PRECISION HEALING: CRISPR'S PROMISE FOR SICKLE CELL DISEASE

Exploring CRISPR as a means of treatment for Sickle Cell Disease (SCD)

Sickle Cell Disease (SCD)

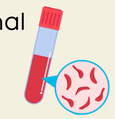
Sickle cell anemia is a **hereditary disorder** that results in the patient having **deformed** Red Blood Cells (RBCs)

So instead of looking like this...

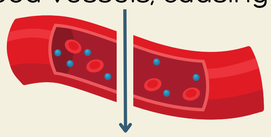
...they have a flat, sickle-like shape!

Causes and Effects of SCD

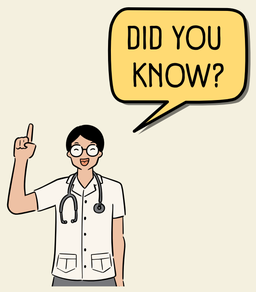
When a person inherits two copies of an abnormal form of the **β-globin gene (HBB)** , which makes haemoglobin, they develop **Sickle Cell Disease**.



Sickle cells, due to their **irregular shape**, get **stuck** in blood vessels, causing anemia.



Body doesn't get **sufficient oxygen**, and this results in **damage** to nerves and organs, and can even be **fatal!**

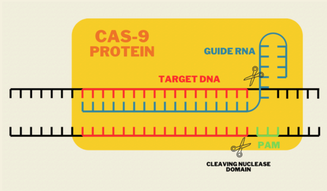


Sickle cells also don't last long - they have a lifespan around **6-12** times shorter than normal red blood cells. This means SCD patients also experience **low haemoglobin counts**!

CRISPR CAS-9

The Cas-9 molecule is an **enzyme** that acts to cleave or perform **breaks in DNA**, like a pair of scissors, but for DNA! It's able to do this on almost **any DNA** sequence as well.

A **guide RNA** (gRNA) molecule is required to **bind** to the Cas-9 molecule to guide it to the **target RNA.** This ensures the cut is only done at the **precise location [target]** of the DNA.



Once the DNA is attached to the Cas-9 molecule, the Cas-9 molecule undergoes a **change in its shape** that **unzips the two strands** of the DNA, then cuts it using **nuclease domains** within itself.

Existing treatments for SCD

1

Hydroxyurea

Prevents formation of sickle cells; It is primarily **drug used** and it is **non-curative**; It's **mechanism of action** is not clearly known

2

Hematopoietic stem cell transplantation

Replacing the **bone marrow** as the source of RBCs with a **healthy transplant**; many risks including **rejection**, infection, surgical mishaps

Did you know?: **Nigeria** accounts for **50%** of all newborns with sickle cell disease **globally**

GPH101

Mechanism of action

This novel treatment employs CRISPR-Cas9 to modify **nucleotides** within the RBC-producing **erythrocytes** such that erythrocytes manufacture **betaglobin** (the component within haemoglobin that's affected by SCD) **correctly**.

Benefits

It attacks the mutation **directly**, may end up being more **generalizable** to other genetic conditions than the **fetal haemoglobin** method (another form of CRISPR treatment), and is a long-term cure unlike hydroxyurea, without the dangers associated with stem cell transplant.

Drawbacks

- It has not gone through **clinical trial** yet; it is still in the **midst of development**
- Gene editing can be quite **costly** - but most SCD cases occur in **poverty-stricken** Sub-Saharan Africa and India
- **Public mistrust** towards genetically modified products and treatments might result in the treatment not being well-received
- Robust regulatory frameworks to address **ethical concerns and patient safety** haven't been developed to oversee this field of medicine yet!

Sources

1. American Society of Hematology (2023). Quantifying the Life Expectancy Gap for People Living with Sickle Cell Disease - Hematology.org. https://www.hematology.org/newsroom/press-releases/2023/quantifying-the-life-expectancy-gap-for-people-living-with-sickle-cell-disease
2. Lanzkron, S., Carroll, C. P., & Haywood, C., Jr. (2017). Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979-2005. Public Health Rep. https://doi.org/10.1177/003335491312800206
3. SynthEgo | Full Stack Genome Engineering. (n.d.). Sickle Cell Gene Therapy Using CRISPR. https://www.synthego.com/crispr-sickle-cell-disease
4. Vertex and CRISPR Therapeutics present new data in 22 patients with greater than 3 months Follow-Up Post-Treatment with Investigational CRISPR/CAS9 Gene-Editing Therapy, CTX001TM at European Hematology Association Annual Meeting | Vertex Pharmaceuticals. (2021). Vertex Pharmaceuticals. https://investors.vrtx.com/news-releases/news-release-details/vertex-and-crispr-therapeutics-present-new-data-22-patients
5. Kanter, J., et al (2021). A First-In-Human, Phase 1/2 Study of the Correction of a single Nucleotide Mutation in Autologous HSCs to convert HBS to HBA to treat SCD [Slide show]. ASH Annual Meeting and Exposition. https://graphitebio.com/wp-content/uploads/2022/06/GPH-CEDAR-TIP-Poster_06DEC2021.pdf
6. IntErview: There are now two pushes to treat sickle cell disease with CRISPR - CRISPR medicine. (2021). CRISPR Medicine. https://crisprmedicinenews.com/news/there-are-now-two-pushes-to-treat-sickle-cell-disease-with-crispr/

This infographic poster, entitled 'Helping the Body to Breathe Again', was created by Ibramsa Idris Ahamed, Surendran Srinikesh, Patrick Nott Pei De, and Jedidiah Eo Shuo, of St. Joseph's Institution, as an entry to the GMAC Students Challenge 2024.The contents of this infographic may not necessarily reflect the views of GMAC.