Acknowledging the Approval of World-First Gene Therapy for Sickle Cell Disease Through CRISPR-Mediated Gene Editing

Dear Editor,

Emerging as a cutting-edge technology, CRISPR has garnered a lot of attention for its potential in addressing various genetic diseases over the past decade. Recently, this promise has materialised with the groundbreaking approval of CASGEVY, a CRISPR-based gene therapy co-developed by the American biopharmaceutical company Vertex Pharmaceuticals Incorporated and the Swiss–American biotechnology company CRISPR Therapeutics, co-funded by the Nobel Prize winner Prof. Emmanuelle Charpentier.

CASGEVY (exagamglogene autotemcel) is a one-time treatment cell-based gene therapy. It is intended for the cure of (i) sickle cell disease in patients aged 12 years and older with recurrent vaso-occlusive crises (VOCs) or (ii) transfusion-dependent β-thalassemia in patients that are eligible for hematopoietic stem cell (HSC) transplantation but lack a suitable human leukocyte antigen-matched related donor for transplantation (1).

Sickle cell disease and β-thalassaemia originate from genetic mutations within the HBB gene, responsible for encoding the β-globin subunit of haemoglobin A (HbA), the primary oxygen-carrying protein in adult red blood cells (RBCs). In individuals with sickle cell disease, the HBB mutation causes the production of abnormal haemoglobin molecules, known as haemoglobin S (HbS). The sickle shape of these cells is problematic as it reduces their flexibility, making them more prone to getting stuck in small blood vessels, leading to pain and other complications (2). On the other hand, in β-thalassemia, the HBB gene mutation results in reduced or absent production of β-globin subunit. This leads to an imbalance in the production of α- and β-globin chains, causing abnormal haemoglobin formation. The insufficient or absent β-globin chains hinder the proper function of haemoglobin, leading to ineffective oxygen transport and, consequently, anaemia (3).

Prior to the development of CASGEVY, the only available treatments for these conditions consisted of transplanting healthy HSCs from a donor to the patient. However, such a procedure is associated with substantial risks, including the potential for life-threatening graft-versus-host disease. Also, only about 10% of patients affected by the disease have a histocompatible sibling donor, making the cure inaccessible to the majority of those affected (4).

CASGEVY capitalises on a unique aspect of human biology related to fetal haemoglobin (HbF). During fetal development, humans produce a distinct form of haemoglobin that is more adept at extracting oxygen from the mother's blood across the placenta. Fetal haemoglobin differs from adult haemoglobin by featuring two γ-globin subunits in place of β-globin subunits. Ordinarily, the gene associated with the production of γ-globin is switched off shortly after birth, and the production of adult haemoglobin takes precedence (5). This is why babies with sickle cell disease and thalassaemia are born healthy.

CASGEVY utilises CRISPR-based genome editing to selectively "knock out" the regulator that inhibits blood stem cells from producing HbF (6). More specifically, this cell-based gene therapy involves collecting autologous CD34+ HSCs. These cells then undergo CRISPR-Cas9-mediated gene editing to silence the expression of the BCL11A gene, a crucial regulator of the gene encoding the γ-globin subunit in adulthood (5). Specifically, the editing occurs at the erythroid-specific enhancer region of the BCL11A gene. Once ready, patients undergo a few days of chemotherapy to eliminate the old cells and create space for the modified ones. The edited cells, now capable of producing HbF, are then reintroduced back into the patient, who, in turn, undergoes a recovery period lasting several weeks in the hospital, allowing the cells time to settle back into the bone marrow. This approach has a distinct advantage over other gene therapies, as it introduces a smaller genetic change compared to the more classical practice of inserting an entire working copy of a gene into the cell's genome. Also, CASGEVY represents a safer and more targeted approach to cure these conditions, marking a transformative step forward in the quest for effective and treatments for these genetic disorders.

This groundbreaking achievement, marked by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and subsequently approved by the U.S. Food and Drug Administration (FDA) earlier this month, signifies a remarkable milestone in the field of CRISPR–Cas9-mediated gene therapy (1, 6). The approval by the MHRA and the FDA represents a significant leap forward in the treatment landscape for these debilitating blood conditions. To this date, CASGEVY is currently under review by the European Medicines Agency (EMA) and the Saudi Food and Drug Agency (SFDA) for both sickle-cell disease and transfusion-dependent β-thalassemia. Moreover, while the safety profile of CASGEVY is highlighted, it is encouraging to see that the MHRA and the manufacturer are diligently monitoring potential side effects and releasing further results.

Despite the groundbreaking achievement, the potential global impact of CASGEVY raises essential considerations about accessibility. Vertex announced pricing CASGEVY at $2.2 million in the United States. The common thread linking all gene therapies is the high associated cost stemming from the elevated manufacturing expenses inherent in personalised medicine. This limitation poses a challenge when

delivering this therapy to low- and middle-income countries. The high cost of such treatments, though not unexpected, underscores the need for continued efforts to make these therapies more accessible on a global scale. Indeed, as we witnessed the cost of sequencing the whole genome dropping from $2.7 billion to $300 in less than 20 years, we can certainly hope that advancements in CRISPR-based gene therapy may lead to a decline in the cost of this treatment too.

Overall, the approval of CASGEVY by the MHRA and FDA marks a transformative milestone in CRISPR–Cas9-mediated gene therapy, demonstrating significant progress in treating blood disorders. However, the high cost of CASGEVY raises concerns about global accessibility, emphasising the need for ongoing efforts to reduce expenses and make such revolutionary therapies more widely available.

Thank you for your dedication to disseminating this critical groundbreaking scientific advancement.

Sincerely,
Martina Rossi*, PhD

*Independent Researcher, Strasbourg, France; martina.rossi108@gmail.com
https://orcid.org/0000-0002-8866-1844

https://doi.org/10.57098/SciRevs.Biology.2.4.3

References

1. Pflaum, C. (2023). "FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease". FDA News Release, 8 December. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease
2. Rossi, M. (2023). "Advancements and Challenges in Gene Therapy Approaches for Sickle Cell Disease: A Comprehensive Review", *SciRevs Biology*, 2(3), p. 3. https://doi.org/10.57098/SciRevs.Biology.2.3.3.
3. Thein, S. L. (2017). "Genetic Basis and Genetic Modifiers of β-Thalassemia and Sickle Cell Disease", Adv. Exp. Med. Biol. https://doi.org/10.1007/978-1-4939-7299-9_2. PMID:29127676.
4. Germino-Watnick, P., Hinds, M., Le, A., Chu, R., Liu, X., & Uchida, N. (2022). "Hematopoietic Stem Cell Gene-Addition/Editing Therapy in Sickle Cell Disease", Cells, 11(11), 1843. https://doi.org/10.3390/cells11111843. PMCID: PMC9180595. PMID: 35681538.
5. Sankaran, V. G., & Orkin, S. H. (2013). "The Switch from Fetal to Adult Haemoglobin", Cold Spring Harb Perspect Med, 3(1), a011643. https://doi.org/10.1101/cshperspect.a011643. PMCID: PMC3530042. PMID: 23209159.
6. Wong, C. (2023). "UK first to approve CRISPR treatment for diseases: what you need to kno, Nature. https://doi.org/10.1038/d41586-023-03590-6.