I2U | Accelerating the Journey from Idea to Utilization

SNAPSHOT CASE STUDY:
CRISPR/Cas9 Technology for Blood Disorders

Introducing Blood Disorders and CRISPR/Cas9 Technologies

Globally, there are millions of patients afflicted by Sickle Cell Disease (SCD), the most common monogenic blood disorder that causes rigid sickle-shaped red blood cells (RBCs)[i]. These deformed RBCs disrupt blood flow, leading to end-organ damage and early mortality in patients. Globally, about 300,000 babies are born each year with SCD[i], and as of 2018, there 5000 patients in Canada[ii] alone. These numbers are expected to grow with elevated immigration rates from countries with high prevalence of the disease. Beta Thalassemia Major is a rare blood disorder that impacts RBC production, impeding oxygen delivery in the body with the potential for early mortality. The incidence rate of symptomatic individuals is 1 in 100,000 throughout the world, with about 60,000 individuals born with it annually[iii].

Until recently, the sole curative therapy for SCD was a bone marrow transplant available to only ~15% of patients, typically from a matched donor[iv]. For Beta Thalassemia, the only treatment was lifelong blood transfusions - associated with a range of health complications that can result in heart, liver, and endocrine system damage[v]. In April 2023, CRISPR Therapeutics and Vertex Pharmaceuticals submitted their FDA approval application for Exa-cel, a one-time medication to treat SCD and Beta Thalassemia using CRISPR-Cas9 gene editing technology[vi]. This curative treatment modifies a patient's own stem cells outside the body (i.e., *ex vivo*), using a pair of biological "scissors" (i.e., CRISPR/Cas9 technique) to remove and replace faulty genes, reactivating cells associated with fetal hemoglobin production. This way, the technology has the potential to restore patients' RBCs and eradicate the mutation that causes either SCD or Beta Thalassemia.

Mechanism and Delivery

Exa-cel is delivered by removing a patient's stem cells, genetically modifying them via CRISPR/Cas9 technique in a lab and infusing them back into the body. The treatment protocol for Exa-cel can be distilled into the following steps:

1. **Stem Cell Harvesting** to extract cells for genetic modification.
2. **Manufacturing of Edited Cells** in a lab using CRISPR/Cas9 technique.
3. **Chemotherapy** to remove remaining stem cells from the patient's body. This is completed to ensure no faulty stem cells are present when gene-edited ones are transplanted.
4. **Hematopoietic Stem Cell Transplant** to infuse the edited cells back into the patient.
5. **Monitoring** to determine when the edited cells begin producing mature blood cells and ensure no adverse side effects from treatment.

Implementation Challenges in Canada

The following implementation challenges are key barriers in the future if Exa-cel is approved in Canada:

1. **Manufacturing Capabilities** to apply CRISPR/Cas9 technique to patients' stem cells and develop Exa-cel for future infusion.
2. **Cold Chain Management** to ensure safe storage of the drug during transport and prior to delivery.
3. **Additional Need for Administrative Infrastructure** including trained personnel to prepare, store and deliver treatment to patients.
4. **Capacity for Post-Infusion Care** to monitor patients after receiving treatment and ensure that they are responding well to it with no adverse events.

Future Scope of CRISPR/Cas Technologies

CRISPR/Cas is a powerful gene-editing approach due to its easy design, rapid turnaround time, high accuracy, and efficiency. As a result, there is a broad spectrum of research to translate it to other clinical applications, including genetic diseases, as well as infectious diseases, cancers, and immunological conditions[vii].

One key focus area for CRISPR researchers is applying it to develop allogeneic, or "off-the-shelf" CAR-T cells that are made from the cells of a healthy donor rather than the patient. The goal of these efforts is to apply this technique to avoid triggering the recipient's immune system from the introduction of non-native cells, and ideally reduce the cost and time until treatment while having a safe, efficacious product[viii].

Conclusion

Exa-cel represents a singular example of the future pipeline of genetic medicines using CRISPR/Cas technology. Like several of the cell and gene therapies showcased through other I2U case studies, it underscores the key implementation challenges that accompany this new wave of medicines. From manufacturing capabilities to cold chain management as well as the need for administrative infrastructure and capacity for post-infusion care, this therapy will require significant system support to ensure optimal delivery. As a promising gene editing approach with several clinical directions under current investigation, it is essential to begin assessing approaches towards reform to ensure system preparedness for this breakthrough therapeutic.

References

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