

Examining the Therapeutic Potential of CRISPR-Cas9 Gene Editing in Spondyloarthritis: Efficacy of TNF Inhibitor Adalimumab

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Abstract

Spondyloarthritis (SpA) encompasses a group of inflammatory rheumatic diseases characterized by axial and peripheral joint involvement, enthesitis, and extra-articular manifestations. Despite advancements in understanding the genetic and immunological underpinnings of SpA, current therapeutic options, including biologic therapies such as the TNF inhibitor adalimumab, primarily focus on symptom management and often show variable efficacy among patients. The advent of CRISPR-Cas9 gene editing technology presents a revolutionary opportunity to directly modify genetic contributors to SpA, potentially transforming the therapeutic landscape and enhancing the efficacy of adalimumab. This review investigates the feasibility and implications of utilizing CRISPR-Cas9 for targeted gene editing in SpA to improve patient response to adalimumab. We review the current knowledge on genetic mutations and polymorphisms associated with SpA pathogenesis, focusing on key genes involved in immune regulation and inflammatory pathways targeted by adalimumab. By leveraging CRISPR-Cas9, we aim to explore how precise genetic modifications can optimize the molecular targets of adalimumab, thereby enhancing its efficacy and reducing refractory cases. Preliminary studies in animal models and cell cultures demonstrate promising results, showcasing the potential of CRISPR-Cas9 to correct genetic abnormalities and synergize with adalimumab to restore normal cellular functions and reduce inflammation. However, translating these findings into clinical applications requires addressing significant challenges, including delivery methods, off-target effects, and long-term safety. Future research directions include optimizing CRISPR-Cas9 delivery systems, such as viral vectors and nanoparticle-based approaches, to enhance specificity and efficiency in conjunction with adalimumab. Additionally, comprehensive preclinical studies and early-phase clinical trials are essential to evaluate the combined therapeutic potential and safety profile of CRISPR-Cas9 and adalimumab in human subjects with SpA. This pioneering approach not only holds the promise of groundbreaking treatments for SpA but also sets the stage for broader applications of gene editing in rheumatology. By targeting the genetic roots of rheumatic diseases and optimizing adalimumab interactions, CRISPR-Cas9 could offer a new era of precision medicine, offering more effective and durable therapeutic outcomes.

Keywords: Spondyloarthritis, CRISPR-Cas9, Gene editing, Adalimumab, TNF inhibitors, Genetic mutations, Immune regulation, Inflammatory pathways, Precision medicine, Viral vectors, Nanoparticle delivery systems

INTRODUCTION

Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases defined by axial and peripheral joint involvement, enthesitis, and a range of extra-articular manifestations. Affecting up to 2% of the global population, SpA is often diagnosed up to a decade after symptom onset, leading to increased disease burden for patients [1].

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Axial involvement typically affects the spine and sacroiliac joints, causing chronic back pain and stiffness, while peripheral involvement results in limb pain and swelling. Enthesitis, the inflammation at tendon or ligament attachment sites, and extra-articular features such as uveitis, psoriasis, and inflammatory bowel disease further complicate SpA's clinical presentation. Additionally, SpA negatively impacts mental health and quality of life [2]. These diverse manifestations underscore the complexity of diagnosing and managing SpA, necessitating a multifaceted therapeutic approach [3].

The current therapeutic landscape for SpA includes nonsteroidal anti-inflammatory drugs (NSAIDs) and biologic therapies aimed at managing symptoms and controlling disease progression. NSAIDs are typically the first line of treatment, offering pain relief and reduced inflammation. For patients with moderate to severe disease, biologic agents such as tumor necrosis factor (TNF) inhibitors, including adalimumab, are employed. Adalimumab targets TNF, a pivotal cytokine in the inflammatory pathway of SpA [4]. Despite the efficacy of TNF inhibitors, there is considerable variability in treatment response, with some patients experiencing significant improvement compared to others. Current treatments focus on symptom management rather than addressing the underlying genetic and immunological mechanisms driving SpA pathogenesis [5,6].

Advancements in CRISPR-Cas9 gene editing technology have shown promise in targeting the genetic contributors to SpA. CRISPR-Cas9 uses a guide RNA to direct the Cas9 enzyme to specific DNA sequences, enabling targeted cuts in the genome to correct mutations or introduce new genetic elements. In the context of SpA, CRISPR-Cas9 offers the opportunity to directly alter genes implicated in disease pathogenesis, potentially leading to more effective and personalized therapeutic strategies [7]. By targeting the genetic factors contributing to SpA, CRISPR-Cas9 could revolutionize the current treatment paradigm, moving beyond symptom management to directly addressing the root causes of the disease.

This comprehensive review investigates the feasibility and implications of utilizing CRISPR-Cas9 for targeted gene editing in SpA. The primary focus includes mechanisms to enhance the efficacy of the most commonly used drug for SpA, biologic therapy adalimumab. Understanding genetic mutations and polymorphisms associated with SpA is crucial for successful CRISPR-Cas9 technology, enabling

precise genetic modifications to optimize the molecular targets of adalimumab. CRISPR-Cas9 holds the potential to introduce personalized medicine in SpA, tailoring treatments based on individual genetic profiles to optimize therapeutic outcomes and mitigate drug resistance. This review aims to shed light on strategies to augment the effectiveness of adalimumab and improve overall patient care.

DISCUSSION

Genetic and Immunological Underpinnings of SpA and Feasibility of CRISPR-Cas9 for Targeted Gene Editing in SpA

Spondyloarthritis is a group of chronic inflammatory diseases affecting the joints and spine, characterized by clinical manifestations such as psoriasis, uveitis, and inflammatory bowel disease, and a strong genetic association with Human Leukocyte Antigen B27 (HLA-B27) [8]. SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), IBD-associated or enteropathic arthritis, reactive arthritis (ReA), juvenile spondyloarthritis, and undifferentiated SpA. While the precise etiology of SpA is not fully understood, genome-wide association studies (GWAS) utilizing single nucleotide polymorphism (SNP) arrays have enhanced the understanding of its genetic associations [8]. SpA has a strong genetic inheritance pattern, with a recurrence risk ratio of 80 for siblings or first-degree relatives of AS, highlighting the significant role of HLA genes in its immunologic implications.

The human MHC (HLA) genetic map, located on the short arm of chromosome 6, spans approximately 7.6 Mb and is vital for immune response. The HLA gene class I loci include -A, -B, and -C, and class II includes -DRB1, -DQB1, and -DPB1; HLA class I genes are highly polymorphic, thereby increasing the risk of autoimmune diseases. The structure of an MHC gene involves a 340 amino acid heavy chain with extracellular domains ($\alpha 1$, $\alpha 2$, and $\alpha 3$) encoded by exons 2, 3, and 4. In contrast, non-MHC genes involve $\beta 2$ -microglobulin and non-polymorphic light chains on chromosome 15 [8]. SpA pathogenesis is primarily associated with HLA-B27, part of the MHC gene domain, involving arthritogenic peptides, unfolded protein response, HLA-B27 homodimer formation, and endoplasmic reticulum aminopeptidase malfunction [9].

The "arthritogenic peptide" hypothesis suggests that HLA-B27's unique peptide binding and tendency to misfold lead to the presentation of unique antigenic peptides,

which elicit cross-reactive cytotoxic CD8+ T-cell responses in joints and tissues [9]. Subtypes HLA-B*2705 and HLA-B*2704 are strongly associated with SpA, whereas HLA-B*2706 and HLA-B*2709 show weaker associations. The “unfolded protein response (UPR)” hypothesis implies that HLA-B27 misfolding in the endoplasmic reticulum (ER) causes ER stress, triggering UPR and upregulation of ER chaperones like immunoglobulin heavy-chain-binding protein (BiP) and endoplasmic reticulum-localized DnaJ 4 (ERdj4) leading to increased production of pro-inflammatory cytokines such as interleukin (IL)-23, IFN- β , and IL-17, and resulting in synovial tissue inflammation [9]. The “homodimer formation” hypothesis involves HLA-B27 homodimers on the cell surface binding to killer cell immunoglobulin-like receptors (KIRs) on natural killer (NK) and T cells, promoting pro-inflammatory cytokine IL-17 upregulation.

Endoplasmic reticulum aminopeptidase (ERAP) polymorphism represents the second strongest genetic link to SpA. ERAP1, involved in peptide trimming at the N-terminus to create an appropriate length for binding to MHC class I molecules and antigen presentation to CD8+ T lymphocytes and NK cells, regulates cellular immune responses [9]. ERAP1 polymorphisms, particularly loss-of-function variations, alter peptide processing and may contribute to AS pathogenesis. These genetic insights have guided the evolution of SpA management, shifting from non-specific anti-inflammatory drugs to targeted therapies addressing specific inflammatory cytokines or cellular pathways critical to SpA pathogenesis [10].

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There are two types of TNF- α receptors: TNFR1 and TNFR2. TNFR1 is expressed on nearly all cell types and induces cytotoxic and pro-inflammatory responses. In contrast, TNFR2 is expressed on monocytes, T cells, and

activated mesenchymal cells, where it promotes cellular proliferation, migration, and other pathological processes in synovial fibroblasts [12]. Studies have shown that patients with SpA have increased levels of NK cells and CD4+ T-cells expressing KIR3DL2 (Killer-cell Immunoglobulin-like Receptor, three domains, long cytoplasmic tail, 2). These KIR3DL2+ CD4+ T-cells recognize antigen-presenting cells on HLA-B27 homodimers, leading to significant production of IL-17 cytokines. Together with TNF- α , IL-17 stimulates the release of inflammatory mediators affecting bone metabolism and influencing joints and surrounding tissues [13]. Since TNF- α plays a direct role in the early stages of SpA, targeting TNF- α has been shown to reduce inflammation by downregulating inflammatory cytokines and chemokines, and increasing circulating regulatory T cells [12]. Despite these targeted therapies, some patients fail to respond or lose response over time due to several factors.

Serum drug levels are influenced by gender, serum albumin, body mass index, inflammatory burden, prior failure of biologic DMARDs, and tissue-specific mechanisms such as loss in stool, local proteases, and recycling by neonatal Fc receptor [12]. Secondary loss of response can be due to pharmacodynamic or pharmacokinetic (immune or non-immune) causes. A major cause of secondary failure to anti-TNF- α therapy is the formation of anti-drug (ADAs), which can cross-react with biosimilar drugs, leading to treatment failure [12]. According to a study by Wcisło-Dziadecka et al., treatment with adalimumab resulted in higher expression of TNFR2 compared to TNFR1 at the mRNA level, counteracting the therapeutic effect and manifesting as drug resistance [14]. This alteration of TNFR, leading to increased TNFR2 expression, results in poor drug efficacy. Precise genetic modification by CRISPR-Cas9 technology offers a solution to this issue. Optimizing gene expression could enhance the effectiveness of biologics like adalimumab and improve symptom management for patients with this debilitating disease.

CRISPR-Cas9 can be introduced in the body using viral vectors (adenovirus), nanoparticles, or electroporation. This process uses single guide RNA (sgRNA) to direct the Cas9 endonuclease to the target DNA sequence within the cell [15]. In plasmid format, the sgRNA and Cas9 are transcribed and translated within the cell to form the active sgRNA-Cas9 complex. This complex targets specific genes involved in multidrug resistance (MDR). Targeting and disrupting these MDR-related genes in miRNAs can weaken drug resistance by causing mRNA degradation,

destabilization, and inhibition of translation. The Cas9 enzyme creates a double-strand break in the target sequence, which the cell repairs using its non-homologous end-joining system, often resulting in gene disruption or the insertion of new MDR-related gene sequences [15]. Thus, targeting TNF- α gene expression using CRISPR-Cas9 technology could reduce TNFR2 expression in response to TNFR1 mutation, enhancing the efficacy of adalimumab and reducing the incidence of refractory cases.

Challenges and Considerations

Addressing the challenges of delivering CRISPR-Cas9 into target cells or tissues in vivo is paramount for successful gene editing applications. Research focuses on developing efficient delivery methods, ensuring the specificity and safety of the delivery system, and minimizing off-target effects. Various delivery strategies have been explored, including viral vectors, nanoparticles, and direct delivery of Cas9 protein and guide RNA complexes. Each method has its advantages and limitations, and the choice of delivery system can significantly impact the efficacy and specificity of gene editing [16,17].

Ensuring the specificity and safety of the delivery system is essential to minimize off-target effects and potential harm to the host organism. High precision in targeting specific cells or tissues helps reduce off-target effects and improves the overall safety profile of the gene editing process. Long-term studies on the safety and toxicity of delivery components, especially nanoparticle carriers, are crucial to understanding the potential risks associated with in vivo delivery of CRISPR-Cas9. Comprehensive assessments of where the components end up in the body, their persistence, and any long-term effects are necessary to ensure the safety of gene editing therapies.

Exploring viral vectors and nanoparticle-based approaches holds significant promise in enhancing the specificity and efficiency of delivering CRISPR-Cas9 into target cells or tissues in vivo. These innovative strategies are poised to revolutionize the field of gene editing [18]. Viral vectors such as adeno-associated virus (AAV), adenovirus, and lentivirus have proven effective for delivering CRISPR components due to their high transduction efficiency and ability to target specific cell types. Engineered viral vectors are designed to carry the Cas9 protein and guide RNA to target cells, thereby reducing off-target effects and enhancing precision by delivering the gene editing machinery directly into the cell's nucleus.

Meanwhile, nanoparticle-based approaches, such as lipid nanoparticles and gold nanoparticles, offer a versatile alternative for CRISPR-Cas9 delivery. These nanoparticles can encapsulate the gene editing components, protecting them from degradation and facilitating their uptake by target cells [19]. Moreover, nanoparticle carriers can be modified to enhance cell specificity and reduce off-target effects, thereby improving the overall efficiency of gene editing. This adaptability underscores their potential as a valuable tool in the field of gene editing.

Strategies to minimize off-target effects in CRISPR-Cas9 editing, such as designing specific guide RNAs, utilizing engineered Cas9 variants with reduced non-specific binding, delivering Cas9 ribonucleoprotein complexes directly, and conducting thorough validation and screening of potential off-target sites, hold immense potential [20]. These approaches, when implemented effectively, can significantly enhance the precision and specificity of gene editing. This potential impact on the safe and effective application of CRISPR-Cas9 in therapeutic settings should inspire further research.

Considerations for the long-term safety and potential risks of CRISPR-Cas9 therapy in human subjects include concerns about off-target effects, immune responses, germline modifications, persistence of edited cells, and insertional mutagenesis by viral vectors. Rigorous preclinical studies and thorough assessment of off-target effects are crucial for addressing these risks. Continuous monitoring of treated individuals is essential, along with ethical considerations regarding germline editing and transparent patient communication about risks and benefits. Ensuring the safe and responsible use of CRISPR-Cas9 therapy in clinical applications requires comprehensive ethical frameworks and universal application guidelines.

The ethical implications of CRISPR-Cas9 technology in precision medicine necessitate careful consideration. While its potential to treat diseases like SpA is promising, ethical concerns bring up questions about safety, unintended consequences, and the potential for genetic modifications to be passed down to future generations. Additionally, there are concerns regarding equitable access to such advanced treatments and the potential exacerbation of existing social inequalities in healthcare. Ethical frameworks must be robustly developed and universally applied to ensure that CRISPR-Cas9 technologies are used responsibly, with full respect for patient autonomy, informed consent, and societal values. Ethical oversight

and transparency in research and clinical applications are essential to navigating these complex ethical landscapes and fostering public trust in the transformative potential of gene editing technologies [21].

Areas for Future Research

One critical area for future research in the application of CRISPR-Cas9 technology is the optimization of delivery systems. Effective delivery of CRISPR-Cas9 components to target cells is paramount to enhance both the specificity and efficiency of gene editing [22]. Current delivery methods, such as viral vectors, lipid nanoparticles, and electroporation, each have their advantages and limitations regarding efficiency, immune response, and off-target effects. For instance, viral vectors like AAVs are highly efficient but can trigger immune responses, limiting their repeated use [23]. Conversely, lipid nanoparticles offer a safer profile but may have lower delivery efficiency. Future research should focus on developing hybrid delivery systems that combine the strengths of these methods while minimizing their weaknesses. For example, combining lipid nanoparticles with targeting peptides could improve cellular uptake and precision, reducing off-target effects and enhancing the therapeutic potential of CRISPR-Cas9 [19].

The importance of comprehensive preclinical studies cannot be overstated in the context of evaluating the therapeutic potential of CRISPR-Cas9, especially when combined with established treatments like adalimumab for SpA. Preclinical studies provide a foundational understanding of the efficacy, pharmacokinetics, and safety profile of new therapeutic strategies before they are tested in humans [24]. Animal models of SpA, such as HLA-B27 transgenic rats, can be instrumental in assessing the potential benefits and risks of CRISPR-Cas9-mediated gene editing combined with adalimumab therapy. These models help in understanding how gene editing might modulate immune responses and inflammation, potentially providing synergistic effects with adalimumab [25]. The data obtained from these studies will be crucial in designing early-phase clinical trials.

Early-phase clinical trials are necessary to translate preclinical findings into potential treatments for patients with SpA. Phase I/II trials focus on evaluating the safety, tolerability, and preliminary efficacy of CRISPR-Cas9 and adalimumab combination therapies in human subjects [26]. These trials will help determine the optimal dosages, administration routes, and treatment regimens. Additionally, these studies will assess the long-term effects and potential risks, such as unintended off-target gene

edits and immune reactions. Patient stratification based on genetic, molecular, and clinical biomarkers will be vital in these trials to identify which subgroups of patients are most likely to benefit from the therapy. This personalized approach could enhance the therapeutic outcomes and minimize adverse effects, paving the way for more targeted and effective treatments [27].

Looking ahead, integrating CRISPR-Cas9 with adalimumab in clinical practice could revolutionize the treatment landscape for SpA. The potential to correct underlying genetic predispositions combined with the anti-inflammatory effects of adalimumab offers a multifaceted approach to managing the disease. This combination could not only alleviate symptoms but also modify disease progression, providing a long-term solution for patients. Furthermore, ongoing advancements in CRISPR technology, such as the development of CRISPR-based editors and prime editors, could further enhance the precision and scope of gene editing [28]. As research progresses, it will be crucial to establish strong ethical frameworks and regulatory guidelines to ensure the safe and equitable application of these novel therapies, especially as it pertains to precision or individualized medicine.

CONCLUSION

The potential of CRISPR-Cas9 in precision medicine marks a significant advancement in rheumatology, particularly for the treatment of complex inflammatory diseases like SpA. This condition affects not only the spine and joints but also various other body systems, including the eyes, skin, and gastrointestinal tract. By targeting the genetic roots of SpA, CRISPR-Cas9 offers the possibility of addressing the underlying causes of the disease rather than merely alleviating symptoms. This precision approach could significantly enhance the therapeutic interactions of adalimumab, improving its efficacy and reducing side effects.

The broader implications of gene editing technologies extend far beyond rheumatology, promising advancements in various fields of medicine by enabling targeted and personalized treatment strategies. This review highlights the transformative potential of CRISPR-Cas9, emphasizing its ability to revolutionize SpA treatment. By paving the way for more effective and durable therapeutic outcomes, CRISPR-Cas9 can improve patient quality of life and set the stage for innovative applications across the medical spectrum. The integration of gene editing with conventional therapies could thus lead to a future where

precision medicine is the norm, offering hope for more comprehensive and lasting solutions to complex diseases such as SpA.

REFERENCES

- Allado, E., Moussu, A., Bigna, J. J., Hamroun, S., Camier, A., Chenuel, B., & Hamroun, A. (2020). Global prevalence of spondyloarthritis in low-income and middle-income countries: a systematic review and meta-analysis protocol. *BMJ open*, 10(10), e041180. <https://doi.org/10.1136/bmjopen-2020-041180>
- Zhao, S., Thong, D., Miller, N., Duffield, S. J., Hughes, D. M., Chadwick, L., & Goodson, N. J. (2018). The prevalence of depression in axial spondyloarthritis and its association with disease activity: a systematic review and meta-analysis. *Arthritis research & therapy*, 20(1), 140. <https://doi.org/10.1186/s13075-018-1644-6>
- Walsh, J. A., & Magrey, M. (2021). Clinical Manifestations and Diagnosis of Axial Spondyloarthritis. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases*, 27(8), e547–e560. <https://doi.org/10.1097/RHU.0000000000001575>
- Wang, R., Bathon, J. M., & Ward, M. M. (2020). Nonsteroidal Antiinflammatory Drugs as Potential Disease-Modifying Medications in Axial Spondyloarthritis. *Arthritis & rheumatology*, 72(4), 518–528. <https://doi.org/10.1002/art.41164>
- Mease, P., Sieper, J., Van den Bosch, F., Rahman, P., Karunaratne, P. M., & Pangan, A. L. (2015). Randomized controlled trial of adalimumab in patients with nonpsoriatic peripheral spondyloarthritis. *Arthritis & rheumatology*, 67(4), 914–923. <https://doi.org/10.1002/art.39008>
- Burgos-Vargas, R., Tse, S. M., Horneff, G., Pangan, A. L., Kalabic, J., Goss, S., Unnebrink, K., & Anderson, J. K. (2015). A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. *Arthritis care & research*, 67(11), 1503–1512. <https://doi.org/10.1002/acr.22657>
- Inman R. D. (2021). Axial Spondyloarthritis: Current Advances, Future Challenges. *Journal of rheumatic diseases*, 28(2), 55–59. <https://doi.org/10.4078/jrd.2021.28.2.55>
- Díaz-Peña, R., Castro-Santos, P., Durán, J., Santiago, C., & Lucia, A. (2020). The Genetics of Spondyloarthritis. *Journal of personalized medicine*, 10(4), 151. <https://doi.org/10.3390/jpm10040151>
- Sharip, A., & Kunz, J. (2020). Understanding the Pathogenesis of Spondyloarthritis. *Biomolecules*, 10(10), 1461. <https://doi.org/10.3390/biom10101461>
- Tian, X., Li, M., Liu, S., Leng, X., Wang, Q., Zhao, J., Liu, Y., Zhao, Y., Zhang, Y., Xu, H., Gu, J., & Zeng, X. (2023). Consensus on targeted drug therapy for spondyloarthritis. *Rheumatology and immunology research*, 4(2), 47–59. <https://doi.org/10.2478/rir-2023-0009>
- Bosè, F., Raeli, L., Garutti, C., Frigerio, E., Cozzi, A., Crimi, M., Caprioli, F., Scavelli, R., Altomare, G., Geginat, J., Abrignani, S., & Reali, E. (2011). Dual role of anti-TNF therapy: enhancement of TCR-mediated T cell activation in peripheral blood and inhibition of inflammation in target tissues. *Clinical immunology (Orlando, Fla.)*, 139(2), 164–176. <https://doi.org/10.1016/j.clim.2011.01.015>
- Evangelatos, G., Bamias, G., Kitas, G. D., Kollias, G., & Sfikakis, P. P. (2022). The second decade of anti-TNF- α therapy in clinical practice: new lessons and future directions in the COVID-19 era. *Rheumatology international*, 42(9), 1493–1511. <https://doi.org/10.1007/s00296-022-05136-x>
- Garcia-Montoya, L., & Emery, P. (2021). Disease modification in ankylosing spondylitis with TNF inhibitors: spotlight on early phase clinical trials. *Expert Opinion on Investigational Drugs*, 30(11), 1109–1124. <https://doi.org/10.1080/13543784.2021.2010187>
- Wcisło-Dziadecka, D., Grabarek, B., Swinarew, A. S., Rozwadowska, B., Zmarzły, N., & Gola, J. (2020). Comprehensive molecular and clinical analysis of adalimumab and etanercept therapeutic potential in patients with psoriatic arthritis. *Postepy dermatologii i alergologii*, 37(2), 262–268. <https://doi.org/10.5114/ada.2020.94847>
- Vaghari-Tabari, M., Hassanpour, P., Sadeghsoltani, F., Malakoti, F., Alemi, F., Qujeq, D., Asemi, Z., & Yousefi, B. (2022). CRISPR/Cas9 gene editing: a new approach for overcoming drug resistance in cancer. *Cellular & molecular biology letters*, 27(1), 49. <https://doi.org/10.1186/s11658-022-00348-2>

16. Liu, W., Li, L., Jiang, J., Wu, M., & Lin, P. (2021). Applications and challenges of CRISPR-Cas gene-editing to disease treatment in clinics. *Precision clinical medicine*, 4(3), 179–191. <https://doi.org/10.1093/pcmedi/pbab014>
17. Sioson, V. A., Kim, M., & Joo, J. (2021). Challenges in delivery systems for CRISPR-based genome editing and opportunities of nanomedicine. *Biomedical engineering letters*, 11(3), 217–233. <https://doi.org/10.1007/s13534-021-00199-4>
18. Anders, C., Niewoehner, O., Duerst, A., & Jinek, M. (2014). Structural basis of PAM-dependent target DNA recognition by the Cas9 endonuclease. *Nature*, 513(7519), 569–573. <https://doi.org/10.1038/nature13579>
19. Hou, X., Zaks, T., Langer, R., & Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials*, 6. <https://doi.org/10.1038/s41578-021-00358-0>
20. Ramakrishna, S., Kwaku Dad, A. B., Beloor, J., Gopalappa, R., Lee, S. K., & Kim, H. (2014). Gene disruption by cell-penetrating peptide-mediated delivery of Cas9 protein and guide RNA. *Genome research*, 24(6), 1020–1027. <https://doi.org/10.1101/gr.171264.113>
21. Shinwari, Z. K., Tanveer, F., & Khalil, A. T. (2018). Ethical Issues Regarding CRISPR Mediated Genome Editing. *Current issues in molecular biology*, 26, 103–110. <https://doi.org/10.21775/cimb.026.103>
22. Lino, C. A., Harper, J. C., Carney, J. P., & Timlin, J. A. (2018). Delivering CRISPR: a review of the challenges and approaches. *Drug delivery*, 25(1), 1234–1257. <https://doi.org/10.1080/10717544.2018.1474964>
23. Kotterman, M. A., & Schaffer, D. V. (2014). Engineering adeno-associated viruses for clinical gene therapy. *Nature reviews. Genetics*, 15(7), 445–451. <https://doi.org/10.1038/nrg3742>
24. Rogge, M.C., & Taft, D.R. (Eds.). (2005). *Preclinical Drug Development* (1st ed.). CRC Press. <https://doi.org/10.1201/9780849360237>
25. Taurog, J. D., Maika, S. D., Satumtira, N., Dorris, M. L., McLean, I. L., Yanagisawa, H., Sayad, A., Stagg, A. J., Fox, G. M., Lê O'Brien, A., Rehman, M., Zhou, M., Weiner, A. L., Splawski, J. B., Richardson, J. A., & Hammer, R. E. (1999). Inflammatory disease in HLA-B27 transgenic rats. *Immunological reviews*, 169, 209–223. <https://doi.org/10.1111/j.1600-065x.1999.tb01317.x>
26. Li, H. L., Fujimoto, N., Sasakawa, N., Shirai, S., Ohkame, T., Sakuma, T., Tanaka, M., Amano, N., Watanabe, A., Sakurai, H., Yamamoto, T., Yamanaka, S., & Hotta, A. (2015). Precise correction of the dystrophin gene in duchenne muscular dystrophy patient induced pluripotent stem cells by TALEN and CRISPR-Cas9. *Stem cell reports*, 4(1), 143–154. <https://doi.org/10.1016/j.stemcr.2014.10.013>
27. Hidalgo, M., Amant, F., Biankin, A. V., Budinská, E., Byrne, A. T., Caldas, C., Clarke, R. B., de Jong, S., Jonkers, J., Mælandsmo, G. M., Roman-Roman, S., Seoane, J., Trusolino, L., & Villanueva, A. (2014). Patient-derived xenograft models: an emerging platform for translational cancer research. *Cancer discovery*, 4(9), 998–1013. <https://doi.org/10.1158/2159-8290.CD-14-0001>
28. Anzalone, A. V., Randolph, P. B., Davis, J. R., Sousa, A. A., Koblan, L. W., Levy, J. M., Chen, P. J., Wilson, C., Newby, G. A., Raguram, A., & Liu, D. R. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature*, 576(7785), 149–157. <https://doi.org/10.1038/s41586-019-1711-4>

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