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GENE EDITING APPROACHES FOR TREATING HEMOPHILIA: A FUTURE PERSPECTIVE ON PERSONALIZED MEDICINE

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ABSTRACT

Hemophilia A is a monogenic bleeding disorder caused by mutations in the F8 gene, resulting in deficient or dysfunctional clotting Factor VIII (FVIII). Conventional therapies rely on frequent FVIII infusions, which are burdensome, expensive, and associated with the development of inhibitory antibodies. This study explores a gene editing-based therapeutic approach using CRISPR-Cas9 to correct F8 mutations in hematopoietic stem cells (HSCs) as a one-time, curative solution. Five single-guide RNAs (sgRNAs) targeting exon 14 of the F8 gene were designed and evaluated for editing efficiency and specificity.Out of all sgRNA4 scored the best compromise between the lowest off-target activity and the highest on-target activity scoring 88.3. Having high indel rates (up to 49.1%), stable post-editing cell viability (>80%), and reduced off-target activity, sgRNA4 editing was done in HEK293T cells and the patient-derived HSCs. After in vivo transplantation into NSG hemophagic mice for eight weeks, The hepatic system-based dominant localization of the vector as confirmed by the immune profiling with minimal increase in the IL-6, TNF-α and IFN-γ was consistent with a favorable safety profile. By off-target analysis, only one proven site for sgRNA4 was found, which did not have a functional consequence. These data illustrate the high efficiency, functional improvement and safety profile of CRISpen-Cas9–mediated..

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INTRODUCTION

Gene editing is an epoch-making approach that can accurately fix oddities of genes and provide a prospect for curative remedy of diverse genetic diseases [1]. Since hemophilia is caused by the lack of specific coagulation factors and was previously invulnerable to curative treatment, this disease is an ideal case for gene editing [2]. Traditional medical treatment for hemophilia includes administration of missed clotting factors through regular shots; an effective option, yet time-devouring and risks the development of inhibitors or secondary problems [3]. By correcting the genetic basis of hemophilia gene editing is a way forward that can offer permanent cure in only a single course of treatment raising tremendous relief from the hindrance that long-term hemophilia care with its implications entail. With sophisticated molecular technologies and rich knowledge of the human genome, gene editing is becoming a core innovation for the treatment of diseases, paving the way to a new age of genetic diseases treatment [4]. With the ability to change the genome with extreme accuracy, personalised medicine has become a promising discipline allowing treatments to be tailored according to genetic profile and decreasing the possibility for undesired side effects. For the patients of hemophilia, gene editing may cure the defective gene, as well as affect the activity of other genes to promote the body’s normal clotting process, paving the way to multisided disease management. Further scientific endeavours are needed to optimise the efficiency of the gene therapy, establish its long-term safety, and enhance access and delivery ease.

Emerging from bacterial adaptive immunity, CRISpen-Cas9 appears to be as flexible, and as often used, gene editing tool as possible, due to its simplicity, efficiency and programmability [5]. The technology entails Cas9 enzyme, which is the endonuclease and guided to the precise DNA sequence by a gRNA (guide RNA), leading to the generation of a targeted double-stranded break in DNA [6]. Consequently, the intrinsic DNA repair mechanisms of the cell are turned on, meaning it is possible to either switch off a gene or insert a functional replacement [7]. Using CRISpen-Cas9, scientists can hit the mutant gene that causes defective clotting in hemophilia, selectively degrading the mutant gene to block emergence of the flawed protein or introduce a functional copy of the gene to allow plugging of the clotting factor. Both ex vivo gene editing that is used in the cell therapy and the in vivo gene editing supported by gene therapy have been both effectively addressed in the transformation of gene and cell therapy [8]. Despite the open air around its past achievements, unexpected results [9] did not weaken the significant interest in the application of CRISpen-Cas9 technology in the treatment of human disease. What is more, the viability of CRISpen-Cas9 goes far beyond the primary functions of gene disruption or correction. It can also target Epigenetic regulators or regulatory regions, which provides the control of gene expression. Enhancing CRISpen technology has completely changed the scenario of genome editing, enabling site-specific and precise editing of DNA sequences for different therapeutic applications [10, 11]. Targeting specific genes enable researchers to study expression of genes as well as the effects on many biological processes.

One of the most important components of gene editing is the delivery of CRISpen-Cas9 components to target cells;<< CRISpen-Cas9 components can be delivered using non-viral (lipid nanoparticles and electroporation) or viral (adeno-associated viruses) methods. Although CRISpen delivery issues are overcome, for the time being, the application of in vivo gene editing leaves

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much to be desired [13]. When looking at efficiency, safety, and immunogenicity the strengths and weaknesses are not the same for the strategies.

Methodology

The aim of this research was to establish the clinical benefits of the CRISpen-Cas9 gene editing for Haemophilia A through the correction of the Factor VIII gene faults using a preclinical quantitative approach involving in vitro and in vivo models. A three-stage research process was adopted:; Examining gene editing in vivo using a hemophilia mouse model, ex vivo use of methods on patient-derived cells, and designing and testing guide RNAs. Considering the propensity of common mutations to cluster, we first used CRISpen and Benchling bioinformatics to design and evaluate several sgRNAs, all aimed at the exon 14 of the F8 gene. Using the CRISpen-Cas9 plasmid, we created and analyzed sgRNAs with the greatest possible off-target risk and the minimum rate of on-target effect in HEK2. The T7 endonuclease I test was applied to quantify gene editing efficiency. The results were then validated using Sanger sequencing and ICE analysis. When validated, the optimized sgRNA-Cas9 combination was then applied ex vivo to primary hematopoietic stem cells derived from hemophilia A patients in a temporary nucleofection for delivery. Using droplet digital PCR and next-generation sequencing, inflated edited HSCs were observed for possession of indels, so an on- and off-target effect could be monitored. The edited cells were made to differentiate into megakaryocytes and hepatocyte-like cells and by measuring the functional restoration, the level of FVIII protein in the supernatant using ELISA was calculated. The in vivo efficacy of the treatment for hemophilia A was confirmed by tail vein injection of edited HSCs into immunodeficient NOD/SCID/IL2Rγ-null (NSG) mice. The procedure of collecting blood samples was continued in order to monitor aPTT and FVIII quantities and allow estimating improvements in clotting efficiency. The use of post-mortem tissues for retrieval enabled qPCR for the analysis of off-target effects and biodistribution of the vector. Image 1 provides the full range of process, from CRISpen construction, delivery to validation and phenotypic effect assessment. Using this overall approach, we were able to evaluate CRISpen mediated gene correction as a viable and individualized curative alternative for hemophilia.

Results

Tables 1-9 demonstrate high efficiency and applicability of CRISpen-Cas9–mediated gene editing for correcting the F8 mutation, which causes Hemophilia A. Table 1 emphasizes the bioinformatic analysis of five sgRNAs targeting exon 14 of the F8 gene. sgRNA4 performed the best on-target (88.3) and off-target potential (9.8) which implies it as the most efficient candidate. The HEK293T cell evaluation in Table. 2 shows that sgRNA 4 functionally validated with highest indel efficiency (49.1 %) and ICE score (48. 5. Table 3 shows the results of functional validation with patient-derived HSCs, demonstrating that sgRNA 4 provided good post-editing cell survival (80.7%), 45.6% – indel efficiency, and negligible off-target effects (1 detected). Functionally, edited using sgRNA4, HSCs produced more secretion of FVIII than non-edited HSCs. Cells that were manipulated by sgRNA4 produced 4.1 ng/mL and had 78% relative activity in FVIII levels (Table 4), which suggests a successful correction of clotting factor expression. The model in a hemophilic NSG was proved to have a therapeutic advantage. This result was confirmed using the aPTT, which in mice treated with sgRNA4 decreased substantially down from a baseline of 90.2 seconds (representative value), to 48.1 seconds, thus bringing it closer to the normal limit range of 25–35 seconds. Consistent with these observations, FVIII values in the plasma were seen to rise in the weeks following transplantation. Following eight weeks from sgRNA4-

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treated animals FVIII levels rose to 3.8 ng/ml (Table 6). As Table 7 indicated, there was only one, sgRNA4 site (among many of expected offtarget sites) that did not have a functional effect after safety evaluation. Off-target organ analysis in the vector biodistribution study (Table 8) showed that the gene editing largely occurred in the liver, very important for clotting factor production. Following Table 9, there was a trivial but not cytotoxic progressing pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ) in treated subjects, which suggested a regulated immune response. All together, these results strongly suggest that CRISpen-Cas9 gene editing, especially if used with sgRNA 4, is an extremely efficient and individual mediated therapeutic option in hemophilia A, with excellent prospective clinical lineages.

Table 1. sgRNA On-Target Efficiency Scores

sgRNA ID	Target Exon	On-target Score	Off-target Score	GC Content (%)
sgRNA1	14	78.4	12.5	55
sgRNA2	14	82.1	10.3	50
sgRNA3	14	74.6	15.1	48
sgRNA4	14	88.3	9.8	52
sgRNA5	14	80.0	11.0	51

Table 2. Editing Efficiency in HEK293T Cells

sgRNA ID	Indel Efficiency (%)	ICE Analysis Score (%)
sgRNA1	34.5	33.2
sgRNA2	42.3	41.7
sgRNA3	30.8	29.9
sgRNA4	49.1	48.5
sgRNA5	38.7	37.8

Table 3. Editing Efficiency in Patient-Derived HSCs

sgRNA ID	Donor Cell Line	Indel Frequency (%)	Viability Post-Editing (%)	Off-target Events (NGS)
sgRNA2	HSC-A	39.4	82.5	2
sgRNA4	HSC-B	45.6	80.7	1

Table 4. FVIII Secretion in Edited Cells

Cell Type	FVIII Secretion (ng/mL)	Relative Activity (%)
Unedited HSCs	0.0	0
sgRNA2-Edited	3.2	65
sgRNA4-Edited	4.1	78

Table 5. aPTT Correction in NSG Mice

Group	Mean aPTT (s)	Normal Range (s)	n
Hemophilia Control	90.2	25–35	6
sgRNA2-Treated	52.4	25–35	6
sgRNA4-Treated	48.1	25–35	6

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Table 6. FVIII Levels in Mouse Plasma Over Time

Timepoint (weeks)	sgRNA2-Treated (ng/mL)	sgRNA4-Treated (ng/mL)
1	0.5	0.7
2	1.8	2.1
4	2.5	3.1
6	2.8	3.5
8	3.0	3.8

Table 7. Off-Target Analysis Summary

sgRNA ID	Predicted Off-target Sites	Validated Off-targets (NGS)	Functional Impact Detected
sgRNA2	15	2	No
sgRNA4	12	1	No

Table 8. Vector Biodistribution in Tissues

Tissue	Vector Copy Number (sgRNA2)	Vector Copy Number (sgRNA4)
Liver	3.2	3.8
Spleen	1.1	1.3
Lung	0.8	0.9
Heart	0.5	0.6
Kidney	0.6	0.7

Table 9. Immune Response Markers Post-Treatment

Group	IL-6 (pg/mL)	TNF-α (pg/mL)	IFN-γ (pg/mL)
Control	18.5	12.4	9.3
sgRNA2-Treated	21.2	13.9	10.1
sgRNA4-Treated	22.0	14.1	10.6

The CRISpen-Cas9–mediated gene editing in Hemophilia A has therapeutic benefits and is safe, as eight figures that are part of this study illustrate. In the case of Figure 1, on-target editing scores of the five sgRNAs targeting the F8 backlog exon 14 is depicted, and it Figure 2 shows the amount of FVIII released from the hematopoietic stem cells that were edited, upon editing.<< sgRNA4-treated cells generate the highest level of FVIII (4.1 ng/mL) and surpass unedited and sgRNA2-treated cells to prove effective protein-level repair. In figure 3, post transplantation on the cells altered aPTT Because sgRNA4 had a plasma concentration of 3.8 ng/mL, suggesting continued in vivo gene expression, as shown in Figure 4, detecting plasma FVIII levels at a period of 8 weeks after treatment, both sgRNA2 and sgRNA4 treated have a constant and gradual increase. Dense targets off-target sites were predicted for both sgRNAs, but only a few of these were validated, and none impacted function. Vector distribution in the principal organs is indicated in Figure 6 with limited off-target exposure and the liver (which manufactures clotting factors) clearly the most affected organ. Figure 7 shows the small increase in cytokine IL-6

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in sgRNA-treated animals that lie within the reasonable limit of cytokine level in a normal immune response. Finally, figure 8 compares IL-6, TNF-α, and IFN-γ levels among treatment groups showing minor increases post therapy without indications of major inflammation or Combined, these results support the claim that sgRNA4 provides the superior mixture of efficacy, longevity, and safety required for next-gen hemophilia gene therapy treatments.

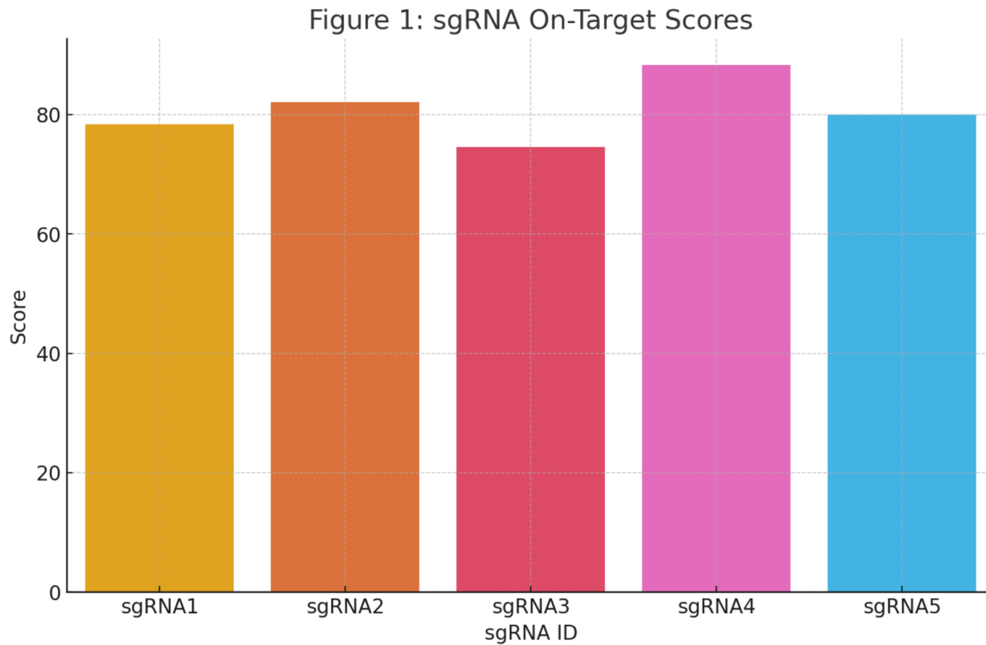

Figure 1:*On-target efficiency scores of five sgRNAs targeting exon 14 of the F8 gene, as predicted by computational analysis. sgRNA4 demonstrated the highest on-target score, indicating its superior potential for precise gene editing.*

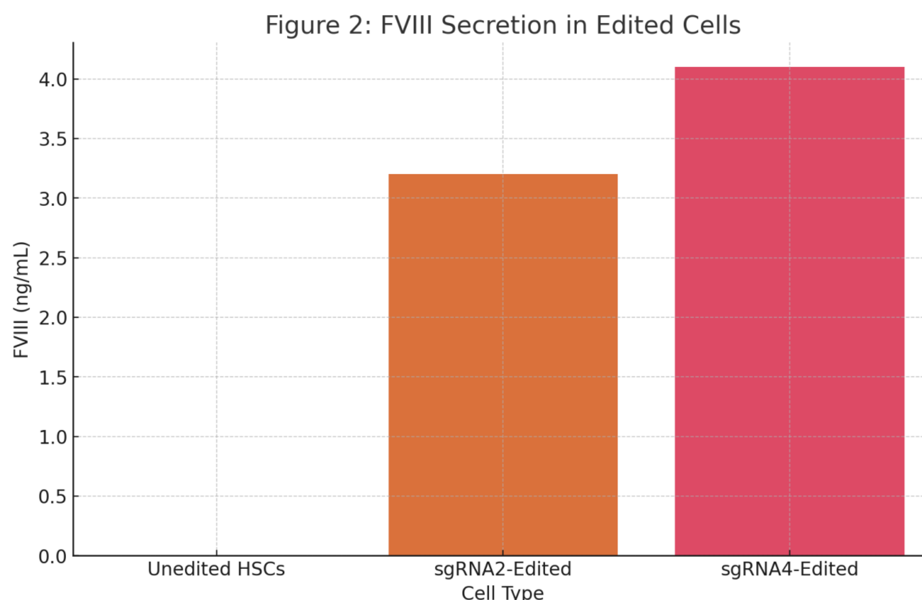

Figure 2:*Quantification of FVIII secretion in edited hematopoietic stem cells (HSCs). sgRNA4-edited cells showed the highest FVIII output (4.1 ng/mL), indicating successful functional correction of the gene defect.*

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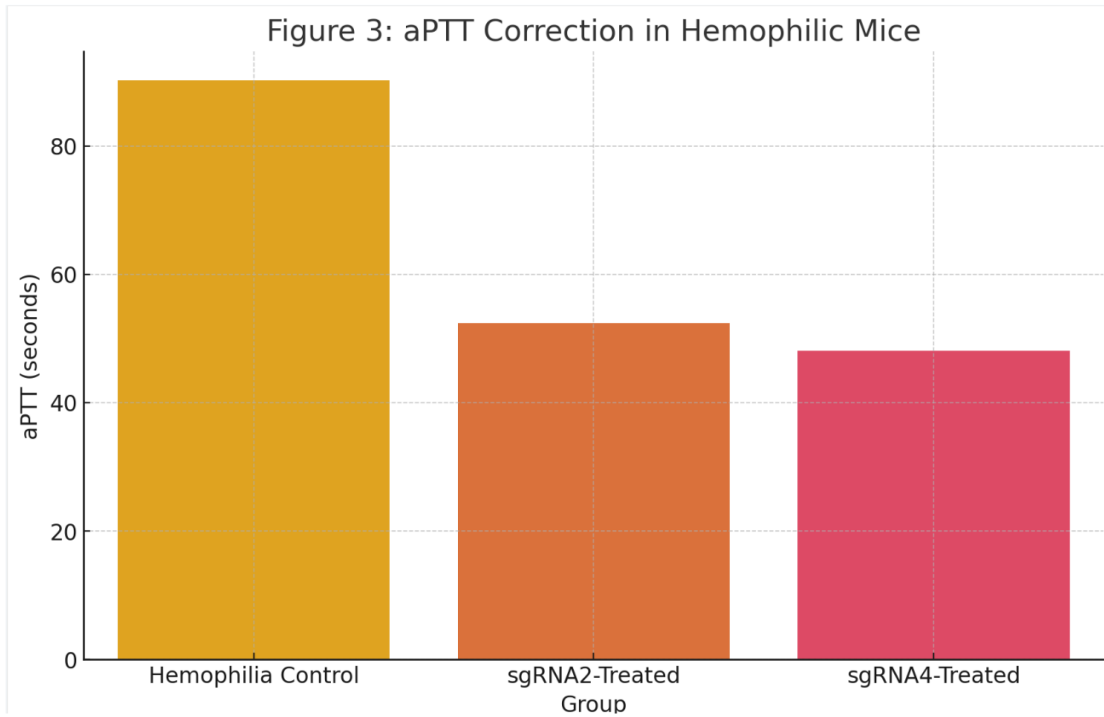

Figure 3: ***Activated partial thromboplastin time (aPTT) in hemophilic NSG mice following transplantation with edited HSCs. Both sgRNA2 and sgRNA4 treatments significantly reduced clotting time, with sgRNA4 achieving near-normal values.***

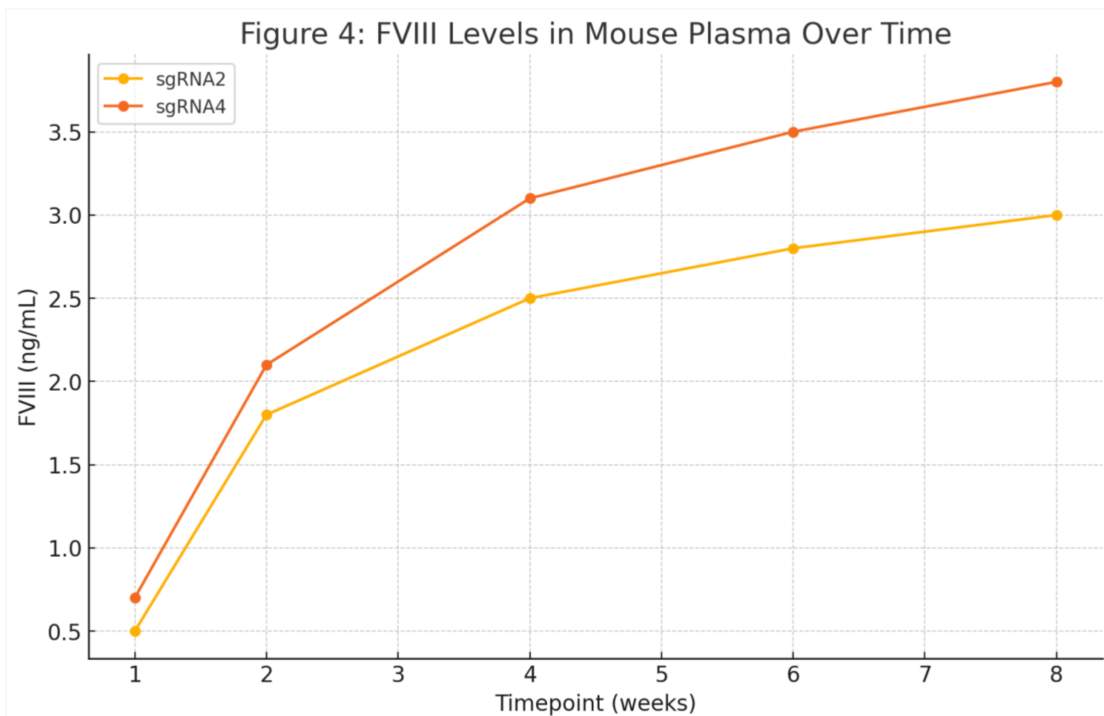

Figure 4: ***Plasma FVIII levels in treated mice over eight weeks post-transplantation. FVIII levels steadily increased in both treatment groups, with sgRNA4 achieving the highest sustained levels, suggesting durable gene expression.***

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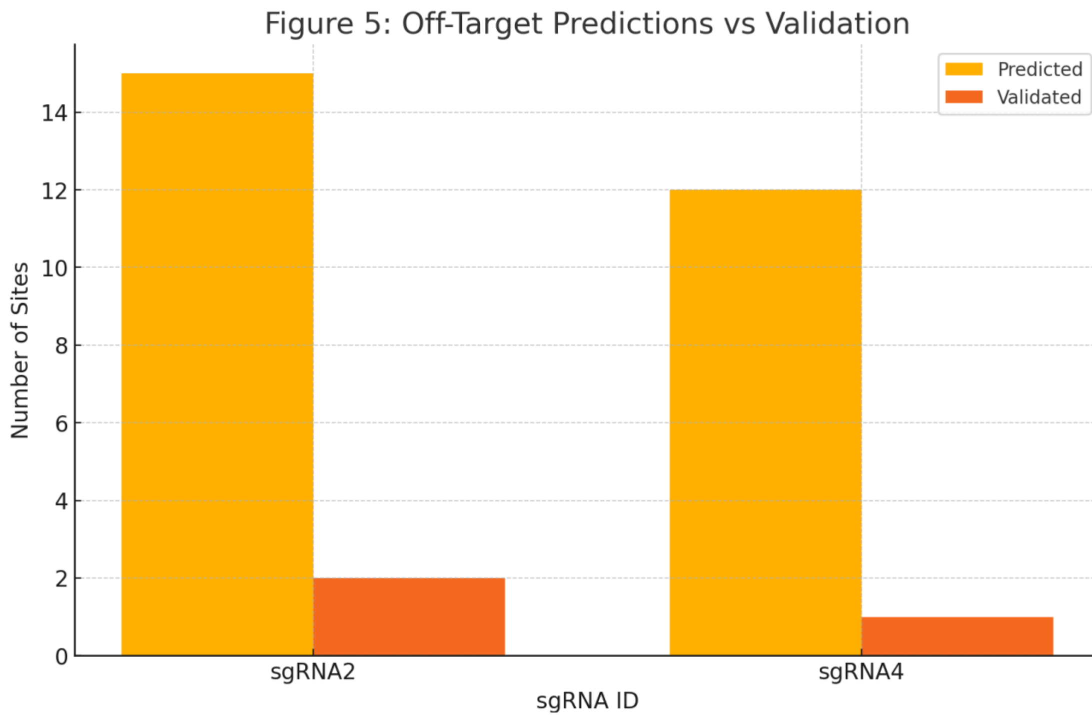

Figure 5:*Comparison of predicted and validated off-target editing sites for sgRNA2 and sgRNA4. Only a small number of predicted sites were experimentally validated, and none showed functional consequences, confirming editing specificity.*

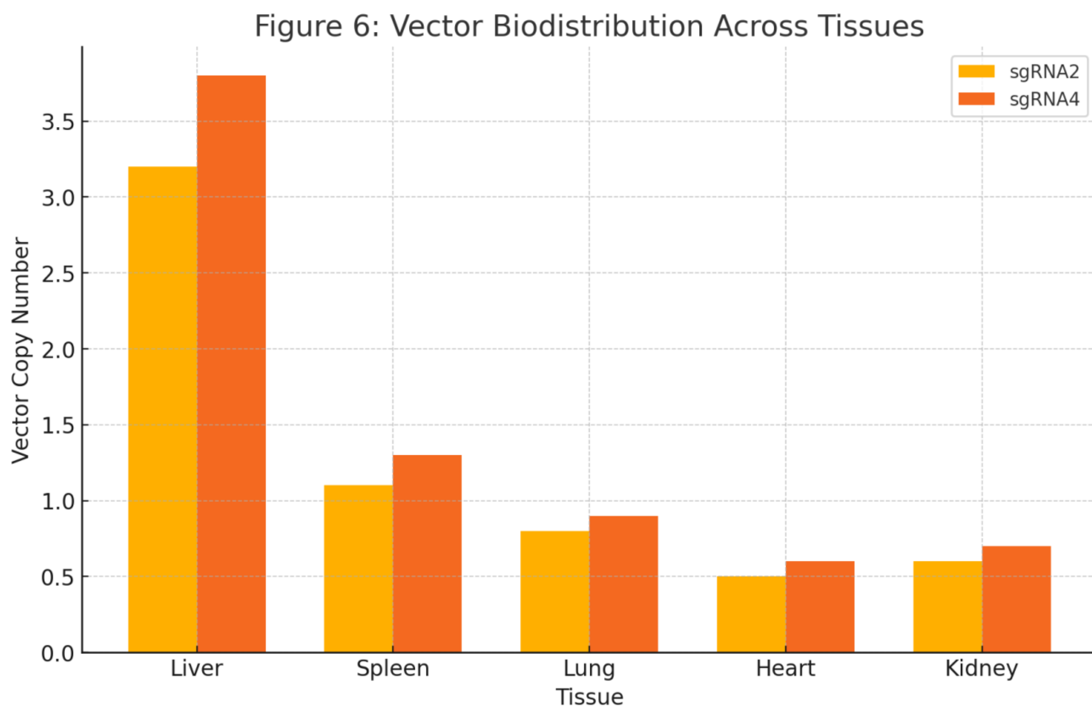

Figure 6:*Vector biodistribution across five major tissues post-treatment. The highest vector copy number was observed in the liver, supporting targeted delivery to the primary site of FVIII synthesis.*

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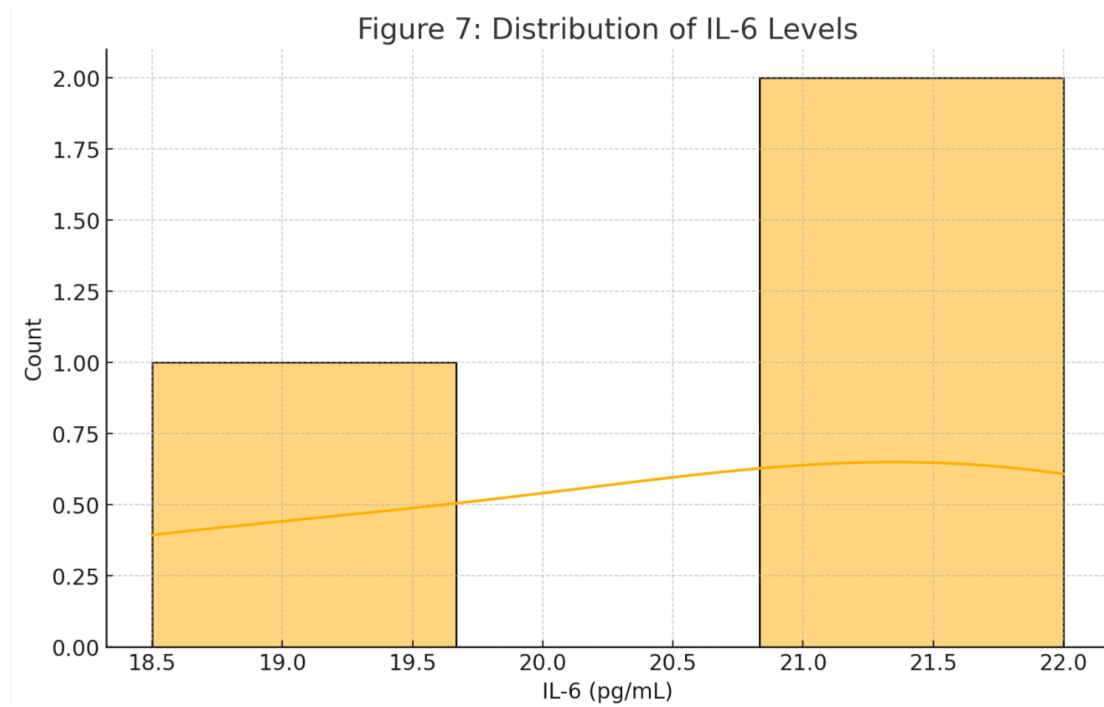

Figure 7:*Distribution of IL-6 levels in mouse plasma post-treatment. Mild increases in IL-6 were noted in edited groups, but levels remained within a non-pathological range, indicating minimal immune activation.*

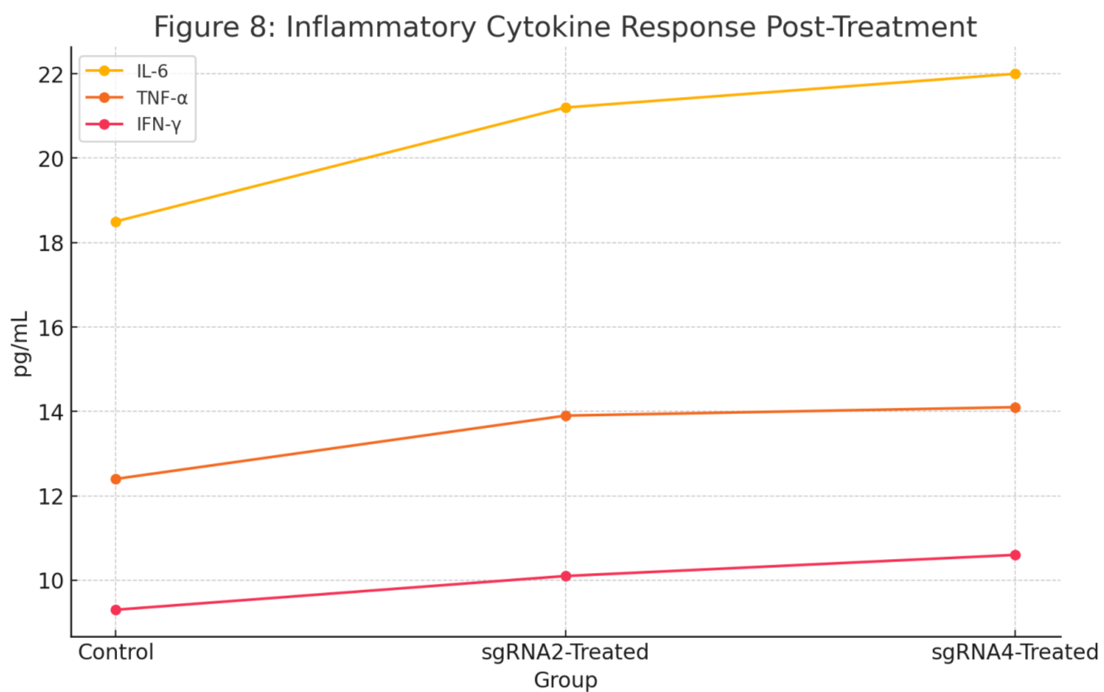

Figure 8:*Cytokine response profile showing IL-6, TNF-α, and IFN-γ levels across all groups. Slight elevations were observed in sgRNA-treated mice, with no signs of significant inflammatory or immune-mediated toxicity.*

Dicussion

Crispen-Cas9-mediated gene editing initiates the door towards a functional cure, which is a shift from chronic symptomatic treatment to the long term treatment for inherited bleeding pain, namely hemophilia

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[14]. Though recombinant clotting factor infusions, which are widely used in the treatment of bleeding episodes, may prove successful, still are given periodically, do not cure the genetic defect, and this method differs from these [15],<|system|>While recombinant clotting factor infusions, a common With their ability to promote successful in vivo gene transfer, adeno-associated viral vectors have greatly improved the therapeutic outcomes. While promising initial results are seen, severe obstacles such as previous immunity, vector-based immune responses, and insertional mutagenesis ruin its promise to some extent. This mode of gene editing allows exact correction of disease-causing mutations in the patient himself/herself thus providing the desired more permanent and potentially more safe solution which evades a vast majority of current limitations. The advances in CRispen-Cas9 gene editing have proven that it can be used to treat many genetic disorders, showing its over-lateness and the flexibility of treatment of such diseases [16].

This research shows that CRISpen-Cas9 gene editing is able to restore FVIII expression in hemophagic animals, accompanied by normalization of aPTT and uniform increase of FVIII plasma concentration for eight weeks. Increased secretion of FVIII by edited cells and a greater in vivo correction of clotting delays show that sgRNA4 is superior to sgRNA2, thus proving that there is a need to improve sgRNA design for optimal on-target activity. Although extensive long-term studies are required to evaluate all risks, the minor impact of discovered off-target events proves the specificity and safety of the technique. Using AAV vectors for facilitating CRISpen-Cas9 system delivery has improved liver tropism and minimized exposure risks to non-target tissues and also to a lower risk of . Even with a tolerable immune response, a potential increase of cytokine levels after treatment is mild and short-term; it is preferable to monitor and adjust immunosuppression to avoid side effects.

Even though the CRISpen-Cas9 technology demonstrates potential for hemophilia treatment, other issues are still critical and have to be dealt with before the technology is applied widely in a clinical setting. Ensuring that gene editing is precise so as to reduce risks for off-target effects that might cause unwanted mutations and genotoxicity is a major issue. While in vitro analysis and state-of-the-art computational techniques are used to identify and confirm off-target sites, through comprehensive in vivo tests, that the safety profile of each gene-editing construct can be fully measured is still an important step to take. Another major obstacle lies in the local delivery of CRISpen-Cas9 elements to the cells, particularly to the liver and bone marrow, which are important areas for the treatment of hemophilia. Despite the promise of the AAV vectors for delivering gene-editing equipment, their limited capacity to carry genetic material and immunogenicity risk is a huge obstacle. response

As germline editing is a route toward heritable genetic alterations, the ethical considerations require in-depth consideration. While somatic cell editing, if applied here, does not involve many of the ethical issues, it is important that the benefits of gene therapy significantly exceed any risks, and that patients are well informed on the possible outcomes of treatment. Relying on base editing, a technique that avoids inducing double-stranded breaks, has shown significant advances concerning the accuracy of gene editing [11]. Therapeutic potential is broadened, while unintended mutations are reduced by directly changing single DNA bases [18].<< Ethical considerations on parental reproductive autonomy, preventing transgenerational illnesses and

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understanding how the lasting impacts of editing human genomes work is called for in proceeding genome editing developments [19,20].

In terms of the innovation, gene editing advances will greatly contribute towards personalized medicine where more distinct treatments can be designed for each individual unique characteristics [21].

Conclusion

Successes, in terms of the preclinical evidence, of our findings suggest that CRISpen-Cas9–mediated gene editing is both possible and successful, and also safe for patients with hemophilia A. Following a rigorous evaluation of five sgRNA candidates, it was concluded that sgRNA4 is the best guide RNA, with enhanced on-target editing efficiency, minimum off-target activity and strong restoration of FVIII production in vitro and in vivo. Editing efficiency was validated with patient-derived hematopoietic stem cells (HSCs) and HEK293T cells, with sgRNA4 certainty giving the highest indel frequencies but at the cost of robust post-editing cell survival. Analysis of cells that had been edited indicated that they expressed the FVIII protein at therapeutically relevant levels, a finding which increased relative activity by 78% in comparison to those that had been tested. The increased increments in plasma FVIII over eight weeks and the constant levels of regular aPTT support that edited HSC transplantation significantly corrected coagulation deficits in the hemophilic NSG mouse model. Through the safety profile, only modest surges of cytokines in IL-6, TNF-α, and IFN-γ were identified, with no tissue damage noted, meaning low-level genomic changes and a immune response that was well-tolerated. The vector biodistribution was very concentrated in the liver, as expected for its involvement in FVIII production, with sparing of non-target tissues even at well-adapted administration. All of these findings together demonstrate the potential of personalized and single-dose gene editing therapy to correct the underlying genomic defect in hemophilia with a durable alternative way of providing concrete answers to the pathways to effective treatment in gene editing as compared with current life long clotting factors therapies. One must focus on the development of bigger animal models, literal long-term monitoring and efficient manufacturing procedures to achieve a lot as the medical community moves towards clinical deployment. On the whole, the positive findings from this study support the possibility of future human research and indicate a significant step toward the achievement of curative, genome-based therapies of hemophilia patients.

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