Overview of the current status of gene therapy for primary immune deficiencies (PIDs)

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List of Design Committee Members: Caroline Y. Kuo, MD, and Donald B. Kohn, MD (authors); Zuhair K. Ballas, MD (editor)

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: D. B. Kohn is a member of the Scientific Advisory Board of Orchard Therapeutics, which markets a gene therapy for adenosine deaminase severe combined immune deficiency (ADA SCID), and is an inventor on a different ADA SCID gene therapy licensed by the UC Regents to Orchard Therapeutics. C. Y. Kuo declares no relevant conflicts of interest. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To understand the potential risks and benefits of gene therapy for primary immune deficiencies (PID).
2. . To understand differences between gene addition therapy and gene editing therapy for PID.
3. To understand emerging approaches in gene therapy for PID aimed at improving clinical outcomes.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Sun-mi Choi, MD, PhD, Lily Grobman, MD, Jessica Galant-Swafford, MD, and Marc A. Riedl, MD, MS.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The examination authors declare no relevant conflicts of interest.

Over 3 decades, gene therapy has advanced from a logical idea to becoming a clinical reality for several of the most severe primary immune deficiencies, as well as other inherited disorders. The first gene therapy medicines have been licensed for marketing and several more are advancing toward that goal to make them widely available, beyond clinical trials. Although common platforms of cells, vectors, or editing reagents are used for these disorders, each individual genetic cause of an immune deficiency requires its own vector or editing tools and a package of preclinical data on efficacy and safety to initiate clinical trials. One-by-one, gene therapy for primary immune deficiencies is being brought to the clinic and hopefully will provide safe and effective therapies. (J Allergy Clin Immunol 2020;146:229-33.)

Key words: *Primary immune deficiencies, gene therapy, lentiviral vectors, gene editing, autologous hematopoietic stem cell transplantation*

Gene therapy, the treatment of inherited disorders by replacing or correcting defective genes in a patient's somatic cells, has been a goal of biomedicine for at least half a century.[1,2] In the mid-1980s, methods were developed for cloning human genes and construction of recombinant viral vectors to carry the genes into patient cells. The use of gene delivery vectors derived from several types of viruses (retrovirus, lentivirus, adenovirus, and adeno-associated virus) began to advance to the clinic. Over 3

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Received for publication March 26, 2020; revised May 12, 2020; accepted for publication May 12, 2020.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.05.024

Abbreviations used
ADA: Adenosine deaminase
HSC: Hematopoietic stem cell
HSCT: Hematopoietic stem cell transplantation
PID: Primary immune deficiency
SCID: Severe combined immune deficiency
XCGD: X-linked chronic granulomatous disease
XSCID: X-linked severe combined immune deficiency

decades, gene therapy has advanced from a logical idea to becoming a clinical reality for several of the most severe primary immune deficiencies (PIDs) (Fig 1), as well as other inherited disorders. The first gene therapy medicines have been licensed for marketing and several more are advancing toward that goal to make them widely available, beyond clinical trials.

The hemoglobin disorders sickle cell disease and beta-thalassemia were considered as early disease candidates for gene therapy, because beta-globin was the first human disease–related gene to be cloned.[3,4] A patient's hematopoietic stem cells (HSCs) could have a normal beta-globin gene inserted by a retroviral vector and transplanted to produce normal red blood cells. However, beta-globin turned out to be a challenging gene for gene therapy, because it requires very high levels of expression in an erythroid-specific manner, which necessitates the use of multiple regulatory elements from the beta-globin locus in the vectors; these complex beta-globin gene units were unstable in retroviral vectors and were not effective. In recent years, gene therapy for sickle cell disease or beta-thalassemia using beta-globin genes carried by lentiviral vectors has conferred clinical benefits for the hemoglobinopathies. An HSC gene therapy for beta-thalassemia using a lentiviral vector is licensed in the European Union, and other gene therapies for both sickle cell and beta-thalassemia are advancing through clinical trials.[5,6]

Instead, severe combined immune deficiency (SCID) due to deficiency of the purine metabolic enzyme adenosine deaminase (ADA SCID) became the first blood cell disease for which clinical gene therapy was performed. The experience with clinical use of allogenic hematopoietic stem cell transplantation (HSCT) to provide a genetically normal source of needed leukocytes for patients with SCID suggested that autologous transplantation of a patient's own genetically corrected HSCs could provide similar benefit. ADA is a housekeeping enzyme that can be expressed from a retroviral or lentiviral vector from a simple cDNA driven by a constitutive promoter. Modest levels of ADA expression across a relatively broad range in all the blood cell lineages from gene-modified HSCs will make sufficient ADA enzyme to restore the deficiency in lymphocytes and restore populations of T, B, and natural killer cells. Normal human ADA cDNAs were cloned and retroviral vectors were constructed to deliver them, leading to correction of the metabolic defects of ADA deficiency in ADA SCID patient-derived T-cell lines.[7]

The initial National Institutes of Health ADA SCID gene therapy study in 1990 treated 2 patients with ADA SCID whose peripheral blood T cells had been rescued by treatment with ADA enzyme replacement therapy.[8] Both subjects attained long-term persistence of some of the ADA gene *ex vivo*–modified T cells, without adverse effects from the gene therapy.[9] However, both subjects also continued to be treated with ADA enzyme replacement therapy, so it was not possible to determine whether there were any beneficial effects on immune function from the gene therapy *per se*.

Subsequent clinical gene therapies of ADA SCID have used HSCs as the target for ADA gene addition using retroviral and lentiviral vectors (Fig 2), with excellent restoration of immunity reported in most patients from multiple publications.[10-13] A critical advance was made by investigators at the San Raffaele Telethon Institute for Gene Therapy with the use of reduced-intensity conditioning before transplant, which markedly improved engraftment of the gene-corrected HSCs and supported immune reconstitution.[14] The ADA SCID gene therapy developed by these investigators in Milan achieved regulatory approval in the European Union in 2016,[15] and other ADA SCID gene therapies are under review for licensure.

Studies of gene therapy for X-linked SCID began once the responsible gene (*IL2Rg*) was cloned, with trials beginning in France and the United Kingdom in the late 1990s. Investigators at Hôpital Necker-Enfants Malades in Paris first reported clinical success with gene therapy in 2 infants with X-linked SCID (XSCID) treated using a retroviral vector and without any pretransplant conditioning.[16] Vigorous T-cell reconstitution occurred, although B-cell function improved only partially. These investigators extended the results to additional patients with XSCID, and patients in another trial in the United Kingdom also showed similar immune-reconstituting effects.[17,18] However, at least 6 of the 20 patients with XSCID treated in these studies developed a severe complication of vector-driven leukemia-like leukoproliferation 2 to 15 years after treatment.[19,20]

New vectors have been developed that have deletions of the viral enhancer elements that can activate cellular *proto*-oncogenes at the integration sites. Both retroviral and lentiviral vectors of this newer design ("self-inactivating" or self-inactivating vectors) carrying the *IL2Rg* cDNA have restored immunity in approximately 20 infants with XSCID and have not produced any leukoproliferative complications.[21,22] One trial used gene therapy to treat older subjects with XSCID who had chronic immune deficiency due to incomplete reconstitution from previous allogeneic HSCT; these patients have realized a significant improvement in health and immunity.[23]

Gene therapies for other PIDs have been developed in parallel to those for SCID. Trials were done in the mid-1990s using retroviral vectors for gene transfer to HSCs for chronic granulomatous disease (X-linked CGD [XCGD] and autosomal-recessive forms) and leukocyte adhesion deficiency-1, but conditioning was not used for these early trials and no significant engraftment levels of gene-corrected cells were achieved.[24-26] Subsequent trials for XCGD used reduced-intensity conditioning with the myeloablative agent busulfan and achieved better frequencies of engraftment of retroviral gene-corrected stem cells and some evidence of improved anti-infectious immunity.[27] One trial using a highly active retroviral vector carrying the *CYBB* cDNA (defective in XCGD) achieved good initial clinical results, but then leukoproliferative complications occurred.[28] Similar results occurred using retroviral vectors for Wiskott-Aldrich syndrome, with initial restoration of immune function and platelet counts but subsequent development of leukoproliferation in 7 of the 9 engrafted subjects.[29]

In the past decade, self-inactivating lentiviral vectors for gene modification of HSCs combined with some degree of cytoreductive conditioning have been applied successfully for gene therapy

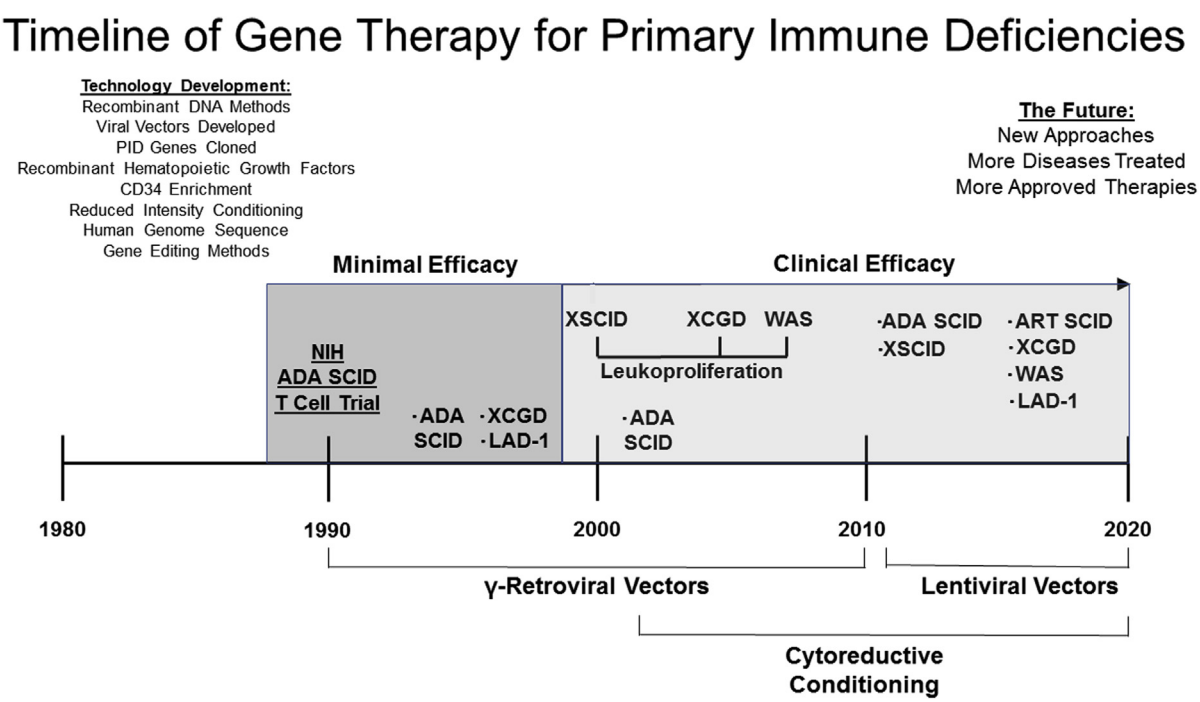

FIG 1. Timeline for the development of gene therapies for PIDs. The technologies that were developed to enable gene therapy are listed. Clinical trials through the 1990s did not demonstrate significant clinical benefits, but also did not have safety problems. Subsequent studies in the early 2000s for XSCID, ADA SCID, XCGD, and WAS led to clinical benefits restoring immunity, but then were marred by development of leukoproliferative complications (with the exception of ADA SCID). Subsequent studies in the past decade, mainly using lentiviral vectors, have led to both clinical benefits and absence of vector-related complications for a growing list of PIDs. *ART*, Artemis (DCLRE1C)-deficient SCID; *LAD-1*, leukocyte adhesion deficiency 1; *WAS*, Wiskott-Aldrich syndrome.

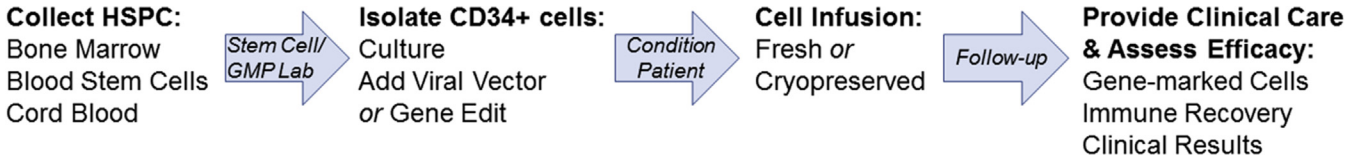

FIG 2. Schema for gene therapy using HSCs. A source of hematopoietic stem/progenitor cells (HSPCs) is collected from the patient with PID and transported to the stem cell or Good Manufacturing Practice (GMP) laboratory. The $CD34^+$ fraction of cells enriched form HSPCs is isolated and gene-modified, whether using gene addition with viral vectors or gene editing using cellular DNA repair pathways to produce the intended gene edits. The patient may receive some cytoreductive conditioning to "make space" in their marrow for re-engraftment. The gene-modified HSPCs may be infused freshly, or cryopreserved for subsequent thawing and infusion back to the patient with PID. Afterwards, the patients are monitored for safety and efficacy, including quantification of gene-marked leukocytes, assessment of immune recovery of the relevant functions, and clinical results, in terms of infections, autoimmunity, and other disease manifestations.

for multiple PIDs, including ADA SCID and XSCID, as described above, Artemis-deficient SCID, Wiskott-Aldrich syndrome, XCGD, and leukocyte adhesion deficiency 1.[13,22,30-35] In general, these treatments are relatively mild transplants, because less chemotherapy and immune-suppressive drugs are used for autologous hematopoietic stem cell transplantation/gene therapy than for allogeneic HSCT. As an autologous procedure, there is essentially no risk of graft versus host disease, a significant contributor to morbidity following allogeneic HSCT. To date, the immune reconstitution reached in the first months after gene therapy has been sustained and stable over observation periods of 10 to 15 years. New lentiviral vectors are also showing success in treating various blood cell diseases other than PIDs, including hemoglobinopathies, leukodystrophies, and lysosomal storage diseases (Table I).

A second major approach to gene therapy that is emerging uses targeted gene editing of the endogenous gene, instead of addition of an exogenous gene with a viral vector,[36] by exploiting the natural DNA repair pathways of cells. This site-specific genome modification is greatly facilitated by inducing a double-stranded DNA break near the sequences to be edited. A series of "designer enzymes" that are site-specific endonuclease have

TABLE I. Inherited blood cell diseases responding to hematopoietic stem cell lentiviral vector gene therapy—2020

Disorder	Clinical Trials.gov no.
PIDs	
ADA-deficient SCID	NCT01852071, NCT03765632, NCT03645460
X-linked SCID	NCT01306019, NCT03601286, NCT03311503
Artemis SCID	NCT03538899
Wiskott-Aldrich syndrome	NCT01560182, NCT01515462, NCT01347242
Chronic granulomatous disease	NCT02234934, NCT01855685, NCT02757911
Leukocyte adhesion deficiency-1	NCT03812263
Metabolic/storage disorders	
X-linked adrenoleukodystrophy	NCT01896102, NCT03727555, NCT03852498
Metachromatic leukodystrophy	NCT01560182
MPS-I (Hurler syndrome)	NCT03488394
Hemoglobinopathies	
Beta-thalassemia	NCT03207009, NCT01745120, NCT02453477
Sickle cell disease	NCT02186418, NCT03282656, NCT03964792
	NCT03964792, NCT02247843, NCT04091737

been produced that can be used for gene editing, including zinc finger nucleases, transcription activator-like effector nucleases, and the clustered regularly interspaced short palindromic repeat–associated protein 9. Gene editing is being developed for many forms of PIDs including XSCID; ADA SCID; recombination activating gene 1 SCID; XCGD; X-linked hyper-IgM syndrome; X-linked agammaglobulinemia; hereditary lymphohistiocytosis; immune dysregulation, polyendocrinopathy, enteropathy, X-linked; X-linked lymphoproliferative disorder; and others. Newer gene editing approaches continue to be invented, with Base Editors that can convert single specific base pairs (eg, C:G to T:A) or print the corrective DNA sequences into a target editing site using clustered regularly interspaced short palindromic repeat proteins without introducing double-stranded DNA breaks.[37,38]

The key challenges for gene editing in HSCs are achieving sufficiently high frequencies of the desired gene edits in a patient's HSCs while preserving the capacity of the edited HSCs to engraft and support blood cell production. These techniques have been continuously improved upon and are moving to clinical trials. Other work is focusing on editing in mature T cells, as potentially more feasible approaches to treatment of disorders such as hereditary lymphohistiocytosis; immune dysregulation, polyendocrinopathy, enteropathy, X-linked; and X-linked lymphoproliferaive syndrome.

Although a common platform of cells, vectors, or editing reagents is used for these disorders, each individual genetic cause of a PID requires its own vector or editing tools and a package of preclinical data on efficacy and safety to initiate clinical trials. One-by-one, gene therapy for PIDs is being brought to the clinic and hopefully will provide safe and effective therapies.

What do we know?

- **PIDs can be successfully treated by autologous hematopoietic stem cell transplantation/gene therapy.**
- **Retroviral vectors led to efficacy, once cytoreductive conditioning was used.**
- **Retroviral vectors led to genotoxicity in studies for several PIDs.**
- **Lentiviral vectors have led to efficacy and no genotoxicity for multiple PIDs.**
- **Gene editing techniques will be advancing to clinic for some PIDs where the relevant gene needs to be precisely expressed.**

What is still unknown?

- **Optimal approach to gene correction for immune dysregulation, polyendocrinopathy, enteropathy, X-linked, recombination activating gene 1 SCID, gain-of-function mutations.**
- **Relative efficacy of lentiviral vectors and gene editing approaches.**

REFERENCES

1. Friedmann T, Roblin R. Gene therapy for human genetic disease? Science 1972; 175:949-55.
2. Anderson WF, Fletcher JC. Sounding boards. Gene therapy in human beings: when is it ethical to begin? N Engl J Med 1980;303:1293-7.
3. Steinberg MH. Review: the sickle hemoglobinopathies–genetic analyses of common phenocopies and new molecular approaches to treatment. Am J Med Sci 1984;288:169-74.
4. Wilson JT, Forget BG, Wilson LB, Weissman SM. Human globin messenger RNA: importance of cloning for structural analysis. Science 1977;196:200-2.
5. Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil JA, Hongeng S, et al. Gene therapy in patients with transfusion-dependent β-thalassemia. N Engl J Med 2018;378:1479-93.
6. Ribeil JA, Hacein-Bey-Abina S, Payen E, Magnani A, Semeraro M, Magrin E, et al. Gene therapy in a patient with sickle cell disease. N Engl J Med 2017; 376:848-55.
7. Kantoff PW, Kohn DB, Mitsuya H, Armentano D, Sieberg M, Zwiebel JA, et al. Correction of adenosine deaminase deficiency in cultured human T and B cells by retrovirus-mediated gene transfer. Proc Natl Acad Sci U S A 1986;83:6563-7.
8. Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, Clerici M, et al. T lymphocyte-directed gene therapy for ADA-SCID: initial trial results after 4 years. Science 1995;270:475-80.
9. Muul LM, Tuschong LM, Soenen SL, Jagadeesh GJ, Ramsey WJ, Long Z, et al. Persistence and expression of the adenosine deaminase gene for 12 years and immune reaction to gene transfer components: long-term results of the first clinical gene therapy trial. Blood 2003;101:2563-9.
10. Cicalese MP, Ferrua F, Castagnaro L, Rolfe K, De Boever E, Reinhardt RR, et al. Gene therapy for adenosine deaminase deficiency: a comprehensive evaluation of short- and medium-term safety. Mol Ther 2018;26:917-31.
11. Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Zhang F, Adams S, et al. Hematopoietic stem cell gene therapy for adenosine deaminase-deficient severe combined immunodeficiency leads to long-term immunological recovery and metabolic correction. Sci Transl Med 2011;3:97ra80.
12. Shaw KL, Garabedian E, Mishra S, Barman P, Davila A, Carbonaro D, et al. Clinical efficacy of gene-modified stem cells in adenosine deaminase-deficient immunodeficiency. J Clin Invest 2017;27:1689-99.
13. Kohn DB, Shaw KL, Garabedian E, Carbonaro-Sarracino DA, Moore TB, De Oliveira S, et al. Lentiviral gene therapy with autologous hematopoietic stem and progenitor cells (HSPCs) for the treatment of severe combined immune deficiency due to adenosine deaminase (ADA-SCID): results in and expanded cohort. Blood 2019; 134:3345.
14. Aiuti A, Slavin S, Aker M, Ficara F, Deola S, Mortellaro A, et al. Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. Science 2002;296:2410-3.

15. StrimvelisTM receives European marketing authorisation to treat very rare disease, ADA-SCID. London, England: GlaxoSithKline; 2016. Available at: https://www.gsk.com/en-gb/media/press-releases/strimvelistm-receives-european-marketing-authorisation-to-treat-very-rare-disease-ada-scid/. Accessed May 11, 2020.
16. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, Gross F, Yvon E, Nusbaum P, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science 2000;288:669-72.
17. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 2002;346:1185-93.
18. Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Adams S, Howe SJ, et al. Long-term persistence of a polyclonal T cell repertoire after gene therapy for X-linked severe combined immunodeficiency. Sci Transl Med 2011;3:97ra79.
19. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 2003;302:415-9.
20. Cavazzana M, Emmanuelle Six, Lagresle-Peyrou C, Andre-Schmutz I, Hacein-Bey-Abina S. Gene therapy for X-linked severe combined immunodeficiency: where do we stand? Human Gene Ther 2016;27:108-16.
21. Hacein-Bey-Abina S, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, et al. A modified γ-retrovirus vector for X-linked severe combined immunodeficiency. N Engl J Med 2014;371:1407-17.
22. Mamcarz E, Zhou S, Lockey T, Abdelsamed H, Cross SJ, Kang G, et al. Lentiviral gene therapy combined with low-dose busulfan in infants with SCID-X1. N Engl J Med 380:1525-1534.
23. De Ravin SS, Wu X, Moir S, Anaya-O'Brien S, Kwatemaa N, Littel P, et al. Lentiviral hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. Sci Transl Med 2016;8:335ra57.
24. Malech HL, Maples PB, Whiting-Theobald N, Linton GF, Sekhsaria S, Vowells SJ, et al. Prolonged production of NADPH oxidase-corrected granulocytes after gene therapy of chronic granulomatous disease. Proc Natl Acad Sci U S A 1997;94:12133-8.
25. Malech HL, Horwitz M, Linton G, Theobald-Whiting N, Brown M, Farrell C, et al. Extended production of oxidase normal neutrophils in X-linked chronic granulomatous disease (CGD) following gene therapy with gp91phox transduced CD34+ cells. Blood 1998;92:690.
26. Bauer TR Jr, Hickstein DD. Gene therapy for leukocyte adhesion deficiency. Curr Opin Mol Ther 2000;2:383-8.
27. Kang EM, Choi U, Theobald N, Linton G, Long Priel DA, Kuhns D, et al. Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. Blood 2010;115:783-91.
28. Stein S, Ott MG, Schultze-Strasser S, Jauch A, Burwinkel B, Kinner A, et al. Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. Nat Med 2010;16:198-204.
29. Braun CJ, Boztug K, Paruzynski A, Witzel M, Schwarzer A, Rothe M, et al. Gene therapy for Wiskott-Aldrich syndrome–long-term efficacy and genotoxicity. Sci Transl Med 2014;6:227ra33.
30. Punwani D, Kawahara M, Yu J, Sanford U, Roy S, Patel K, et al. Lentivirus mediated correction of Artemis-deficient severe combined immunodeficiency. Hum Gene Ther 2017;28:112-24.
31. Hacein-Bey Abina S, Gaspar HB, Blondeau J, Caccavelli L, Charrier S, Buckland K, et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. JAMA 2015;313:1550-63.
32. Ferrua F, Cicalese MP, Galimberti S, Giannelli S, Dionisio F, Barzaghi F, et al. Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study. Lancet Haematol 2019;6:e239-53.
33. Kohn DB, Booth C, Kang EM, Pai SY, Shaw KL, Santilli G, et al. Net4CGD consortium. Lentiviral gene therapy for X-linked chronic granulomatous disease. Nat Med 2020;26:200-6.
34. Kohn DB, Shaw KL, Garabedian E, Carbonaro DA, Moore TB, De Oliveira SN, et al. Lentiviral gene therapy with autologous hematopoietic stem and progenitor cells (HSPCs) for the treatment of severe combined immune deficiency due to adenosine deaminase deficiency (ADA-SCID): two year follow-up results. Mol Ther 2020;28:554.
35. Kohn DB, Rao G, Almarza E, Terrazas D, Nicoletti E, Fernandes A, et al. A phase 1/2 study of lentiviral-mediated ex-vivo gene therapy for pediatric patients with severe leukocyte adhesion deficiency-I (LAD-I): initial results from the first treated patient. Mol Ther 2020;28:56.
36. Morgan RA, Gray D, Lomova A, Kohn DB. Hematopoietic stem cell gene therapy: progress and lessons learned. Cell Stem Cell 2017;21:574-90.
37. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature 2016;533:420-4.
38. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 2019;576:149-57.