HAABB 2025

There and Back Again,

A Blood Bank Story

By David Baker

Prologue

Writing My Adventure Tale

1993-1st Job working Night Shift at Barnes-Jewish

Early Adventure

- Trauma
- Triple A's
- Liver Transplantation

2000 to now... (some, not all)

- Universal Leukoreduction
- Out of Group Solid Organ Transplants on Newborns
- Sickle Cell Protocols (C, E, and Kell negative)
- Automated Blood Bank Analyzers and Rules Based Computer Systems
- Stem Cell Transplants become normal everyday care

Prologue

What hasn't changed

- Type and Screens.
- Antibody ID's with panels.
- Absorptions
- Thawing, splitting, and washing
- RBCs, Platelets, and Plasma are still mostly human derived.

For most Blood Bankers, we are living in our procedure driven world without a lot of new adventure.

Chapter 1

About Blood Bankers and Hobbits

Hobbits and Blood Bankers

Hobbits: (according to Tolkien)

Are a peace-loving, comfort-seeking folk who prefer a quiet life of home, food, and family over the "nasty, disturbing, uncomfortable" business of adventures.

Laboratory/Blood Bank Folk: (according to me)

Love the quiet life of the laboratory and the procedural nature of the lab. It's not that we don't like adventure, but adventure doesn't always find us.

Was Bilbo Baggins a Blood Banker

- **Resourceful & Intelligent:**
  - Despite his initial fear and hesitation, Bilbo proves to be clever and resourceful.
- **Kindness & Generosity:**
  - Bilbo is generally a kind and hospitable hobbit who is generous with his home, affection, and belongings.
- **A "Reluctant Hero":**
  - He is not a traditional hero; rather, he is unsure of himself and lacks confidence but nonetheless performs great deeds.
- **Deep-Seated Wanderlust:**
  - Although he loves his comfort, a secret love of adventure and a passion for maps remain, driving his eventual departure from home.

Our Story...

This is a story about a new adventure for our Blood Bank. It's about forming a Fellowship with our providers, lab team, nursing, our blood provider, and our pheresis team to help one of our friends seek a lifetime of Adventure...

Chapter 2

The Adventure Begins

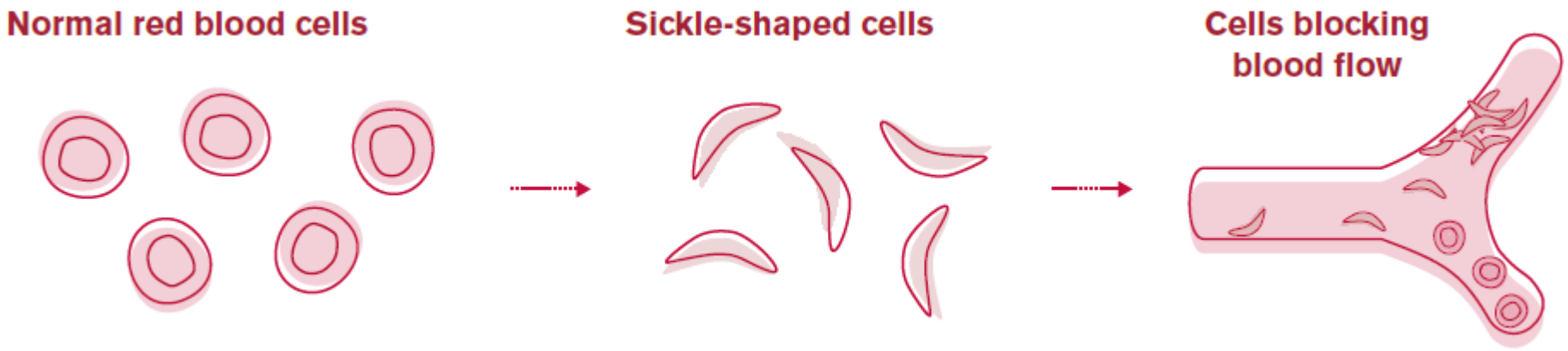
The Hero of Our Story

- 18-year-old female
- Hb SC disease
- History of vaso-occlusive events (VOE) with severe pain
- Poor quality of life due to VOEs
- History of receiving exchange transfusions prior to developing an anti-Js^b in 2024.

I know that you all thought this was going to be a Lord of the Rings/Hobbit themed story, but we do work at St. Louis Children's Hospital, so we are heading into a new direction!

What is Hemoglobin SC disease?

- Hemoglobin SC (Hb SC) disease is a genetic blood disorder where a person inherits two abnormal genes, one for sickle cell hemoglobin (Hb S) and one for hemoglobin C (Hb C)
- This disease is characterized by hemolytic anemia and recurrent vaso-occlusion causing pain and tissue injury
- hb SC disease is typically less severe than hb SS disease.



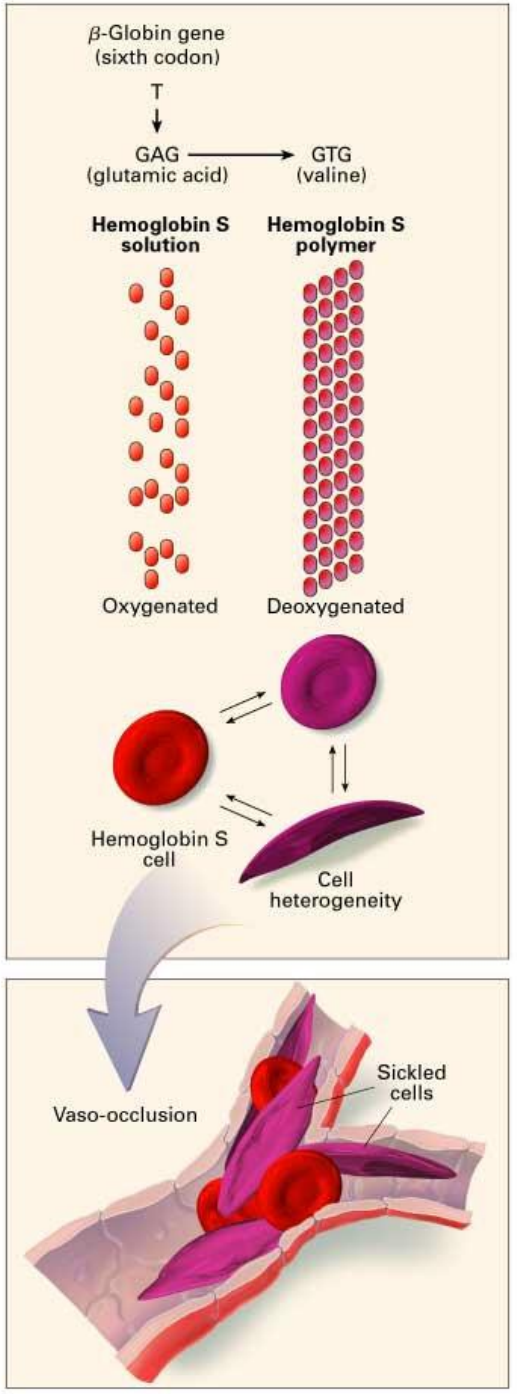
Sickled Cells

Polymerization:

- When oxygen levels are low (deoxygenated), HbS molecules stick to each other and polymerize, forming long, rigid fibers within the red blood cell.

Sickle shape:

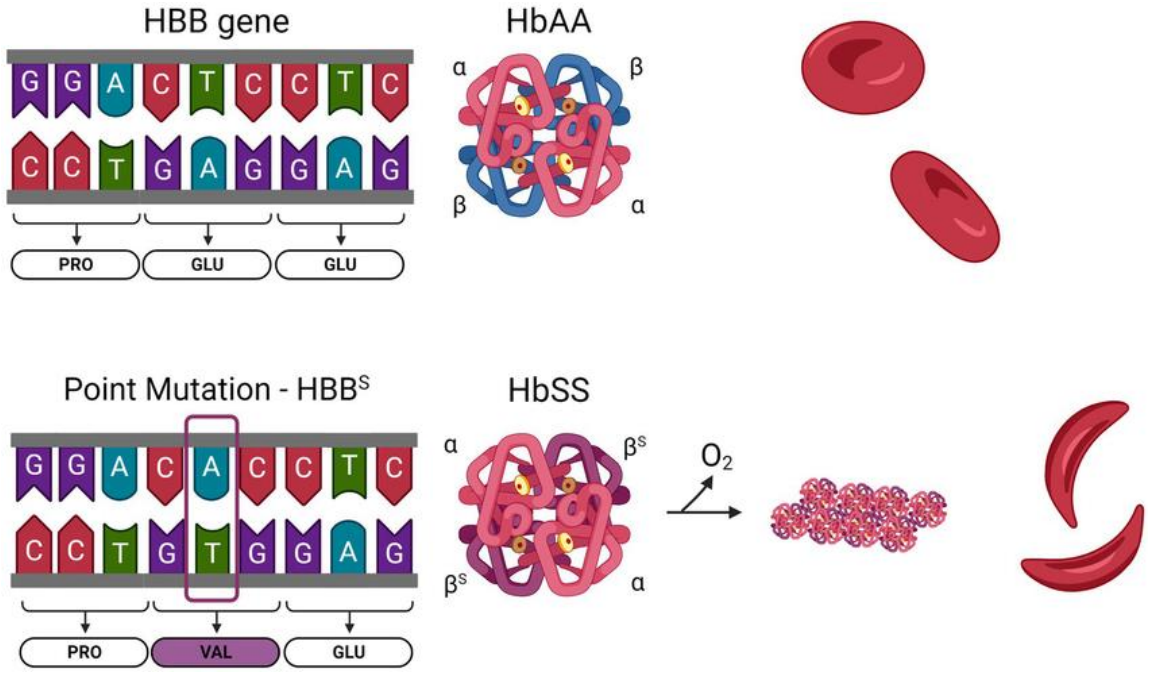
- These fibers distort the cell, forcing it into a crescent or sickle shape. The resulting sickled cell is stiff and fragile.



New England Journal of Medicine

Sickle cell disease is caused by a single point mutation

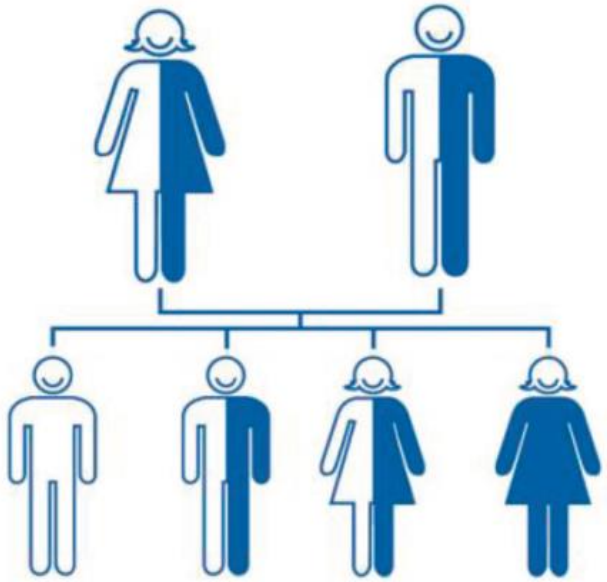
- Point mutation in hemoglobin β globin gene (HBB) involving substitution of adenine for thymine
- hb S production: glutamic acid is replaced with valine
- hb C production: glutamic acid is replaced with lysine.
  - hb C doesn't cause sickling on its own.

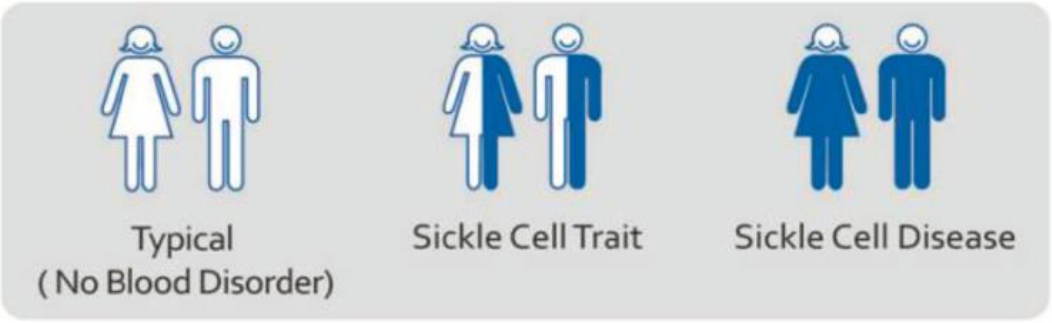


CDC.gov

Disease inheritance is autosomal recessive

- If 2 trait parents have a child…
- There is a 25% change of developing forms of Sickle Cell Disease.





www.CDC.gov/sicklecell

SCD by the numbers

Sickle cell disease (SCD) affects about 100,000 people in the United States

More than 90% are non-Hispanic Black or African American

3%–9% are Hispanic or Latino.

The estimated life expectancy of those with SCD in the United States is more than 20 years shorter than the average expected.

https://www.cdc.gov/ncbddd/sicklecell/data.html

Clinical symptoms of sickle cell disease

Complications requiring transfusion

- Anemia
- Vaso-occlusive pain crisis
- Acute chest syndrome
- Stroke

Other Complications

- Death of Bone Tissue
- Blood Clots
- Hand-Foot Syndrome
- Kidney/Liver Problems
- Other

https://www.cdc.gov/sickle-cell/complications

Treatment Options

Transfusion

Simple Transfusions

Exchange Transfusion

Medications

Hydroxyurea-HbF production

Others that lessen the ability of the RBC to sickle.

Transformative Care

Allo SCT

Gene Therapy/Auto SCT

Option 1: Transfusion

Simple transfusion

- Risk of hyperviscosity with high Hb targets
- Poor control of HbS%
- Short intervals between procedures
- High levels of iron accumulation
- Peripheral access is usual

Manual exchange transfusion

- Less risk of hyperviscosity
- Intermediate control of HbS%
- Intermediate intervals between procedures
- Intermediate levels of iron accumulation
- Intermediate requirement for central access

Automated red cell exchange

- Less risk of hyperviscosity
- Best control of HbS%
- Long intervals between procedures
- Low levels of iron accumulation
- High requirement for central access

Sickle Cell at St. Louis Children's Hospital

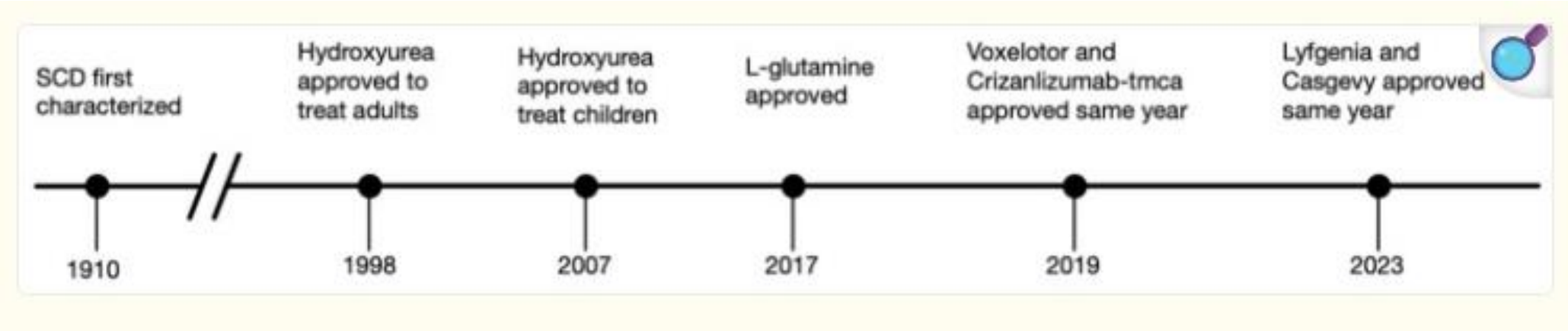
Red Blood Cell Transfusion

Previous 12 months

- 970 Transfusion events (18% of all RBC transfusions)
  - 67 patients
  - ~ 15-20 patients on chronic transfusion (manual and automated)
- Prophylactic C, E, and Kell typed
  - ~ 100 patients seen in the last 2 years
  - 11 patients with a clinically significant antibody
  - Patients may receive non-C, E, or Kell negative units prior to SLCH.
- Why have a C, E, and Kell strategy
  - Prevent anti-C, E, and/or Kell, lessen the risk of developing other antibodies.

Option 2: Pharmaceutical Treatment

- Hydroxyurea. Production of hb F
  - Used at SLCH likely on many patients
  - We only know about it when a patient makes antibodies complicating transfusion support
- Lyfgenia and Casgevy to be discussed later
- Other treatment options. Increase RBC oxygenation/Reduce HbS polymerization



Option 3.1: Allogeneic stem cell transplant

- Indication:
  - Severe disease
  - The patient doesn't respond well to drug or transfusion support
- Limited by available donor
  - <20% of eligible patients have a related HLA matched donor
- Transplant related morbidity and morality
  - Toxicities related to conditioning regimen
  - Graft failure
  - Graft-versus-host-disease (GVHD)
- Nonmyeloablative/reduced-intensity conditioning
  - Increased safety, tolerability, and high rates of stable engraftment
  - Mixed chimerism sufficient to improve SCD
  - Associated with lower rates of GVHD
- 11 SCD patients received allo BMTs at SLCH in roughly the last year.

Cure rate for children undergoing SCT with a matched sibling donor is 95%!

Kassim et al. J Clin Med. 2022
Saraf et al. J Clin Med. 2019

Option 3.2: Autologous SCT with Gene Therapy

- Indication: (Note: Same as allo SCT)
  - Severe disease
  - The patient doesn’t respond well to drug or transfusion support
- No HLA matched donor
- Myeloablative Conditioning and risk
  - Toxicity risk related to conditioning
  - Infertility concerns

What is gene therapy?

We take the bad gene

We modify that gene

We get a good gene


THANK YOU AND
GOOD NIGHT!

lyfgenia™
(lovotibeglogene autotemcel)
suspension for IV infusion

- **Gene therapy**: rather than gene editing.
- Uses a lentiviral vector to deliver a therapeutic gene into the patient's own blood stem cells.
- This gene enables the cells to produce HbAT87Q, a functional hemoglobin that mimics the function of normal adult hemoglobin (HbA) and reduces sickling of red blood cells.

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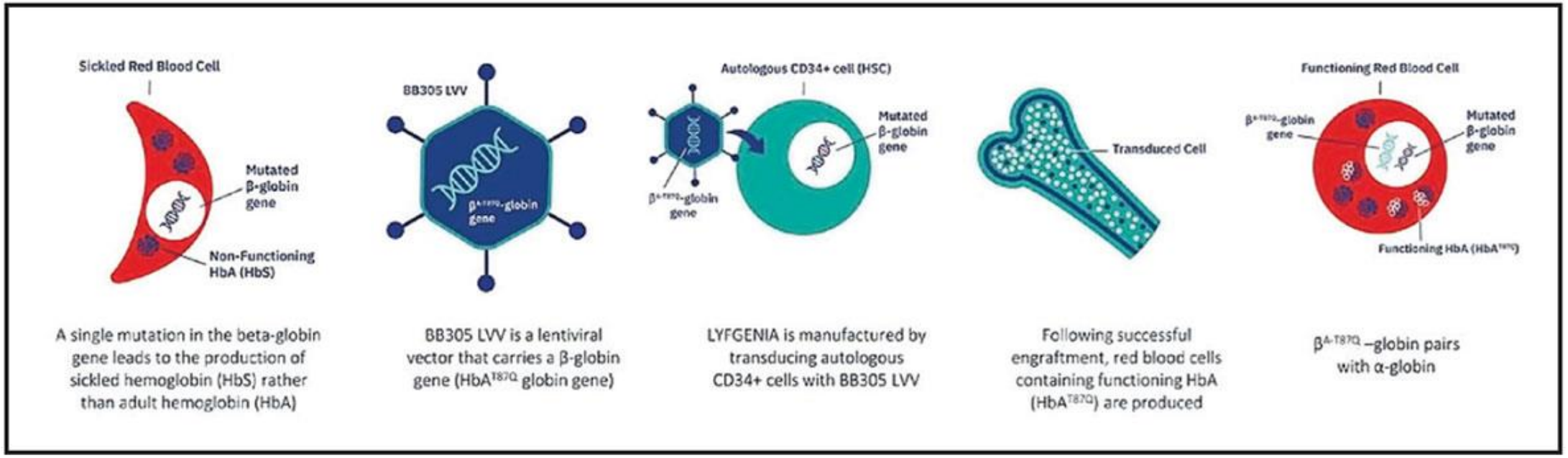
Figure 1. Basic Elements of the LYFGENIA Gene Therapy Process



A single mutation in the beta-globin gene leads to the production of sickled hemoglobin (HbS) rather than adult hemoglobin (HbA)

BB305 LVV is a lentiviral vector that carries a β-globin gene (HbA^{T87Q} globin gene)

LYFGENIA is manufactured by transducing autologous CD34+ cells with BB305 LVV

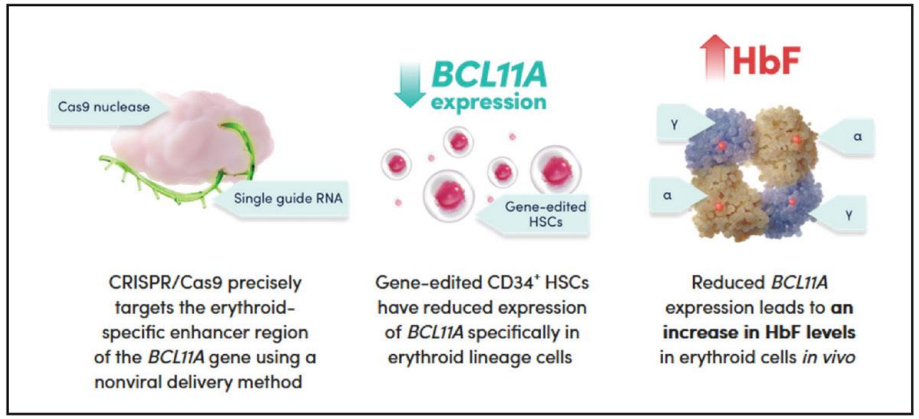
Following successful engraftment, red blood cells containing functioning HbA (HbA^{T87Q}) are produced

$\beta^{A\text{-}T87Q}$–globin pairs with α-globin

Source: LYFGENIA FDA Approval. Accessed at www.sec.gov/Archives/edgar/data/1293971/000119312523292087/d84993dex991.htm.

casgevy®
(exagamglogene autotemcel)
suspension for IV infusion

Figure 2. Basic Elements of the CASGEVY Gene Therapy Process



Source: CASGEVY® is a CRISPR/Cas9-modified autologous CD34+ cellular gene therapy. Accessed at www.casgevyhcp.com/transfusion-dependent-beta-thalassemia/mechanism-of-action.

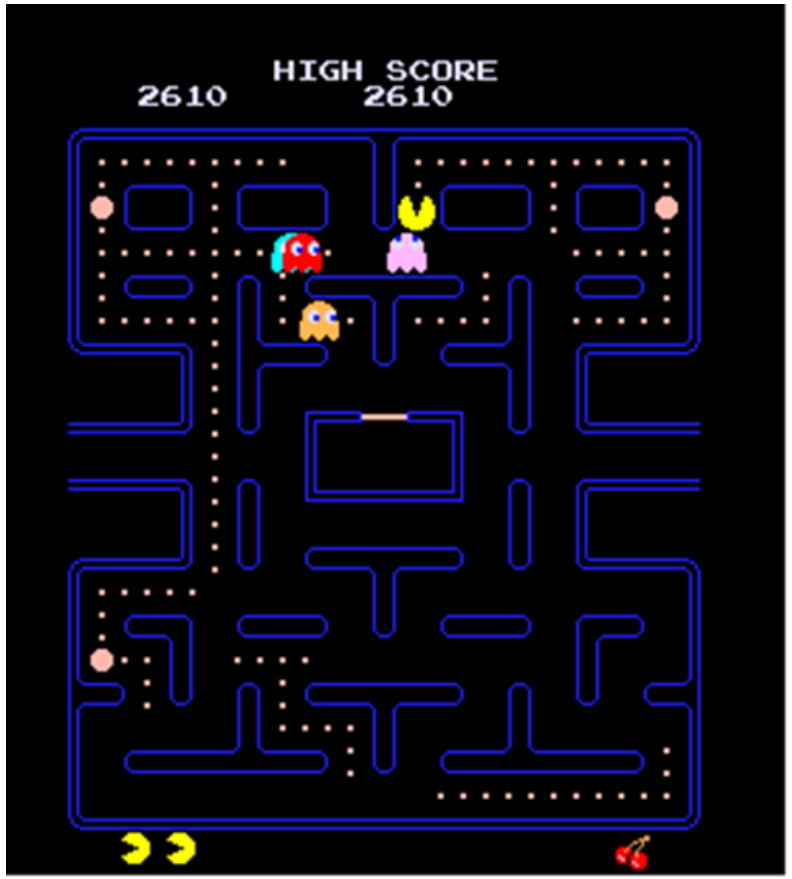
A gene-editing therapy that uses the CRISPR/Cas9 system.

It works by "cutting" specific points in a patient's DNA to alter a gene. In this case it then reactivates the production of fetal hemoglobin (HbF).

The increased production of HbF dilutes the effect of the faulty hemoglobin, preventing the red blood cells from sickling.

Lyfgenia vs Casgevy

Casgevy: Pacman (Crispr) eats the hb S gene and you then make hb F.



Lyfgenia: Mosquito (Lentivirus) bites the hb S gene and a hb A gene takes over

Disclaimer

The presenter of There and Back Again, A Blood Bank Story has just enough information to sound smart to his family but not enough knowledge to answer a whole lot more about how Gene Therapy works. If the Pacman/Mosquito analogy didn't resolve your questions, additional questions should be directed at a few other Gandalf like-Blood Bank Wizards in the room. (You know who they are!)

Thank you in advance for going easy on me at the end of this presentation.

Eligibility for Gene Therapy

In December 2023, the FDA approved Lyfgenia and Casgevy for the treatment of SCD patients age 12 years and older with a history of VOEs.

- Though clinical trials were not done on patients with stroke, the FDA allows for treatment of SCD patients with stroke.
- Early treatments on stroke patients has also been successful.

The cost of a cure vs lifetime of medical costs

Casgevy: $2.2 million

Lyfgenia: $3.1 million

Lifetime SCD: ~ $1.7 million

Johnson et al, Blood Adv. 2023

Let’s go back to day 1…

- It’s February of 2025
- We have our new patient
- I get a direct call about this patient.
- They want to do 2x~2500ml RBC exchanges (7 units each)
- And by the way, this patient has an anti-Js^b

Js^b

The Js^b antigen (KEL7)

- Part of the Kell system
- High-frequency antigen: It is found in nearly 100% of Caucasians and 99% of people of African descent.
- 1:10,000 donors

The anti-Js^b (anti-KEL7) antibody

- Clinically significant IgG antibody that causes both hemolytic reactions and HDN
- Difficult to manage: The rarity of the Js(b-) blood type makes finding compatible blood for transfusion challenging. This is especially problematic for pregnant women with anti-Jsb, as transfusions for the fetus or newborn may require donations from compatible family members.

What happens now only happens in the Movies

One of my staff ask if they can coordinate with pheresis and the ARC to get the units needed for transfusion.

She's an SBB candidate… she's one of those people!

Ultimately, we had to figure out how to get 14 units of Js^b negative blood.

Coordination

Blood Bank: Working with the blood center/American Red Cross to get the blood. Determining whether the blood will be liquid or frozen.

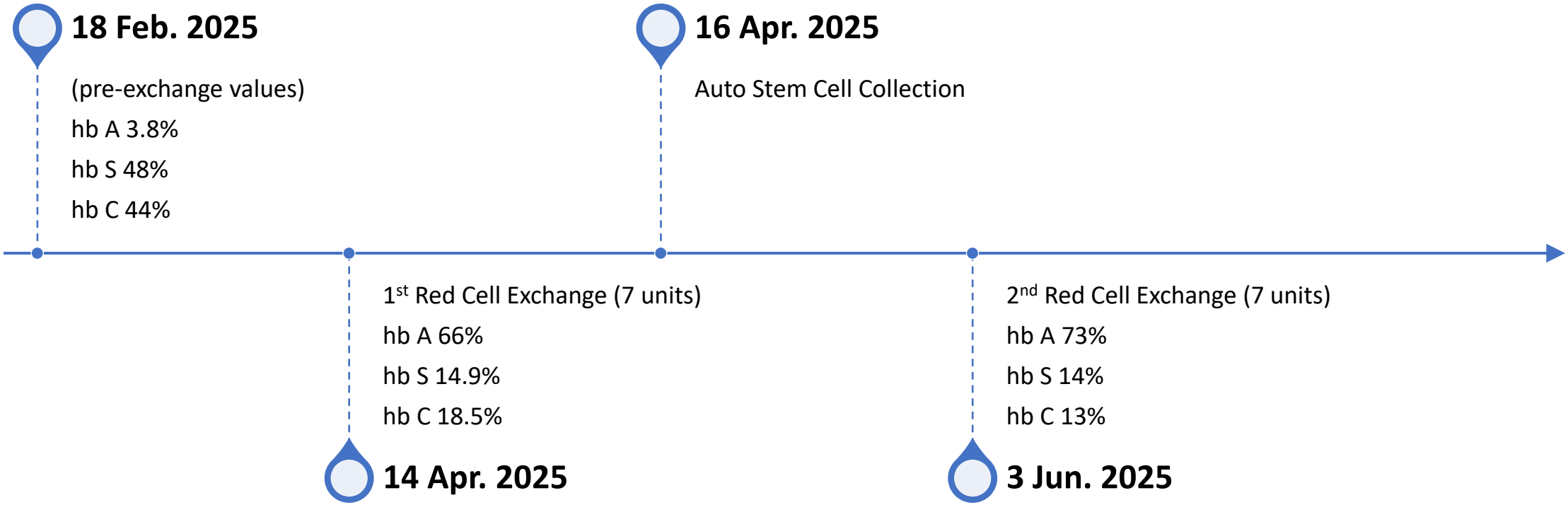
Pheresis: When will be have the blood to do the procedure. If the blood is frozen, how do we assure that the exchange happens.

Providers: Coordinating with the blood bank, pheresis, and the patient to assure that dates are selected based upon the availability of blood for the case.

Goals of Red Cell Exchange

- hb S levels are decreased to below 30% both for stem cell collection and prior to the autologous transplant.
  - Less Viscosity
  - Less risk of SCD complications
  - Improves Stem Cell mobilization

RBC Exchange and Stem Cell Collection

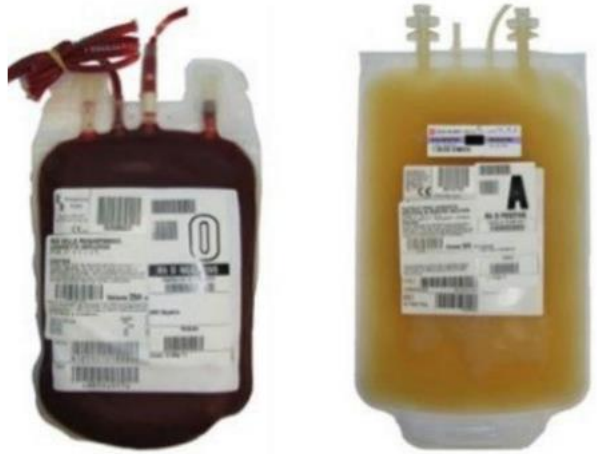


Transplant Day

- Our patient is still scheduled to receive her auto-SCT
- She'll receive one final RBC exchange.
- She'll receive her conditioning regimen and then her modified SCT
  - Busulfan

Post Transplant Transfusion Support

- Our patient is likely to continue to make an anti-Js^{b} for life.
  - Only temporary immune suppression.
  - However, the end game is to prevent future RBC dependency.
- Like all patients undergoing myloablative conditioning, our patient will need red blood cell and platelet support post transplant.
- Engraftment (clinical trial data)
  - Neutrophil engraftment:
    - Median time was 20 (12-35) days
  - Platelet engraftment
    - Median time was 35 (19-136) days
  - No incidence of graft failure



Kanter et al. ASH Poster. 2023
Kanter et al. NEJM. 2021

The End Game

- Successful engraftment
- Regression of SCD symptoms (pain goes away first), hopefully stabilization of vasculopathy and eventually repair.
- Long term production of hb A
- Patients see benefit in that they are not hospital bound any more, better QOL, etc.

Is this a cure?

- The answer is yes!

- Patients exhibit improved Hb levels, > 10g/dl or 3g/dl higher than baseline
- The transplanted Hb A functions normally
- The impact of Sickle Cell Disease subsides
- No long-term immune suppression

- Patients have only had this therapy for 10 or so years now. Long term impacts are still TBD.

Let’s Wrap This Up

It takes a team

- It took a lot of coordination to assure that the units and patient were ready and available when needed.
- The Team: Our **INCREDIBLE** providers, pheresis team, blood providers, and blood bank staff.

Adventure is out there!

Blood Bankers do secretly like adventure!