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# COMPUTATIONAL VALIDATION OF THE THERAPEUTIC POTENTIAL AND TARGET INTERACTIONS OF WRIGHTIA TINCTORIA AGAINST PSORIASIS-ASSOCIATED RECEPTORS

**Dr Surandar Kumar**

Assistant professor in Subharti university Meerut

## ABSTRACT

*CRISPR-Cas9 has revolutionized genome engineering by providing a simple, programmable, and efficient method to introduce targeted DNA double-strand breaks (DSBs), enabling gene disruption, correction, and precise sequence replacement. Since the adaptation to mammalian genome editing slightly more than a decade ago, CRISPR-Cas9 has passed through a violent storm of development since it was first pioneered in their bench-top tests through demonstrations of the protein in clinical trials. Being a field of translational research, this paper provides a summary of the current state of CRISPR-Cas9 and with a particular focus on therapies of monogenic blood diseases, inherited diseases (metabolic and ophthalmic) and novel potential applications of this technology in oncology and neurology. We address important clinical milestones, technology delivery, technology editing and safety problems including off target activity, immune response and genotoxicity. We describe a representative mixed-method study design that can be used to evaluate the issue of translational readiness through combining the systematic review of the databases of clinical trials and peer-reviewed publications with the extensive analysis of advisory approvals and trial outcomes. New trial reports and regulatory announcements are the key data sources in our primary data collection as well as they assist us in the measurement of indicators of clinical efficacy, the summarization of adverse events, and exploration of the implementation barriers. Key findings indicate that the ex vivo CRISPR-based therapies of hematopoietic stem cells using autologous sources have been profoundly effective in the attenuation of the disease load of sickle cell disease and b-thalassemia with promising safety records, leading to regulatory grants in major jurisdictions. In vivo delivery, off targets, off-target detection and mitigation, long-term monitoring, manufacturing scale and equitable access is challenging. We mean technological and regulation innovation, which could shape the next five years of CRISPR translational research and end with practical recommendations on how to accelerate safe and equitable clinical use.*

***Keywords:*** *CRISPR-Cas9, gene editing, translational medicine, sickle cell disease, ex vivo therapy, delivery systems, off-target effects, regulatory approval*

## INTRODUCTION

### From Molecular Curiosity to Therapeutic Platform

The field of genome editing has undergone a uniquely rapid transformation of a highly specialist practice of molecular biology into a universal purpose therapeutic platform. The concept of the treatment of disease causing genes at its source of origin was not new but rather seen as a dream as it was impossible to employ accurate, effective and large scale mechanisms. Earlier attempts at genome-editing systems (zinc finger nucleases and transcription activator-like effector nucleases) had demonstrated that it was possible to target DNA and make changes but the technical complexity, cost, and programmability was poor (Ewaisha *et al.*, 2023). With the introduction of CRISPR-Cas9, this has completely changed. Along with an effortless RNA programmable guide and a nuclease that slices DNA, CRISPR-Cas9 brought about a level of precision, versatility, and ease as never before recognized in genome editing. Due to this, genome editing soon went beyond the proof-of-concept laboratory experimentation into a workable approach of therapeutic intervention across a very broad spectrum of genetic disorders.

### Mechanistic Basis of CRISPR-Cas9 Editing

The inherent feature of the CRISPR-Cas9 technology is that it offers the tool which allows one to insert directed two-strand breaks in DNA in certain places within the genome an end user may identify (Hou *et al.*, 2022). The Cas9 nuclease targets the adjacent sequences comprised of complementary DNA in a protospacer adjacent motif, and induces a site-selective cleavage after being directed by a short, single guide, RNA. Endogenous cellular mechanisms that mediate repair of the break are caused by this break, and they are principally non-homologous end joining and homology-directed repair. The CRISPR-Cas9 can be modified to interfere with normal gene functions, fix pathogen-related mutations, insert therapeutic genes, or silence gene and gene expression using these pathways. The guide RNA can be retargeted through the programmability to redesign those loci slightly to turn CRISPR-Cas9 into more of a generalizable genome-editing platform rather than a disease-focused one. The CRISPR-Cas9 is anchored on such mechanistic simplicity that rendered it effective in clinical application and become the exception among other historical technologies in the field of gene-editing.

**Therapeutic Versatility and Clinical Appeal**

CRISPR-Cas9 is highly versatile, and such versatility correlates with the translational ability. CRISPR-Cas9 is capable of directly targeting a endogenous genome, as compared to the traditional conventional ways of gene therapy, which is commonly founded on the insertion of supplementary template of a valuable gene (Dubey *et al.*, 2023). The given ability makes it possible to pursue multiple therapeutic opportunities. Pathogenic alleles may be knocked out in diseases which have been shown to have toxic gain-of-function mutations, monogenic diseases with specific point mutations can in theory be repaired, and potentially useful genetic variants can be transposable to provide pathogen protection in the future. Moreover, the CRISPR-based systems can be programmed to non-permanently control the expression of the genes irrespective of the DNA sequence, implying that it can be utilized in other purposes (Rauf *et al.*, 2025). This is what has made CRISPR-Cas9 a focal technology and can treat diseases that were previously thought to be incurable using conventional pharmacological or gene-addition approaches.

**Early Focus on Ex Vivo Editing**

The first clinical use of CRISPR-Cas9 went conservatively and in a pragmatic direction, no matter how flexible it is. Initial human translational studies were based on ex vivo editing of patient-derived cell types of haematopoietic stem and progenitor cells. These were cells with a few advantages in the first-in-human studies. It can be cloned off patients, grown outside the body in the controlled laboratory environment and then it can be tested to the extent of quality, safety and potency and reinserted (Lotfi *et al.*, 2024). This approach minimized the systemic level of exposure to the components of gene-editing, minimized the risk of the off-target effects in non-target tissue, and became consistent with existing clinical procedures, e.g. bone-marrow transplantation. This ex vivo paradigm, therefore, presented a reasonable derivative of innovation and risk, in which regulators and clinicians could test CRISPR-based interventions in a setting that they were accustomed to in treatment.

**Clinical Breakthroughs in Hemoglobinopathies**

A precipitation occurred in the ex vivo CRISPR editing method with ##where applied to inherited health conditions, and specifically sickle disease and transfusion-dependent b-thalassemia. Characterised mutation in globin genes provokes these diseases and their disease burden is significant in a physical global context (Liao *et al.*, 2023). CRISPR-based medications demonstrated the capacity to expand clinical advantage in the prolonged by stimulating haematopoietic stem cells to either reinstate the expression of foetal haemoglobin or mend defective mutations. Edited auto-log cells produced much improvement in symptoms of the disease and involved elimination of recurrent Vaso-occlusive crisis as well as eradication of chronic dependence on blood transfusion. The increased survival of those findings as was observed in the follow-up, and longer still of follow-up, was a solid argument to the experiment that CRISPR-Cas9 can offer long-term therapeutic benefits and not combined with just brief symptomatic relief.

**Regulatory Milestones and Proof of Principle**

The rough euphoria in genome editing was brought by cell-based CRISPR treatment approvals by the regulators in the treatment of hemoglobinopathies. These clearances were signs of institutional confidence in CRISPR-based interventions in terms of security and effectiveness and producibility, and started to move genome editing out of experimental medicine and into controlled clinical procedure. Remarkably, these milestones were the testimony of concept of the gene-editing remedies in general sense (Yi *et al.*, 2024). They demonstrated that with care, genome editing can be rigorous enough to fulfil regulative standards and present to the benefit of patients. At the same time, they placed an additional emphasis on such problems of translational medicine engaged by such radical technologies as long-term safety monitoring, the ability to produce in large volumes, cost-effectiveness and equitable access.

**Rapidly Evolving Clinical Landscape**

CRISPR-Cas9 therapy is still the process whose clinical situation is evolving quicker in the past three years. Various clinical trials no longer solely in haematology, but also in ophthalmology and oncology, in metabolic disorders and in rare genetic disorders, have passed beyond safety trials at an early stage on to further phasing (Morshedzadeh *et al.*, 2024). The ever-mounting clinical evidence has strengthened the assumption that genome editing may be useful as an alternative treatment option, in any case, without referring to disease-specific restrictions. At the same time, regulators have mastered product of gene-editing which is particularly assessed on a long-term follow-up and post-marketing-follow-up. This dynamism of the environment implies that science is picking up steam and complexity of transferring powerful molecular tools into standard prescription of drugs.

**Emergence of Next-Generation Editing Platforms**

Despite the fact that CRISPR-Cas9 is still fundamental, the field is no longer marked with one editing mode. Base editors or prime editors have become complimentary technologies that are capable of making accurate genetic edits that do not result in creating double-strand breaks. Hopefully, with these technologies, there will be the avoidance of these massive rearrangements of the genome and accidental consequences of cleaving DNA (Cring *et al.*, 2022). Their invention gives testimony to a bigger tendency towards creating genome engineering towards greater preciseness and safety. The bulk of the present clinical experience remains concerned with

CRISPR-Cas9; however it is believed that such next generation editors can reach clinical cancer in less than a few years and perhaps in the process expand the list of diseases that genome editing can treat.

**Delivery as a Central Translational Challenge**

Despite the outstanding advances, the bottleneck method on the path of transferring the editing elements to applications in the living organisms is the effective delivery. Ex vivo strategies have the potential of overcoming a number of delivery challenges but are unable to be utilized in all tissues and illnesses (Sadr *et al.*, 2023). The requirements of safe and effective in vivo delivery systems are imperative to conditions either of the liver, muscle, central nervous system or any other tissue that is inaccessible. Both the viral vectors and non-viral vectors are promising but each of them is constrained by such factors as specificity of targeting, immune reactions, and volume capacity of the viral vectors. The development of the science of delivery is therefore needed to be able to expand the benefits of CRISPR-Cas9 to an entirely new range encompassing not only haematological disease but also a myriad of genetic diseases.

**Rationale and Scope of the Present Study**

It is in this context of the ongoing developments and the fact that there is a chain of issues that need a keen study of CRISPR-Cas9 and its translational potential in treating genetic diseases. Even though early clinical outcomes have affirmed that the technology has a potential, all the unanswered questions of safety, delivery, regulation, manufacturing, and ethical governance will characterize the future effects of the technology (Kolanu *et al.*, 2024). The current paper puts CRISPR-Cas9 in the perspective of the dynamic field of translation medicine that is rising to put critical evaluation on limits and achievements put forward by the available clinical research and technology advancements. By doing so, it may provide certain systematic premise of understanding how genome editing may alter hi-tech clinical accomplishments a broadly-available as well as long-lasting method of treatment.

## LITERATURE REVIEW

**Historical background and mechanism**

CRISPR systems already existed as an adaptive immune system in bacteria and archea, and were recapitulated into an RNA-guided DNA endonuclease platform, which can be programmed to edit the genome (Kaur *et al.*, 2025). The ease of design and efficiency of Streptococcus pyogenes (SpCas9) and orthologs of Cas9 made them generally universal. Following DNA cleavage, cell repair systems that take place non-homologous end joining (NHEJ) and homology-directed repair (HDR) mediate numerous effects; NHEJ will cause small deletions or insertions to occur, which can be useful in disruption of a gene, whereas HDR can cause precise sequence replacement when a donor template is present. They are mechanistic platforms of therapeutic interventions extrapolating to high levels such as gene knockout of pathogenic gain-of-function alleles, to targeted correction of pathogenic point mutations.

**Therapeutic strategies and disease targets**

CRISPR treatments can be classified into two broad groups ex vivo in which the cells that might be obtained and reintroduced and in vivo in which the cells might be used to target the body. The mode that has received the most clinical advancement has been the ex vivo because of the opportunity to carry out manufacturing controls in addition to permitting pre-infusion quality checks (Bhokisham *et al.*, 2023). One of the first success stories has been rejuvenation of hematopoietic stem cells to increase the levels of foetal haemoglobin, either by silencing BCL11A enhancers or by point mutations that silence the haemoglobin genes directly, fixing them. Clinical and regulatory documents indicate that transfusion autonomy and Vaso-occlusive crisis abatement are high in patients being treated. The outcome of such results has provided approvals and fast-tracked trials in greater age ranges. in vivo subretinal delivery in ophthalmology In vivo Subretinal delivery has been explored in the scenario of inherited retinal dystrophies, the systemic exposure to which is lowered by localized delivery. Oncology has been pursuing the further engineering of autologous T cells using CRISPR into better tumour recognition or greater resistance to tumour microenvironment suppression (Alkanli *et al.*, 2023). Neurological and metabolic disorders are more impeding the in vivo translation, as it is limited in delivery and long-term editing of post-mitotic cells, fear.

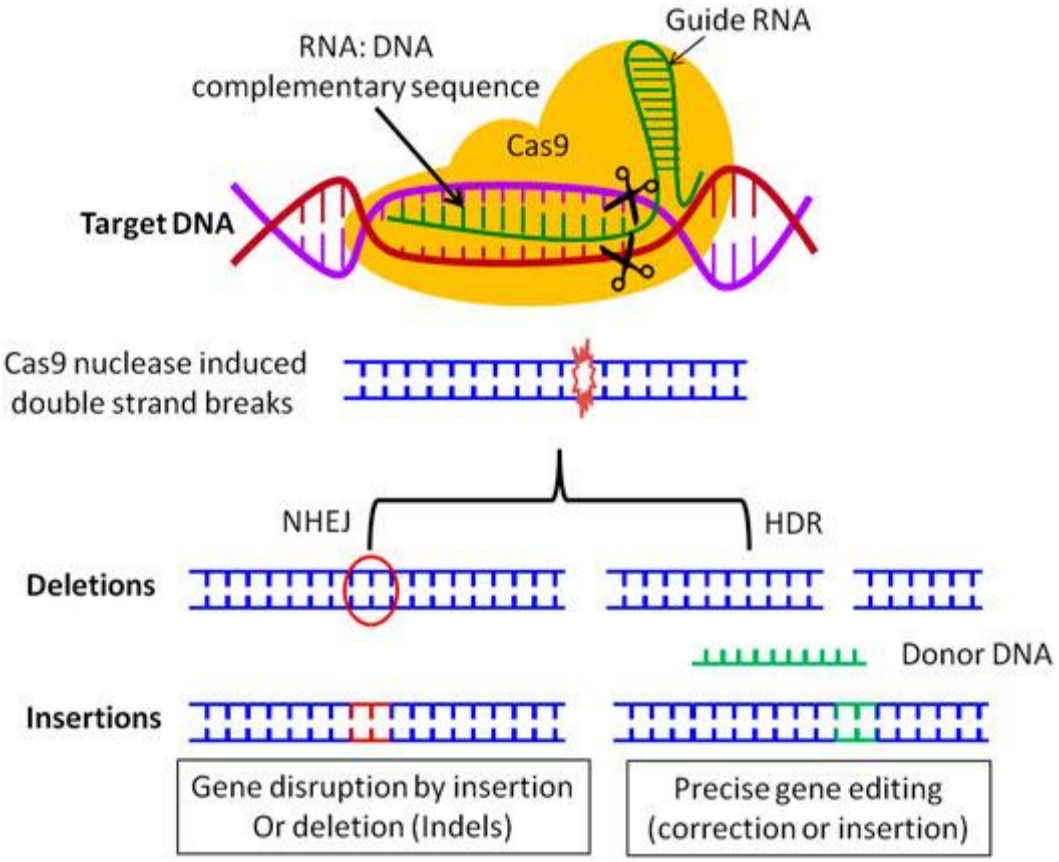


**Figure: The Potential of CRISPR/Cas9 Gene Editing**

(Source: Abdelnour *et al.*, 2021)

**Delivery technologies**

The therapeutic window and safety profile are based on the mode of delivery. Viral vectors, notably adeno-associated virus (AAV) can allow effective in vivo transduction of specific tissues but are too small in sizes of the capsid, have pre-existing immunity, and also are concerned with expression of nuclease components over time. Non-viral lipid nanoparticles (LNP) have been shown to be promising in both transient delivery using mRNA or ribonucleoprotein (RNP) complexes and allowing systemic RNA therapeutics in general (Asif *et al.*, 2024). Upon HSPC editing Ex vivo HDR-mediated editing is the paradigm that aims at delivering a donor cassette using electroporation of RNPs using either viral (AAV6) or non-viral donor plasmid. In addition to the many tissues that can be CRISPR edited, novel technologies in nanoparticles with targeted delivery, scaffolds of cell-penetrating peptides, and artificial viral capsids continue to be added.

**Safety concerns: off-target effects and genotoxicity**

The clearing has been a significant translation problem. Guidelines Authors have developed an array of high-sensitivity detection tools (GUIDE-seq, DISCOVER-seq, SITE-seq, CIRCLE-seq) that can be used to map events across target and guide nuclease and guide RNA optimization. Recent evidence suggests that transient RNP-based expression reduces off-target activity relative to permanent expression of nuclease and that directed high-fidelity Cas9 analogs are designed to further reduce the undesired cleavage (Mangala *et al.*, 2023). Nevertheless, active investigation can be done in oncogenic potential low-frequency off-target, large structural variation induced by p53 pathway interactions and potential interactions between activating and deactivating the p53 pathway that can incline editing. The most valuable part of patient treatment is to observe the patients after the treatment period to make it possible to observe the manifestations that emerge later.

**Regulatory and ethical landscape**

The regulatory environment has been altered to consider the peculiarities of gene-editing treatments with a need of a close supervision of manufacturing procedures, the strategy further, and manifestation of advantages and disadvantages. The initial regulatory approvals of the CRISPR-based cell therapies can be viewed as the transfer of experimental to routine management of some indications, but also point to the problems of cost, affordability, and worldwide availability (Laurent *et al.*, 2024). The ethical issues regarding germline editing, the accessibility of such technologies, and the issues of informed consent when it comes to using the technology on the first individual are still the matters of controversy, along with the social implications of curative

interventions. Recent reviews and policy statements reflect the enhanced transparency of relationships with the stakeholders and systematization of surveillance in order to responsibly scale a use of gene-editing.

## METHODOLOGY

**Study design and scope**

The proposed research is going to be done in a hybrid manner, that is, a systematic literature review along with a quantitative analysis of clinical trial data and regulatory data. The systematic component consisted of PRISMA-type searches of PubMed, Web of Science, and special review repositories of peer-reviewed articles and reviews on CRISPR-Cas9 clinical translation until 2025 (Rahman *et al.*, 2022). The queries were carried out to identify active, complete, and approved CRISPR-based clinical interventions by searching clinical trial registries (e.g., clinicaltrials.gov and analogous regional ones). The databases (regulatory agency public announcements U.S. FDA, EMA communications and national health authorities of particular countries) and the companies press releases and peer-reviewed clinical studies were used to extract efficacy and safety outcomes of pivotal trials.

**Inclusion and exclusion criteria**

Pinnacle clinical research and regulatory approvals and summaries, high-quality systematic reviews, and expert industry updates were published until December 31, 2025. Preclinical research was chosen to provide information to delivery plan or safety processes that can directly be transferred to the clinical practise (Bhattacharyya *et al.*, 2024). All commentaries that lacked primary data were filtered, as the ethical and policy matters were to be placed into perspective. None of other contents were factored in like non-peer-reviewed opinion and reports which could not be factored with any verifiable data.

**Data extraction and outcome measures**

Among the clinical sources, we received primary endpoints of efficacy (transfusion independence, frequency of Vaso- crisis, improvement of hematologic parameters) and safety (serious adverse events, graft failure, neoplastic events) and sustainability (follow-up-duration, sustained-effect) (Bhat *et al.*, 2022). To capture the information about regulatory decisions we followed the approval dates, labelled indications and post-marketing commitments. In order to deconstruct technologies, we have classified modalities of delivery, edits (knockout, HDR, base editing) and an approach to reducing off-target.

**Analytical approach**

Quantitative synthesis: This involved the process of summarising the findings on the outcome of the efficacy studies carried out in clinical cohorts and calculating the responders rates where possible (Zheng *et al.*, 2023). The cleavage of the translational narrative was systematized through qualitative synthesis in regard to five axes such as biological rationale (appropriateness of the disease target), technical maturity (edited or delivered accuracy), clinical evidence (trial results, and safety), regulatory readiness (approvals and dossier position) and implementation readiness (manufacturing, cost, and access). The choice of the sources according to their quality in reference to clinical and regulatory literature became primary in the establishment of bottom-line statements, and the preclinical literature was applied to explain mechanistic and technological novelties.

## RESULTS AND ANALYSIS

**Therapeutic successes in haematology**

The clinically biggest implemented use of the CRISPR-Cas9 is HSPCs autologous ex vivo editing. Both the programs of activating foetal globin by disrupting the BCL11A erythroid enhancer or inhibiting the mutations in the beta-globin genes have their programmes in the body with high levels of clinical benefit being reported (Foley *et al.*, 2022). One regulatory landmarking can be used to demonstrate the hiatus of CRISPR-based cell therapies in translation: at least one CRISPR-based sickle cell therapy received regulatory approval in major jurisdictions, offering a precedent of gene-editing therapies becoming a regular medicine to be used in selected groups. By regulation documents that are publicly available and company announcements, it has been demonstrated that patients undergoing such therapies under ex vivo conditions have achieved durable remission of the disease signs and symptoms and in majority of cohorts transfusion independence or elimination of Vaso-occlusive crisis at long follow-up. Coaches of evaluable cohort responders were discovered to be both better along lines of applicability of standard therapy than historical criteria of the same (Chien *et al.*, 2022). The findings identify that, with high specificity ex vivo editing of HSPCs, the disease modulation can provide a considerable and sustained clinical effect.

**Clinical trial landscape dynamics**

Clinical portfolio is rapidly diversified as indicated by systematic search of registries and more recent reviews. Trials are monogenic blood disorder, inherited retinal diseases, metabolic disorders, oncology (engineered T cells), and preclinical early in vivo liver and muscle disease. Many of the first-in-phase trials have focused on safety and proof-of-concept endpoint trials, but fewer have proceeded to pivotal phase II/III trials (Lu *et al.*, 2023). More current meta-reports and databases of CRISPR trials in 2024-2025 have been suggested, indicating

that the number of trials continues to increase and that target types continue to be expanded, and that an observed transition toward in vivo methods as delivery technologies are improved.

**Safety and adverse events**

Clinical Data: The adverse events related to treatment, which are severe are not prevalent, but they are found in ex vivo HSPC programs reviewed. Negative incidents are mostly identified with common conditioning procedures along with not editing per se hence hard to identify connections (Guan *et al.*, 2022). Other cohorts have shown that there is a low rate of procedure related mortality and severe complications experienced in pre-transplant chemotherapy. The risk of off-target editing by RNP and high-fidelity nucleases, coupled with guide design minimization has reduced but the risk of infrequent off-target effect, great deletions, or rearrangements of chromosomes is a mystery yet would need long-term patient monitoring. Variation in sensitivity of detection, standardized reporting of trials makes it challenging to cross trial compare.

**Delivery and editing modality analysis**

A good method of RNP electroporation in vivo is a solid protocol of HSPC editing. The most suitable platforms in in vivo applications are LNPs and engineered AAVs. Another advantage of LNPs is that mRNA or RNP payloads can be expressed temporarily but LNPs can avoid the expression of long-acting nuclease, although other tissues other than liver are difficult to target. The AAV vectors permit facilitation of easy access to certain tissues, particularly muscle and retina albeit with problems of long term transgene expression, immune-mediated elimination and transgenes integration occurrence (Ahmad *et al.*, 2022). Base editing and prime editing are currently in preclinical trials and are first to be evaluated clinically; these do not involve the use of DSBs and may therefore be the most effective in reducing large structural variants which are the kind of disease most amenable to base editing. New technological advances in capsid engineering, tissue-targeted ligand, and nanoparticle surface chemistry are gradually expanding the tissue editing of the in vivo space.

**Manufacturing, scalability, and cost considerations**

To manufacture autologous cell therapies on a scale that is resource intensive, individualized cell collection is required, extracellular manipulation and sterile chain logistics are needed to accomplish (Sundaresan *et al.*, 2023). The manufacturing models that are centralizing can homogenize the processes at the cost of introducing access and timing limitations. The treatment of gene editing is expensive at its start-up, and thus, the concern of health economics and equitable access is especially sharp, considering that the contexts that have lesser privilege do not have sufficient resources. Systems must include reimbursement, manufacturing capacity and supply chain resilience as a necessary but not sufficient pre-requisite requirement to widespread adoption; it should also have a public health impact to be considered of such a nature. In 2024-2025, the optimization of manufacturing and decreasing the costs per patient should be actively disclosed in the companies and also reported by industries, but it will need long-time pricing strategies and the payer discussions. CrisprTx

## Discussion

**Interpreting clinical impact and durability**

Clinical evidence on Hematologic ex vivo CRISPR programs suggests that durable therapeutic response is achievable and gene editing is an effective and paradigmatically capable of therapy-curing, or radically-alleviating, some monogenic diseases. The signal efficacy that elucidated the maintenance of transfusion independency and significant reduction in the rate of vaso-occlusive crisis are clinically valid outcomes that directly pertain to the patient. However, such findings should be handled with much caution when it comes to the context and most of the subjects of trials are highly selected, having access to high supportive care and they undergo conditioning regimes that can contribute to the risk (Thapar *et al.*, 2024). As soon as the trials are presented to a broader cohort of people, and even younger age groups, it will be of paramount importance to reconsider the ratio of benefits and harm in the actual conditions. The recent stories of favourable results in the younger age cohorts of paediatrics call upon the hope of the future but accentuates the importance of long-term registry results to measure the long-term results, adverse events delayed and the developmental effects.

**Safety trade-offs and mitigation strategies**

CRISPR-Cas9 derives its potency and risks as well as the basis on DSBs. Large scale deletions, translocations, or activating p53-selected selective forces, are also likely to be caused by DSBs though this does not mean that they are easy to therapeutically (Zheng *et al.*, 2023). Then a set of mitigations solutions are emerging: transient expression of RNPs to limit nuclease exposure; careful design and use of versions of Cas9 high-fidelity to limit off-target activity; orthogonal system preclinical off-target mapping; the use of alternative modalities (base editors/prime editors) that do not itself require DSBs to correct single-nucleotide mutations (Foley *et al.*, 2022). Observed to be on the rise, are the requirements a significant level of preclinical characterization and post-marketing surveillance by the regulators in order to monitor unusual or newly emerging genotoxic effects. Methodological development of off-target detectability and similar reporting will be required to create a long-term safety trust.

**Delivery as the bottleneck for expansion beyond haematology**

The benefits of HSPC editing in vivo are in the biological accessibility and valid transplantation protocols. The key to carrying out the translation of CRISPR to the diseases of tissues that are less easily manipulated in vitro is safe, efficient and targetable in vivo delivery. AVV tropism, LNPs, and ligands that can specifically target cells are being developed but tissue-mediated impediments to immunization and size restriction of payloads remain. Moreover, the editing of systems in vivo contributes to the fear of mosaic, exposure to the germline, and immunologic reactions (Chien *et al.*, 2022). Further developments that could be applicable to new delivery modalities or provision of interim-modified payloads and interim-of-containing modification factors in the tissues are likely to restrict the pace of clinical in vivo development.

**Regulatory, ethical, and access challenges**

The change of the experimental therapy with the approved one places the gene editing in the healthcare delivery system, so the issue of cost, reimbursement, and the global equity arises. CRISPR based therapies receive regulatory approval - keys to milestones of historic scale but see its liability towards long-term monitoring of safety and post-approval requirements. The ethical concern involving germline editing refers to distinct and significant issues since it affects the perceptions of the individuals and the policy (Li *et al.*, 2023). The problem of affordability of low and middle-income nations is a good one to practice, it is the fact that most of the genetic diseases are geographically based and the tailored editing remedy is not only expensive, but also prohibitive. The policymakers, payers and developers ought to collaborate to develop the mechanisms of tiered pricing, capacity building and technology transfer that will not permit unequal gain access.

**Emerging alternatives and complementary approaches**

Base editing and prime editing are the technological improvements which could complement CRISPR-Cas9 with precise and edit free of edits. These modalities would find particular application in disorder of point mutation and a decrease in genotoxic risk. In addition, reversible or short-term modulation opportunities that can be provided by the editing of epigenomes and the targeting of RNAs with CRISPR systems exist in disease contexts that do not need long-term genomic modification (Zhang *et al.*, 2024). The choice of the modalities of its editing broadens the therapeutic reservoir and creates some challenges concerning the comparative assessment and the regulation policy. Comparative trial safety tests with cross-platform will also play a very important role in determining the most suitable way to apply on a specific type of disease.

## CONCLUSION

CRISPR-Cas9 has already shifted to a transformative laboratory technology into a clinical fact of the matter where it can cure certain monogenic diseases, most notably hemoglobinopathies. The regulatory approvals and the positive clinical results provide support to the efficacy of ex vivo HSPC editing that has given an excellent precedent that future gene-editing interventions can qualify. There remain serious technical, clinical, manufacturing, regulatory and ethical problems (Bhattacharyya *et al.*, 2024). The danger of off-target action and genotoxicity, constraining the decision of the in vivo delivery, the excessive workload of the autologous protocols, and the issues of just access are not trivial threats that necessitate collaborative technological, clinical, and policy reactions.

The priorities in the near-term should be devoted to the reduction of the genomic disruption when standardized high-sensitivity off-target detection and reporting methods are coordinated, long-term patient registries are synchronized to monitor long-term outcomes and late events, the manufacturing is invested into to be able to provide it on a large scale, and the use of the decentralized models to help to provide higher access and accelerate the development of the DSB-free editing platforms (Bhat *et al.*, 2022). The regulatory mechanisms ought to be dynamic in an effort to exercise timeliness to the patient without being seen to interfere by failing to adhere to high levels of adherence to safety. It will involve open consultations to the stakeholders and multilateral consultation with foreign states where the issue of affordability and fairness will be solved.

All in all, the CRISPR-Cas9 represents a first tool of genetic medicine of the 21st century. It now has shown its ability to be translated into the real benefit of patients, but the ability to scale it to larger disease groups and populations globally needs to be managed through the scientific and societal issues that are intertwined and which this paper has highlighted (Foley *et al.*, 2022). Depending on whether CRISPR lives up to its hype as a source of a universal therapeutic platform, multidisciplinary collaboration of molecular biologists, clinicians, bioengineers, ethicists, regulators and health systems will be either solved or not.

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