Molecular Therapy
Nucleic Acids
Review

The landscape and trajectory of global CRISPR therapeutics

Ceren Şahin,[1,28] Teresa Maria Formica,[2,3,27,28] Alfredo Silva,[4,28] Giulia Della Pelle,[5] Maria C. Davis,[6] Daniel Gottenborg Andersen,[7,21] Mısra Çavdar,[8] Lúcia Santos,[9,10] Liyan Qiu,[11] Amalie Lykke Olsen,[11] Anne Louise Askou,[11,12] Mariana Köber,[13,14] Cecilia Jimenez-Mallebrera,[15,16] Marina Cortijo Gutiérrez,[17,18,19,20] Johannes Frasez Soerensen,[7,21] Francisco Martín,[17,18,19,20] Rasmus O. Bak,[11] Aylin Sendemir,[8] Paula Río,[22] Alessia Cavazza,[23,24] Karim Benabdellah,[18] Rajeevkumar Raveendran Nair,[25] and Yonglun Luo[11,26,27]

[1]Department of Physiology, Genetics and Microbiology, University of Alicante, Alicante, Spain; [2]University of Naples Federico II, Pharmacy Department, Naples, Italy; [3]Molecular Cardiology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy; [4]San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy; [5]Jožef Stefan Institute, Jamova 39, Ljubljana 1000, Slovenija; [6]Department of Molecular Biology and Genetics, Aarhus University, Aarhus C, Denmark; [7]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark; [8]Department of Bioengineering, Ege University, İzmir, Türkiye; [9]IBET-Instituto de Biologia Experimental e Tecnológica, Apartado 12, 2781-901 Oeiras, Portugal; [10]Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Av. da República, 2780-157 Oeiras, Portugal; [11]Department of Biomedicine, Aarhus University, Aarhus, Denmark; [12]Department of Ophthalmology, Aarhus University Hospital, Aarhus N, Denmark; [13]Institut de Ciència de Materials de Barcelona, ICMAB-CSIC, Campus UAB, 08193 Bellaterra, Catalonia, Spain; [14]CIBER de Bioingeniería, Biomateriales y Nanomedicina, Instituto de Salud Carlos III, 08193 Bellaterra, Spain; [15]Laboratorio de Investigación Aplicada en Enfermedades Neuromusculares, Unidad de Patología Neuromuscular. Institut de Recerca Sant Joan de Déu, 08950 Barcelona, Spain; [16]CIBER for Rare Diseases, ISCIII, Madrid, Spain; [17]Department of Biochemistry and Molecular Biology III and Immunology, Faculty of Medicine, University of Granada, 18006 Granada, Spain; [18]Centre for Genomics and Oncological Research, Genomic Medicine Department, Pfizer-University of Granada-Andalusian Regional Government (GENYO), 18006 Granada, Spain; [19]Biosanitary Research Institute of Granada (ibs.GRANADA), University of Granada, 18006 Granada, Spain; [20]Excellence Research Unit "Modeling Nature" (MNat), University of Granada, 18006 Granada, Spain; [21]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [22]Division of Hematopoietic Innovative Therapies, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain, Advanced Therapies Unit, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain, Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain; [23]Infection, Immunity & Inflammation Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, University College London, 20 Guilford Street, London WC1N 1DZ, UK; [24]Center for Genomic Medicine and Rare Diseases, Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [25]Kavli Institute for Systems Neuroscience, Center for Algorithms in the Cortex, Egil and Pauline Braathen and Fred Kavli Center for Cortical Microcircuits, Norwegian University of Science and Technology, Trondheim, Norway; [26]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus N, Denmark

With the first regulatory approval in 2023 of a CRISPR-based therapy for sickle cell disease followed by the recent demonstration of an accelerated, personalized CRISPR treatment for congenital severe carbamoyl-phosphate synthetase 1 deficiency, CRISPR-Cas9 genome editing has progressed from a laboratory technology into a clinical reality in just over a decade. While enthusiasm for deploying CRISPR-Cas9 to treat a range of human genetic diseases continues to grow, broad clinical application remains constrained due to technical, regulatory, manufacturing and economic challenges. Here, scientists from the European Cooperation in Science and Technology (COST) action *Genome Editing to Treat Human Diseases* (GenE-HumDi) provide a comprehensive global overview of the CRISPR therapeutic landscape. We systematically analyze CRISPR-based therapeutic trials registered on ClinicalTrials.gov and the EU Clinical Trials Register, providing a thorough assessment of the current clinical activity and the trajectory of CRISPR technology as it advances toward routine clinical interventions.

INTRODUCTION

Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins (Cas) have undergone a remarkable

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[27]These authors contributed equally

[28]These authors contributed equally

Correspondence: Teresa Maria Formica, University of Naples Federico II, Pharmacy Department, Naples, Italy.
E-mail: formica.teresamaria@gmail.com
Correspondence: Karim Benabdellah, Centre for Genomics and Oncological Research, Genomic Medicine Department, Pfizer-University of Granada-Andalusian Regional Government (GENYO), 18006 Granada, Spain.
E-mail: karim.benabdel@genyo.es
Correspondence: Rajeevkumar Raveendran Nair, Kavli Institute for Systems Neuroscience, Center for Algorithms in the Cortex, Egil and Pauline Braathen and Fred Kavli Center for Cortical Microcircuits, Norwegian University of Science and Technology, Trondheim, Norway.
E-mail: rajeevkumar.r.nair@ntnu.no
Correspondence: Yonglun Luo, Department of Biomedicine, Aarhus University, Aarhus, Denmark.
E-mail: alun@biomed.au.dk

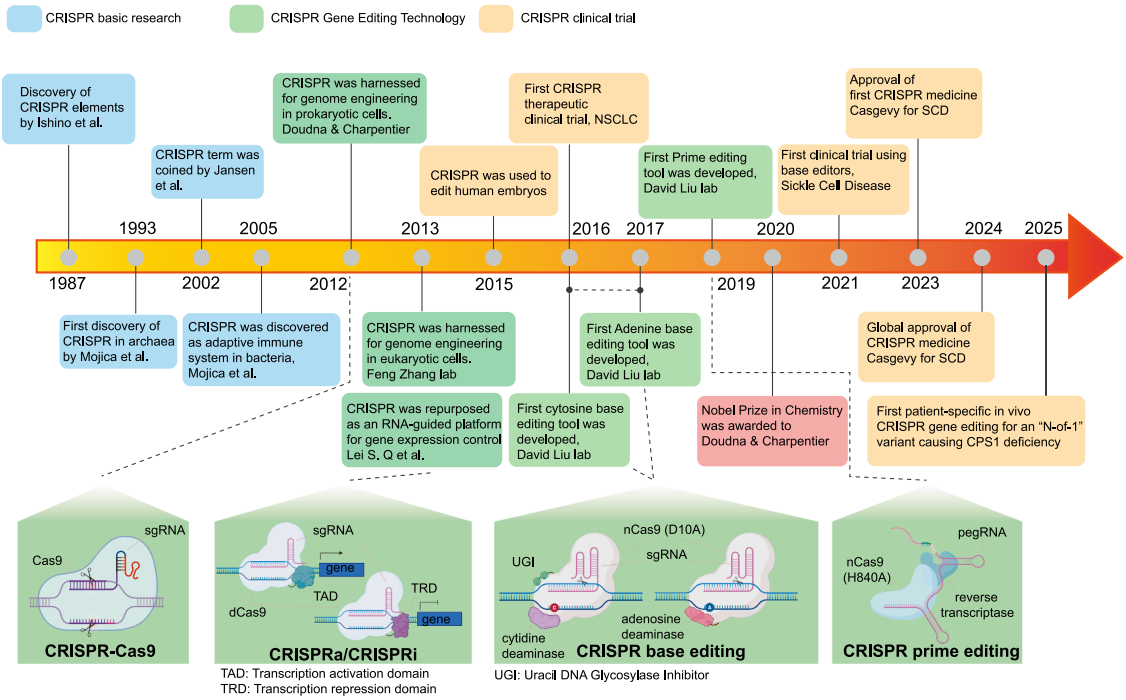

Figure 1. Timeline of key breakthroughs in the CRISPR field

This brief timeline outlines selected milestones in CRISPR research, from fundamental discoveries to the development of next-generation CRISPR-based gene-editing tools (CRISPR 2.0 research), and the initiation of clinical trials. This also depicts schematics of the CRISPR-Cas9 based gene-editing repertoire, including native and modified CRISPR-Cas systems, specifically prime editing and base editing that hold therapeutic relevance. Some CRISPR icons are prepared with Biorender.com with license for publication (Luo Y. 2026).

transformation since their identification as components of adaptive immunity in bacteria and archaea.[1] Following the demonstration that CRISPR-Cas could be programmed for targeted genome editing in prokaryotes, this RNA-guided genome editing system was rapidly adapted for precise and efficient genetic manipulation across eukaryotic models and numerous multicellular organisms.[2–4] Compared to the earlier genome-editing platforms, CRISPR technologies offered unprecedented simplicity, cost-effectiveness and specificity, catalyzing their widespread adoption in research and translational applications. In recognition of the conceptual and technical breakthroughs that laid the foundation of CRISPR-Cas9 gene-editing technology, Jennifer Doudna and Emmanuelle Charpentier were awarded the 2020 Nobel Prize in Chemistry.

The classical CRISPR gene-editing mechanism relies on Cas9-mediated induction of a DNA double-strand break (DSB), directed to a specific genomic locus by a complementary single-guide RNA (gRNA or sgRNA).[5] In mammalian cells, the resulting DSB is repaired predominantly by the endogenous non-homologous end joining (NHEJ) pathway which introduces small insertions or deletions (collectively known as indels) that disrupt the coding sequence and typically lead to disruption of the encoding gene product. Alternatively, when a homologous donor DNA template is supplied, homology-directed repair (HDR) can mediate precise sequence modification or targeted insertion of an exogenous gene, though this pathway is restricted to specific cell-cycle phases. While classical DSB-dependent genome editing has proven highly efficient for gene disruption, large intra- and inter-chromosomal alterations introduced at the on-target and off-target sites respectively remain a major genotoxicity concern.[6,7] Building on the high structural flexibility and programmability of Cas9, a rapidly expanding suite of engineered CRISPR-based technologies has emerged to overcome the limitations of DSB-dependent genome editing. These include base editors, which facilitate single-nucleotide modifications without generating DSBs, thereby enhancing precision and minimizing undesired repair outcomes,[8] and prime editors, which allow targeted insertions, deletions, and diverse sequence substitutions without the need for DNA donor templates or DSB formation.[9] These advances have transformed the genome editing landscape, offering unprecedented versatility and safety, positioning CRISPR platforms as leading candidates for therapeutic correction of human genetic diseases. In this review, we provide a comprehensive overview of CRISPR technologies with a particular focus on their clinical translation potential, systematically evaluating ongoing and completed clinical trials targeting human genetic diseases.

OVERVIEW OF CRISPR GENE-EDITING STRATEGIES

To provide an overview of the landscape of the CRISPR-based gene-editing strategies relevant to therapeutic applications, we stratified the currently developed approaches into four categories (Figure 1),

including the classical CRISPR gene editing (NHEJ and HDR), base editing (BE), prime editing (PE), and epigenome editing.

Classical CRISPR-based gene editing (NHEJ and HDR)

The RNA-guided activation of Cas9 endonuclease activity rendered gene editing programmable, with classical CRISPR-Cas9 systems inducing site-specific DSBs that are subsequently repaired via the endogenous DNA repair mechanisms in cells, primarily NHEJ or HDR.[5] In mammalian cells, DSBs are repaired predominantly by the NHEJ, an error-prone mechanism that introduces indels at the cleavage site. This property has been harnessed therapeutically to achieve gene inactivation, often yielding knockout efficiencies exceeding 60%, depending on gRNA design, cutting, and delivery efficacy.[10,11]

In contrast, the CRISPR-based HDR relies on homology-directed recombination in the presence of a single or double-stranded donor DNA template with flanking homology arms. Following Cas9-induced DSB, HDR mediates precise insertion, replacement, or repair of target sequences within the genome.[12] In the context of double-stranded DNA donor templates, longer homology arms generally improve HDR efficiency. However, they also increase the donor DNA design complexity and impose significant challenges for delivery into target cells.[13] For CRISPR-based HDR applications, single-stranded oligodeoxynucleotides (ssODNs) are commonly used as donor templates for introducing the intended genetic mutations. The efficiency of ssODN is significantly influenced by donor design, with several studies demonstrating that asymmetric homology arms, introduction of blocking mutation(s), using targeting strand as donor, and chemical modifications enhance ssODN-based HDR outcomes in cells.[14,15] One limitation of ssODN-dependent HDR is the size constraint, which confines its application to the introduction of small modifications to the target locus.

Despite its precision, CRISPR-Cas9-mediated HDR remains inefficient in non-dividing or slowly dividing cell types, as homologous recombination is restricted to S/G2 phases of the cell cycle.[16] These intrinsic limitations of NHEJ- and HDR-mediated gene editing have catalyzed the development of next-generation CRISPR platforms that function independently of DSB formation and exogenous donor DNA templates. In the following texts we briefly highlight major CRISPR-based strategies that enable efficient and programmable gene correction strategies without relying on canonical DNA break and repair mechanisms.

BE

BE is a next-generation genome editing technology that leverages an enzymatic deamination route to generate precise nucleotide base transitions, and in some cases transversions, without generating DSBs. Two major classes of base editors have been developed, cytosine base editors (CBEs), which mediate C→T (G→A) transitions, and adenine base editors (ABEs), which catalyze A→G (T→C) transitions, together enabling all four possible transition substitutions.[17] Structurally, base editors consist of a targeting strand-specific Cas9 nickase (nCas9, D10A) fused to a DNA deaminase domain, chosen based on the desired base conversion, and guided to the genomic target via a sgRNA.[18] Upon binding its target locus, nCas9 creates a single-strand nick at the targeting strand and exposes the non-targeting single-strand DNA, within which the deaminase converts the target nucleotide into a modified base intermediate. Endogenous cellular repair pathways subsequently process this intermediate into a stable, desired base pair, thereby achieving highly precise editing without errors associated with DSB repair or the need for donor DNA templates.[17,19] However, a key limitation of base editors is the unintended edits of nearby nucleotides within the editing window, referred to as bystander edits/mutations. To mitigate this, several strategies have been developed, such as engineering base editors with narrower editing window[20] and the application of machine learning and deep learning tools for rational design of editing sites.[21,22]

PE

PE is a novel CRISPR-based genome editing strategy that enables targeted insertions, deletions, and base substitutions across diverse cell types and organisms without inducing DSBs or requiring donor DNA templates.[9,23] The PE system comprises a non-targeting strand-specific Cas9 nickase (H840A) fused to an engineered reverse transcriptase (RT), guided to the genomic target locus by a PE guide RNA (pegRNA). The pegRNA consists of four key elements: (1) a spacer sequence that directs the PE complex to the target site, (2) a primer-binding site (PBS) that anneals to the nicked non-target DNA strand, (3) a reverse transcriptase template encoding the desired edit, and (4) the canonical gRNA scaffold for Cas9 recruitment. Following target recognition and nicking, the PBS hybridizes to the exposed DNA end, allowing the RT to synthesize a DNA fragment containing the programmed edit from the pegRNA. Endogenous DNA repair pathways then integrate this edited flap into the genome, completing the modification without relying on DSB repair mechanisms.

Epigenome editing

CRISPR-based epigenome editing tools have been developed to modulate gene expression either transiently or permanently by fusing transcriptional activators, repressors, or epigenetic effector domains to catalytically inactivated Cas9 (dCas9).[24–27] Beyond transcriptional modulation, CRISPR-based epigenome editing can also be achieved at the chromatin level, by fusing histone/chromatin or DNA methylation-modifying domains to dCas9 DNA, enabling targeted installation or removal of specific epigenetic marks, thus expanding the potential for new therapeutic strategies.[26–30] Among these approaches, epigenetic silencing using CRISPR interference (CRISPRi) is particularly promising for clinical applications, as it achieves robust and reversible gene repression without introducing permanent changes to the underlying DNA sequence, making it an attractive strategy for therapeutic development.

CRISPR THERAPY STRATEGIES: *EX VIVO* AND *IN VIVO* APPROACHES

Efficient gene editing relies critically on the successful delivery of editing tools into target cells, a challenge that becomes particularly

significant for *in vivo* applications. Both viral and non-viral delivery technologies have advanced considerably, enabling the use of systems like lentiviral, adenoviral, adeno-associated viral vectors, as well as virus-like particles and lipid nanoparticles. Although viral vectors remain robust and widely used in gene therapy, concerns regarding immunogenicity, pre-existing immunity, and limited cargo capacity have accelerated the development of non-viral platforms. These include nanoparticles and extracellular vesicles which offer safer and promising alternatives. For a comprehensive overview of CRISPR delivery strategies, readers are directed to the recent review by the GenE-HumDi workgroup.[31] CRISPR-based therapeutic strategies are broadly categorized into two modalities: (1) *ex vivo* approaches, in which patient-derived cells are edited *in vitro* and subsequently reinfused and (2) *in vivo* approaches, in which CRISPR components are administered directly to the patient locally or systemically. Each modality presents distinct advantages and limitations, and the choice is largely determined by the target tissue, disease context, and intended therapeutic outcome.

Ex vivo genome editing

Ex vivo gene therapy involves harvesting relevant patient cells (particularly progenitor or stem cells), introducing CRISPR-Cas9 components *in vitro* using physical (electroporation, sonoporation), viral (AAVs, lentiviruses), or chemical (lipid nanoparticles, polymer-based carriers) delivery systems, and subsequently reinfusing the edited cells.[32] Despite offering high editing efficiency and safety prior to reinfusion, this approach is complex, resource intensive, and costly. It requires stringent GMP-compliant workflows, specialized cell culture infrastructure, rigorous sterility requirements, and highly trained personnel. In certain scenarios, it necessitates invasive procedures for cell procurement or transplantation, adding clinical complexity and patient burden.[33]

In vivo genome editing

In vivo genome editing involves the direct administration of CRISPR therapeutic agents into the patient via various routes, such as intravenous (systemic), intrasynovial (into joints), intramuscular, perioocular (a route with minimal immunological barriers and direct access to retinal cells[34]), and intraparenchymal (to bypass the blood-brain barrier). Localized delivery offers significant advantages including reduced dosing, improved safety and enhanced patient compliance. These features make *in vivo* editing suitable for tissues that are anatomically accessible or require targeted, region-specific intervention. However, compared to *ex vivo* approaches, several technical limitations currently restrict the broad clinical applicability of *in vivo* genome editing. These include the risk of prolonged expression of genome-editing components when delivered via viral or DNA vectors, which may potentially lead to higher genotoxicity, as well as challenges in controlling editing specificity in a complex *in vivo* environment. Besides, the necessity for invasive procedures to assess on-target editing outcomes and potential off targets remains another limitation. For a more detailed discussion and comparison of *ex vivo* and *in vivo* genome editing strategies, we refer readers to recent reviews from us and other groups.

The clinical translation of CRISPR-Cas9 to treat human genetic disorders is rapidly progressing. This progress is marked by the first regulatory approval in 2023 of a CRISPR-based therapy targeting sickle cell disease (SCD), followed by the recent development of a personalized CRISPR treatment for congenital severe carbamoyl-phosphate synthetase 1 deficiency, and a growing number of CRISPR therapeutics entering clinical trials. Despite this momentum, widespread clinical adoption of CRISPR-based therapies remains hindered by various technical, regulatory and ethical challenges. To address these issues, a consortium of scientists within the European Cooperation in Science and Technology (COST) Action *Genome Editing to Treat Human Diseases* (GenE-HumDi) has undertaken a comprehensive evaluation of the field. In this review, we provide a systematic analysis of current CRISPR-based therapeutic studies and offer a comprehensive perspective on the current landscape and the future trajectory of CRISPR-based clinical applications.

LANDSCAPE OF GLOBAL CRISPR-BASED CLINICAL TRIALS

To provide an overview of the global CRISPR-based gene therapy, we compiled registered trials from two major sources: the US-based clinical trial registry (https://clinicaltrials.gov/), which offers comprehensive details on clinical studies conducted worldwide, and the European Union Clinical Trials Register (https://euclinicaltrials.eu/), which catalogs ongoing trials within the European Union. Relevant information extracted from these sources was curated and organized to facilitate easy accessibility and interpretation by scientists.

In the United States, numerous gene-editing therapies have progressed beyond pre-clinical stages and entered at least phase 1 of clinical trials. These clinical trial activities are summarized in Table S1, with trials that were withdrawn excluded due to limited information for meaningful evaluation. Among the gene-editing strategies represented, CRISPR-Cas9 is the most widely used platform for gene knockout applications, typically delivered via AAV vectors for *in vivo* administration (Figure 2). *Ex vivo* gene editing is also extensively applied for engineering immune cells to treat solid tumors and hematologic malignancies. The predominant disease targets across these trials include leukemia, lymphoma, and multiple myeloma, and hematologic disorders such as β-thalassemia and SCD. Ophthalmologic conditions constitute another significant focus area, as the eye represents an accessible, relatively immune-privileged site well suited for gene-editing interventions.

Most ongoing clinical trials are actively recruiting participants, with many positioned in phase 1, where primary endpoints include safety, tolerability, and characterization of adverse events. A substantial number of studies have advanced to phase 2, marking a shift toward evaluating therapeutic efficacy after meeting safety benchmarks. The growing proportion of phase 2 trials underscores the field's maturation and increasing confidence in the safety of these investigational gene-editing platforms. These trials span immuno-oncology, hematology, hereditary disorders, and congenital hearing loss, employing

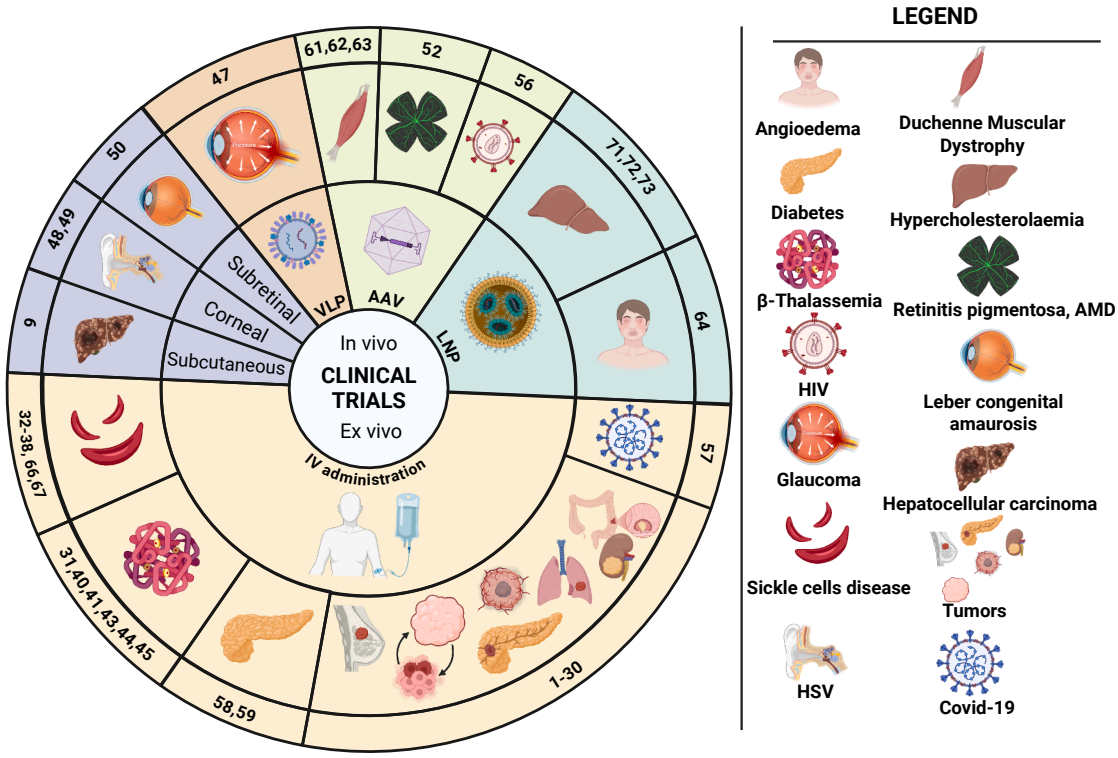

Figure 2. Schematic representation of current clinical trials

Subdivided by delivery route and organ/target therapy; numbers refer to the specific trials listed in Table S1. Figure is prepared with Biorender.com with license for publication (Luo Y., 2026).

diverse strategies such as engineered chimeric antigen receptor T (CAR-T) cells, *ex vivo*-edited $CD34^+$ stem cells, and innovative RNA base-editing approaches that correct pathogenic mutations at the post-transcriptional level.

A few studies listed in the US Clinical Trials registry have been terminated prematurely, largely due to insufficient funding, reflecting the high cost of gene-editing technologies and trials, or due to emerging safety concerns. For instance, one company redirected efforts toward developing an allogeneic version of NTLA-5001 after challenges with its autologous counterpart, which has been reverted to preclinical development to avoid complexities inherent to patient-derived therapies. One trial for hereditary transthyretin (ATTR) amyloidosis was temporarily paused due to a serious adverse event, but the FDA lifted the clinical hold in January 2026, allowing patient enrollment and dosing to resume under enhanced safety monitoring. The VERVE-101 trial, an *in vivo* base-editing therapy targeting PCSK9 for the treatment of heterozygous familial hypercholesterolemia, represents another important example. Notably, the occurrence of severe cardiac adverse events in 3 of the 13 treated patients raised significant concerns and contributed to the company's decision to shift clinical development toward VERVE-102, which employs a different delivery system compared with VERVE-101.[35] Since early 2017, fourteen registered CRISPR-related clinical trials have been completed. While modest in number, this is notable for a field with less than a decade of clinical experience. These early completions highlight both the rapid technological maturation of gene-editing platforms and increasing acceptance of gene editing therapy-based treatments within modern medicine. Although some trials have successfully completed phase 2, publicly available data remain limited. One example includes a study evaluating PD-1-knockout CAR-T cells targeting aberrantly glycosylated MUC1 in advanced MUC1-positive breast cancer, in which CRISPR-Cas9-mediated PD-1 disruption enhances antitumor potency by preventing the PD-1/PD-L1 inhibitory pathway within the tumor microenvironment. To date, the only clinical trial that has completed phase 3 is CTX001, also known as CASGEVY, the first CRISPR-based gene therapy for SCD and transfusion-dependent β-thalassemia (TDT) approved by the Food and Drug Administration (FDA) in January 2024. This landmark achievement in CRISPR therapeutics is discussed in greater detail in the following text. Moreover, three trials employ a PD-1 knockout *ex vivo* CAR-T approach like the one described earlier, while others include BD111, a CRISPR-based therapy targeting herpetic stromal keratitis caused by Herpes Simplex Virus type I, and PEC210A, an allogeneic pancreatic endoderm cell therapy engineered with CRISPR-Cas9 for diabetes mellitus.

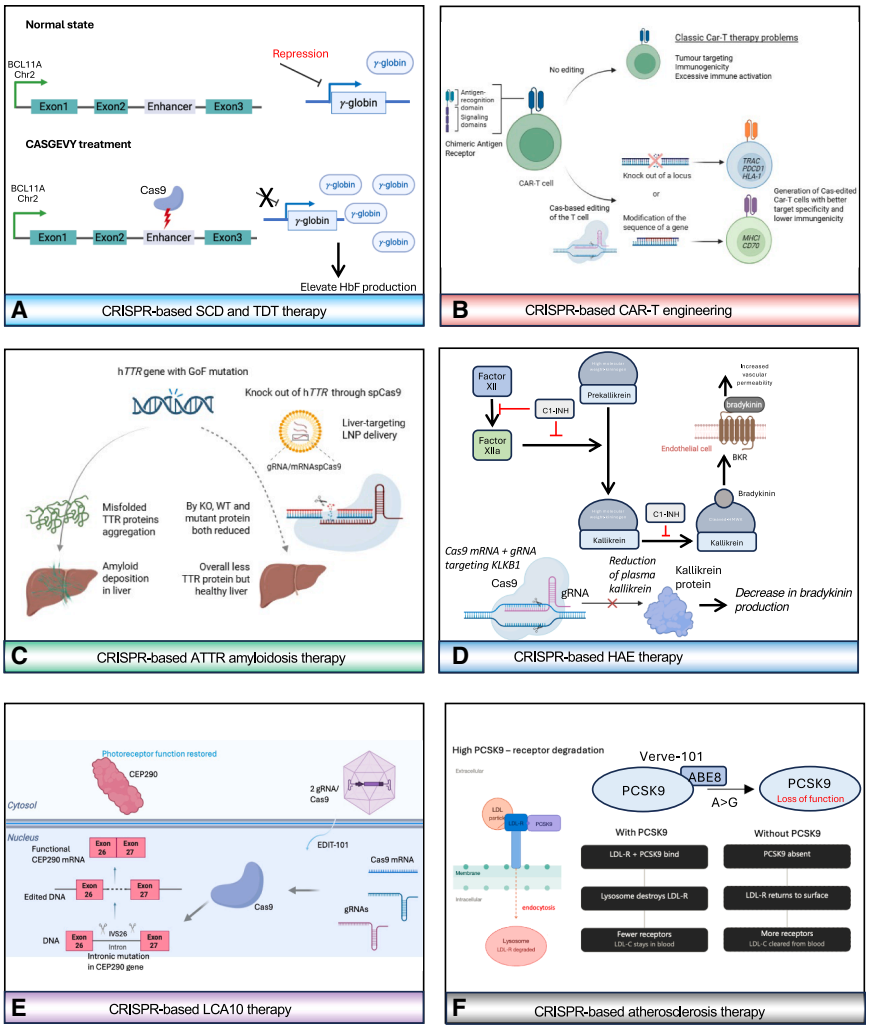

Figure 3. Schematic illustration of CRISPR-based therapeutics of six diseases

(A) CRISPR-based therapy of sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT). (B) CRISPR-based engineering of CAR-T cells for cancer therapy. (C) CRISPR-based therapy of hereditary transthyretin-mediated amyloidosis (hATTR). (D) CRISPR-based therapy of Hereditary Angioedema (HAE). (E) CRISPR-based therapy of Leber Congenital Amaurosis type 10 (LCA10) eye disease. (F) CRISPR-based therapy of atherosclerotic cardiovascular diseases (ASCVDs). Figure is prepared with Biorender.com with license for publication (Luo Y., 2026).

Table S1 summarizes the five CRISPR gene therapy trials conducted to date in the EU, three of which evaluate the CTX001 therapy described previously. The relatively small number of EU-based trials may reflect more stringent regional regulatory and safety requirements. The three CTX001 studies, sponsored by Vertex Therapeutics, are multicountry phase 1/2/3 trials assessing a single dose of autologous CRISPR-Cas9-modified CD34^{+} hematopoietic stem and progenitor cells (HSPCs) in patients with severe SCD or TDT. These studies have generated interim safety and efficacy data from phase 1/2 cohorts, and a phase 3 β-thalassemia trial remains ongoing. Another EU trial evaluates NTLA-2002, a phase 2 CRISPR-based therapy for hereditary angioedema (HAE), which is also under investigation in the US. Early clinical results demonstrated substantial reductions in attack frequency alongside a favorable safety profile, and a global phase 3 trial (HAELO) has recently begun. The final EU study explores a CAR-T immunotherapy, aligning with the broader momentum of gene editing CAR-T strategies to improve antitumor efficacy and expand therapeutic indications.

While most clinical trials rely on SpCas9 delivered either as mRNA or as ribonucleoprotein complexes, for efficient gene knockout, next-generation CRISPR platforms such as base editors are emerging as clinically viable alternatives. Recently, the Innovative Genomics Institute reported the first on-demand, personalized *in vivo* CRISPR therapy for an infant with carbamoyl phosphate synthetase 1 (CPS1) deficiency, using a mutation-specific adenine base editor formulated in lipid nanoparticles. Developed within six months, the therapy underwent accelerated preclinical safety evaluations and comprehensive off-target analyses, prior to emergency FDA authorization. Early clinical observations reveal no serious adverse events and notable symptomatic improvement, representing an important milestone for precise, individualized base-editing therapies for rare genetic disorders. Concurrently, VERVE Therapeutics is advancing *in vivo* base-editing therapies targeting familial hypercholesterolemia and atherosclerotic cardiovascular disease using lipid nanoparticles to deliver mRNA-encoded adenine base editors to inactivate liver *PCSK9* and lower LDL-C. Together, these programs highlight the rapidly expanding potential of CRISPR-based base-editing therapeutic modalities across multiple disease areas.

HIGHLIGHTS OF ADVANCED CRISPR THERAPY APPLICATIONS

A rapidly expanding portfolio of CRISPR-based therapies is now progressing through clinical development, targeting severe life-threatening conditions in multiple disorders. Collectively these trials span early phases through late-stage evaluation, reflecting both the technological maturity of gene editing and growing confidence in its clinical potential. The following section highlights several of the most advanced and therapeutically impactful CRISPR applications, illustrating how distinct editing platforms are being leveraged to address specific genetic and acquired disorders (Figure 3).

SCD and transfusion-dependent β-thalassemia

CRISPR-based therapy of SCD and TDT is the first CRISPR medicine approved for treatment. CASGEVY (exagamglogene autotemcel, exa-cel) is an *ex vivo* CRISPR-Cas9-based therapy that elevates fetal hemoglobin (HbF) levels by disrupting the erythroid-specific enhancer of BCL11A (Figure 3A), a critical regulator of HbF silencing.[36] Restoring HbF mitigates the pathological consequences of sickle hemoglobin and improves oxygen delivery. The treatment involves harvesting autologous HSPCs, editing them *ex vivo* using CRISPR-Cas9, and reinfusing the modified cells as a one-time therapy. Following engraftment, patients consistently exhibit sustained HbF production, leading to substantial clinical benefit.[37,38] In parallel, the FDA has approved LYFGENIA, a lentiviral gene therapy that introduces an HBB transgene encoding HbA (T87Q), a non-sickling hemoglobin variant. Like CASGEVY, LYFGENIA requires autologous HSPC collection, *ex vivo* modification, and reinfusion.[39]

Both therapies have demonstrated strong safety and efficacy profiles in clinical studies. Most patients achieved successful engraftment without graft failure or rejection. For CASGEVY, 29 of 31 patients with adequate follow-up remained free from severe vaso-occlusive crises (VOCs) for at least 12 consecutive months, while 28 of 32 LYFGENIA-treated patients experienced complete resolution of vaso-occlusive events (VOEs) within 6–18 months post-treatment. Reported adverse events, such as mucositis, nausea, musculoskeletal or abdominal pain, and febrile neutropenia were expected from these cell-based therapeutic procedures.[40]

The data collected about the first 14 months of market availability of CASGEVY after its FDA approval show that 301 TDT and SCD patients started the therapeutic protocols, 147 had their 1st cell collection and 64 patients had received an infusion of CASGEVY. The approval of these first-in-class *ex vivo* gene therapies marks a major milestone for gene editing and genetic medicine, offering the first potential functional cures for SCD, however, access remains a critical barrier. In fact, people treated with them are few compared with the global population affected by SCD and TDT that counts millions of people, CASGEVY is priced at $2.2 million per patient, and LYFGENIA at $3.1 million, posing substantial challenges to broad clinical adoption despite their promising transformative clinical outcomes.[36]

Another gene-editing approach for reactivating the γ-globin and inducing fetal hemoglobin expression is to disrupt the BCL11A transcriptional repressor-binding site (TGACCA) at the HBG1 and HBG2 promoters. This indel induction approach has made the development of *ex vivo* gene-editing therapy feasible for a broader spectrum of editing tools. Several investigational treatments of patients with TDT and SCD have been reported using CRISPR-Cas12a (Renizgamglogene autogedtemcel, reni-cel: 9 participants for the TDT trial and 28 participants for the SCD trial),[41,42] adenine base editor (ristoglogene autogetemcel, risto-cel: 31 SCD participants),[43] and a high-precision transformer base editor (CS-101, five TDT participants).[44] Among all four clinical trials, expression of the fetal hemoglobin (HbF) was successfully induced in all participants. For instance, the mean HbF as a fraction of total hemoglobin was more than 60% in the risto-cel trial. Despite these encouraging efficacy outcomes, a few adverse events with grade 3 or higher (87% of participants for the risto-cel trial), as well as the report of serious adverse events (39% of participants for the risto-cel trial), have been reported for the participants. However, most of the adverse events of grade 3 or higher were not considered by the investigator to be related to gene edited $CD34^+$ HSPCs.

Cancer therapy with CAR-T

CAR-T cell therapy has emerged as a transformative modality for malignant tumors, particularly hematologic malignancies.[45] CRISPR-Cas9 has greatly facilitated the engineering of next generation CAR-T cells with enhanced tumor targeting, reduced immunogenicity, and mitigating excessive immune activation (Figure 3B). Multiplex gene-editing targets by CRISPR include *TRAC* and *PDCD1*, whose disruption improves persistence and cytotoxicity in mesothelin-positive solid tumors, and *TRAC* plus *CD52*, which enable allogeneic CD19-directed CAR-T cells resistant to lymphodepleting agents.[46,47] *B2M* knockout further reduces immune rejection by suppressing MHC class I expression. Additional edits including *TCR, MHC-I*, and *CD70* are under investigation for multiple myeloma, renal carcinoma, and other hematological cancers.[48,49] Several of these strategies are in clinical evaluation, including PD-1-edited CD19-directed CAR-T cells for non-Hodgkin lymphoma (NCT04213469) and CAR insertion into TRAC locus to generate "universal" CAR-T products (NCT04557436).

CRISPR-engineered cellular therapies have recently expanded beyond oncology. A first-in-human study (NCT05859997) applied multiplex CRISPR editing to generate a hypoimmunogenic CAR-T product (TyU19). Donor-derived T cells were edited at five loci—*HLA-A*, *HLA-B*, *CIITA*, *TRAC*, and *PDCD1*, using Cas9 RNP electroporation, producing CD19-targeted therapy suitable for autoimmune indications.[50] TyU19 was administered to patients with refractory SRP-associated immune-mediated necrotizing myopathy and diffuse cutaneous systemic sclerosis. A single infusion induced profound B cell depletion for two to three months and yielded sustained clinical improvement over six months, including reversal of fibrosis, an outcome rarely observed in these conditions. Notably, no cytokine release syndrome or serious adverse events occurred.

Collectively, these advances highlight the widening therapeutic scope of CRISPR-engineered CAR-T cells, demonstrating potent antitumor activity while opening new avenues for treating severe, treatment-refractory autoimmune disorders.

Transthyretin amyloidosis

Hereditary transthyretin-mediated amyloidosis (hATTR) is a progressive life-threatening disorder caused by autosomal dominant mutations in the *TTR* gene, leading to misfolded transthyretin aggregation and amyloid deposition across multiple tissues.[51] Clinically, hATTR presents with peripheral sensorimotor neuropathy,

autonomic dysfunction, and/or cardiomyopathy.[52] Existing therapies including *TTR* silencers, stabilizers, and amyloid removal strategies offer partial benefit but do not fully halt disease progression. Since TTR is produced mainly in the liver and the disorder is monogenic, hATTR represents an attractive target for CRISPR-Cas9-based gene silencing therapies.

NTLA-2001 (Nexiguran ziclumeran, nex-z), developed by Intellia Therapeutics (NCT04601051), is the first systemically administered, single dose therapy to enter human trials based on classical CRISPR-Cas9 gene-editing strategy (Figure 3C). Delivered via a liver-targeted lipid nanoparticle (LNP) formulation, the therapy consists of human-codon-optimized mRNA encoding SpCas9 and a sgRNA designed to introduce a DSB in *TTR*, thus reducing production of both wild-type and mutant protein.[53]

In the phase 1 trial, six patients with sensory polyneuropathy received one of two RNA dose levels (0.1 mg/kg or 0.3 mg/kg) of the therapy. By day 28, only mild adverse events were reported. Mean serum TTR levels were reduced by 52% in the low dose cohort and 87% in the higher-dose cohort, demonstrating a potent, dose-dependent gene knockdown. Comprehensive specificity assessments including computational prediction, biochemical assays, and cell-based studies were conducted to characterize potential off-target editing under conditions yielding robust TTR suppression. In October 2025, the FDA placed the NTLA-2001 program on clinical hold following a grade 4 liver transaminase elevation with hyperbilirubinemia in a trial participant. Recently, Intellia Therapeutics announced that the FDA has lifted the hold on its MAGNITUDE-2 phase 3 trial of NTLA-2001/nex-z, permitting patient enrollment and dosing to resume under enhanced safety monitoring. Overall, NTLA-2001/nex-z provides compelling early evidence that systemic *in vivo* CRISPR editing can achieve substantial and durable suppression of a disease-causing hepatic gene with a promising early safety and efficacy profile.

HAE

HAE is a rare genetic disorder defined by recurrent episodes of peripheral, gastrointestinal or airway edema.[54] The disease most commonly results from mutations in *SERPING1*, leading to quantitative (type I) or functional (type II) deficiency of C1 esterase inhibitor (C1-INH).[55] C1-INH is a key regulator of the complement and fibrinolytic pathways, whose loss results in uncontrolled activation of plasma kallikrein and excessive bradykinin generation. Notably, bradykinin is the principal mediator of increased vascular permeability and tissue edema. Existing therapies target acute attacks or provide short-term and long-term prophylaxis, requiring lifelong, repeated administration but do not correct the underlying molecular defect.

NTLA-2002 (lonvo-z) developed by Intellia Therapeutics, is the first *in vivo* CRISPR-Cas9 therapy designed to provide a durable, single dose treatment for HAE (Figure 3D). Building on the same LNP-based delivery platform as NTLA-2001, the NTLA-2002 contains an mRNA encoding SpCas9 and an sgRNA targeting KLKB1, the gene encoding plasma prekallikrein. Functional knockout of KLKB1 is intended to durably reduce kallikrein activity, thereby lowering downstream bradykinin and preventing angioedema attacks.

Currently, patients are enrolled in a phase 1/2 trial in Europe evaluating safety, tolerability, pharmacokinetics, and pharmacodynamics, with completion expected in 2026. Interim results have shown a potent, dose-dependent reduction in plasma kallikrein levels and an approximate 95% mean reduction in monthly HAE attacks with no severe adverse events.[56]

Based on encouraging early data, Intellia has launched HAELO, a multinational, double-blind, placebo-controlled phase 3 study. Sixty patients will be randomized 2:1 to receive a single IV injection of NTLA-2002 or a placebo. The primary endpoint is the time-normalized rate of investigator-confirmed HAE attacks, from weeks 5–28 following treatment, with secondary endpoints including patient-reported outcomes such as the Angioedema Quality of Life score. Together, these developments position NTLA-2002 as a promising one-time, *in vivo* CRISPR therapy with the potential to redefine long-term management of HAE.

Inherited eye diseases

Inherited retinal disorders (IRDs) comprise a heterogeneous group of genetic diseases that cause progressive vision loss due to mutations in genes essential for retinal function. These primarily affect photoreceptors and the retinal pigment epithelium, leading to degeneration, impaired vision and, ultimately, blindness.[57]

EDIT-101 is an *in vivo* CRISPR-Cas9 gene therapy to treat Leber Congenital Amaurosis type 10 (LCA10) (Figure 3E), a severe IRD caused most commonly by mutations in CEP290, particularly the intronic IVS26 (c.2991 + 1655 A>G) variant.[58] This pathogenic mutation introduces a cryptic exon, disrupting CEP290 expression and impairing photoreceptor structure and function. EDIT-101 uses subretinal delivery of AAV5 viral vectors encoding SaCas9 (an ortholog Cas9 protein with smaller size, approximately 2/3 of SpCas9), under the photoreceptor-specific promoter GRK1, together with two gRNAs designed to excise IVS26 sequence. Preclinical evidence demonstrates that both deletion and inversion of the excised fragment restore CEP290 function in photoreceptors. The BRILLIANCE phase 1/2 trial evaluated single ascending doses in 14 participants. Visual improvements were observed in 11 patients, with no dose-limiting toxicities or severe ocular adverse effects, supporting the feasibility of CRISPR-mediated editing in the retina.[58] However, despite encouraging early outcomes, the trial was paused by Editas Medicine, due to a limited number of eligible patients, only 300 of 1,500 individuals with LCA10 in the US are homozygous for the IVS26 variant targeted by EDIT-101 therapy.

Hypercholesterolemia and atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular diseases (ASCVDs), most commonly manifesting as myocardial infarction and ischemic stroke, remain

the leading cause of mortality worldwide, especially in high-income countries. Low-density lipoprotein cholesterol (LDL-C) is the most extensively studied validated causal factor, with large epidemiological and clinical trial meta-analyses establishing a clear, dose-dependent relationship between circulating LDL-C and ASCVD risk.[59,60] Therapeutic strategies therefore focus on durable LDL-C reduction. Current guidelines, such as the European recommendations, endorse a stepwise approach based on patient risk, maximum tolerated statins, followed by ezetimibe and finally PCSK9 inhibitors if LDL-C remains above target. However, these regimens require lifelong adherence, creating cost and limiting long-term effectiveness in some patients.[61]

The emergence of *in vivo* gene editing offers the possibility of single-dose, durable modulation of lipid-regulatory pathways. VERVE-101 exemplifies this approach, which is an adenine base editor delivered via LNP to introduce a loss-of-function edit in *PCSK9*, thereby achieving sustained LDL-C lowering in patients with familial hypercholesterolemia or ASCVD (Figure 3F). Preclinical studies in non-human primates demonstrated high editing efficiency (median 70% ± 9.9% at 1.5 mg/kg) with stable 71% PCSK9 disruption over time, resulting in reductions in circulating PCSK9 (89% ± 8.7%) and LDL-C (68% ± 12.3%) at one year. Transient increases in liver aminotransferases resolved spontaneously, glucose homeostasis remained normal, and no germline editing or transmission was detected.[62] The encouraging safety data supported initiation of a phase 1b clinical trial in 44 patients (Table S1). Clinical results showed a mean 46% reduction in LDL-C at 0.45 mg/kg dose (with reductions up to 73%), but the study was temporarily paused after two asymptomatic grade 3 adverse events in one patient, both of which resolved without intervention.[63] In parallel, the company is advancing VERVE-102, which employs GalNAc-targeted LNPs to improve hepatocyte specificity and mitigate the safety concerns observed in VERVE-101 (Table S1).

OUTLOOK

While most highlighted CRISPR-based gene-editing clinical trials rely on DSB-dependent mechanisms, promising clinical trial results have recently been reported using PE, BE, as well as epigenome editing. For example, prime-edited autologous $CD34^+$ hematopoietic stem cells have been successfully used to treat two patients with chronic granulomatous disease (CGD), a monogenic immunodeficiency caused by a two-nucleotide deletion in exon 2 of the *NCF1* gene. Besides, Scribe Therapeutics Inc. reported that epigenome editing based silencing of *PCSK9* transcription (STX-1150) achieved up to 90% reduction in PCSK9 and up to 68% LDL-C lowering in non-human primates, supporting the recent initiation of a first-in-human clinical trial (May 21, 2026). For base editor therapies, the momentum has been greatly demonstrated with the successful N-of-1 BE intervention for baby "KJ" in which a disease-causing *CPS1* mutant allele was corrected in the liver.

Despite the transformative lifesaving possibilities of CRISPR-based therapeutics for numerous severe diseases, several critical challenges must be addressed before the interventions can be broadly implemented. Key considerations include efficient and tissue-specific delivery, precise installation of the intended edit without bystander mutations, rigorous avoidance of off-target activity and ensuring long-term safety. Equally important are issues of affordability and equitable access, as the exceptionally high cost of single-dose genome editing medicines currently threatens to widen existing disparities in healthcare access.[64] Clinical programs may be deprioritized for strategic and commercial reasons despite demonstrating proof of concept, particularly in rare diseases with small patient populations. EDIT-101 BRILLIANCE phase1/2 in LCA10 exemplifies this challenge, as its further development was not pursued due to limited commercial viability. Realizing the full potential of CRISPR therapies will require deeply coordinated efforts across the biomedical ecosystem, from early-stage molecular design and optimization of delivery platforms to proactive engagement with regulatory authorities, patient organizations, and pharmaceutical partners, alongside robust participation and engagement of clinical trial units. Such integrated collaboration will be essential to translate CRISPR from a breakthrough technology into a globally accessible class of curative medicines.

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AUTHOR CONTRIBUTIONS

K.B., R.R.N., and Y.L., conceptualization, supervision, writing – original draft, and writing – review and editing; Y.L., visualization (figure preparation); C.S. and T.M.F., literature search, writing – original draft, visualization (figure and table preparation), and writing – review and editing; A.S., G.D.P., M.C.D., D.G.A., M.C., L.S., and L.Q., literature search, writing – original draft, and visualization (figure and table preparation); A.L.O., A.L.A., M.K., C.J-M., M.C.G., J.F.S., F.M., R.O.B., A.S., P.R., C.A., K.B., writing – review and editing.

DECLARATION OF INTERESTS

R.O.B. holds equity in Kamau Therapeutics and UNIKUM Therapeutics and is a cofounder of UNIKUM Therapeutics. Neither company was involved in the present study. R.O.B. is listed as an inventor on patents and patent applications related to CRISPR-Cas and cellular therapies. R.O.B. reports research funding from Novo Nordisk. K.B. holds equity in EvoStem Theranostics, which was not involved in the present study. P.R. has received honoraria as consultant and holds stock options and royalties for licences to Rocket Pharmaceuticals, which was not involved in the present study.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.omtn.2026.103011.

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