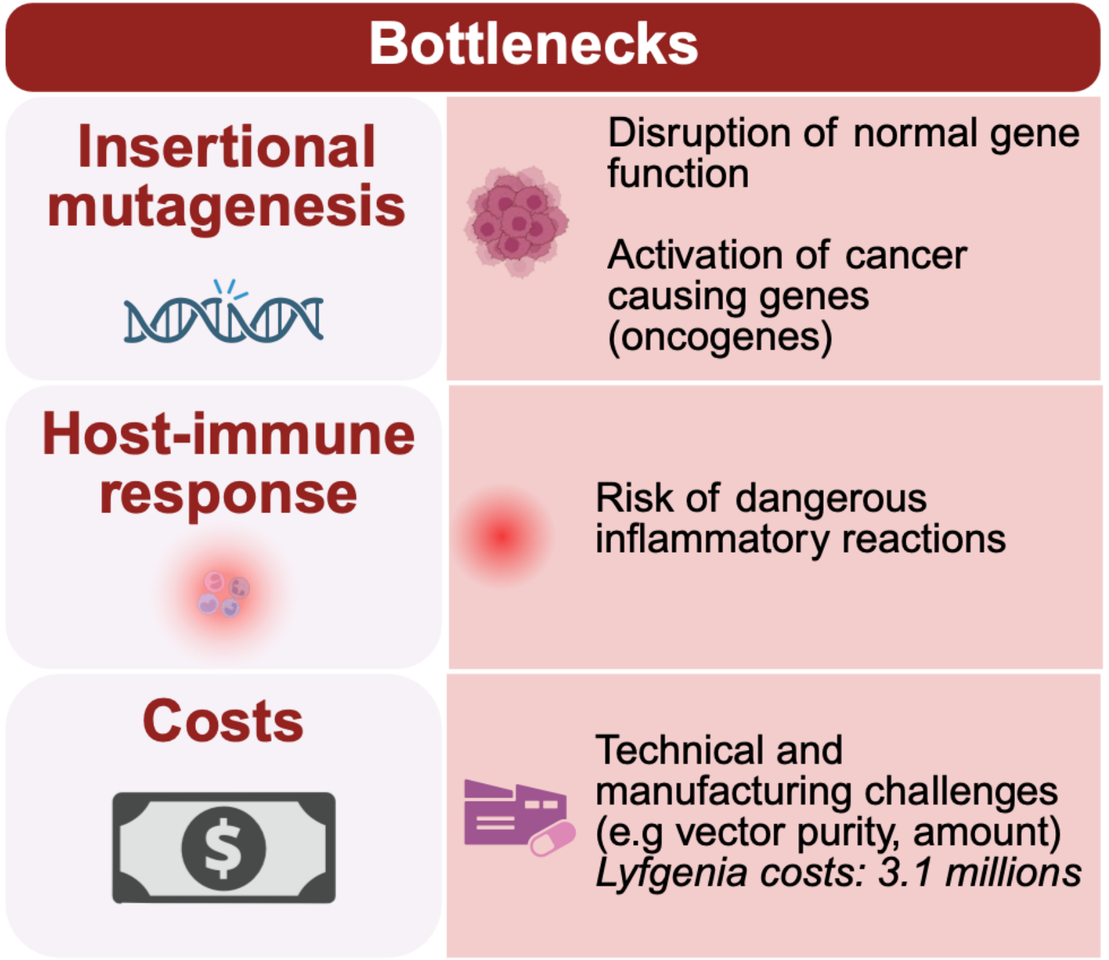
Lentiviral approaches – Drawbacks

Lentiviral-based therapies come with some potential limitations and bottlenecks

Lentiviral-based gene therapy is a powerful tool for treating genetic diseases, but its use is associated with specific limitations and potential side effects that require careful consideration and long-term monitoring.

Overcoming such challenges will be essential to ensure that lentiviral-based therapies for SCD become safer, cheaper and more accessible to patients worldwide.

So far, clinical trials using lentirival vectors for treating hemoglobinopaties have shown no evidence of insertional mutagenesis or host immune response.



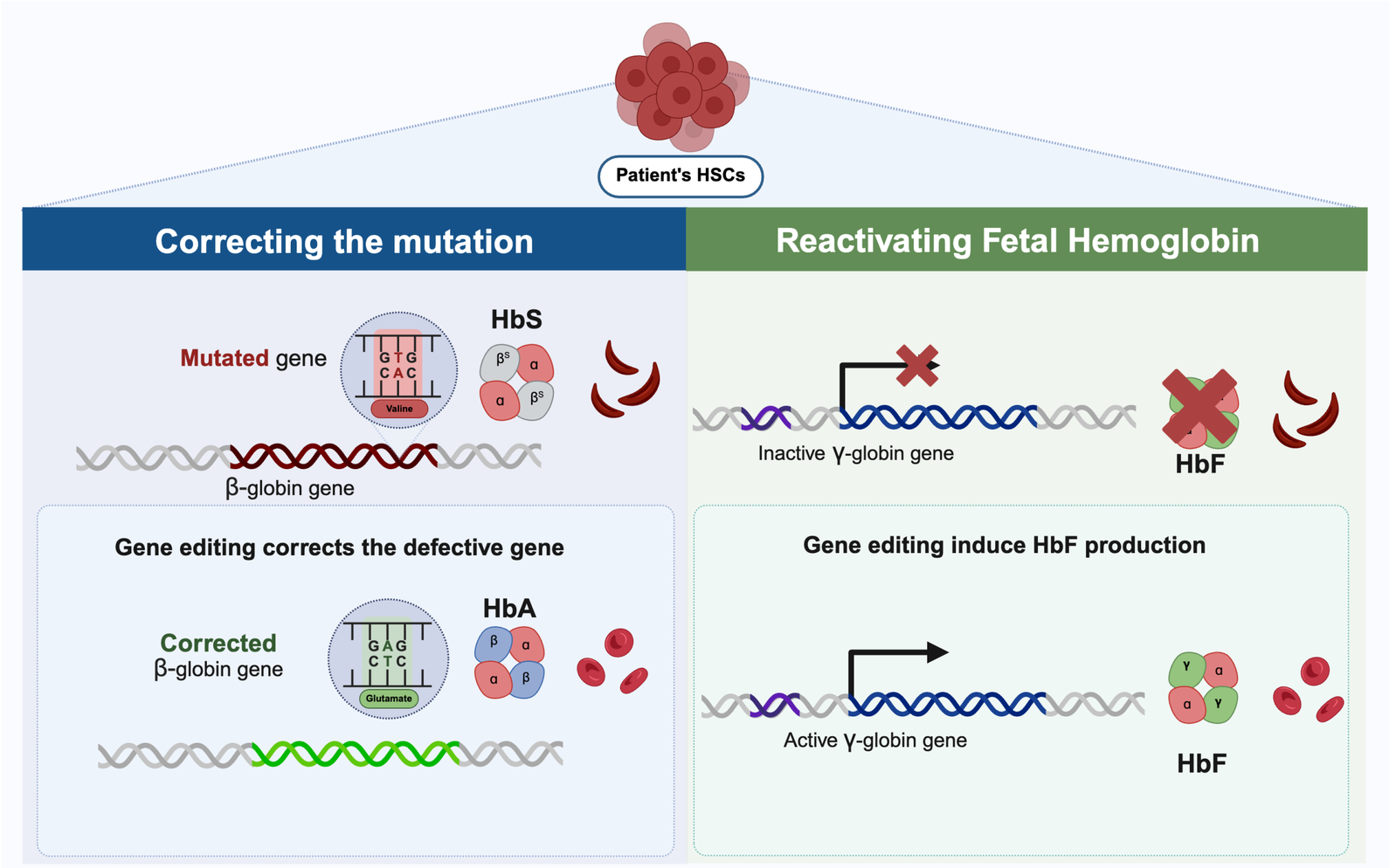
05

INTRODUCTION TO NEXT WEBINAR

We will introduce the topics of the next webinars in this 7-part series.

Annarita Miccio
Imagine Institute

Gene Editing approaches to treat Sickle Cell Disease



To learn more about these topics, stay tuned for:

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

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

Scan the QR codes to register to the next sessions!

Future Webinars

Session 3: Genome Editing: CRISPR/Cas9 and SCD – how it works and its uses
Claudio Mussolino, Mario Amendola, and Annarita Miccio
February 2026

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
David Morrow
September 2026

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