



REVIEW

# Advances of gene therapy for primary immunodeficiencies [version 1; referees: 2 approved]

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**Abstract**

In the recent past, the gene therapy field has witnessed a remarkable series of successes, many of which have involved primary immunodeficiency diseases, such as X-linked severe combined immunodeficiency, adenosine deaminase deficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome. While such progress has widened the choice of therapeutic options in some specific cases of primary immunodeficiency, much remains to be done to extend the geographical availability of such an advanced approach and to increase the number of diseases that can be targeted. At the same time, emerging technologies are stimulating intensive investigations that may lead to the application of precise genetic editing as the next form of gene therapy for these and other human genetic diseases.



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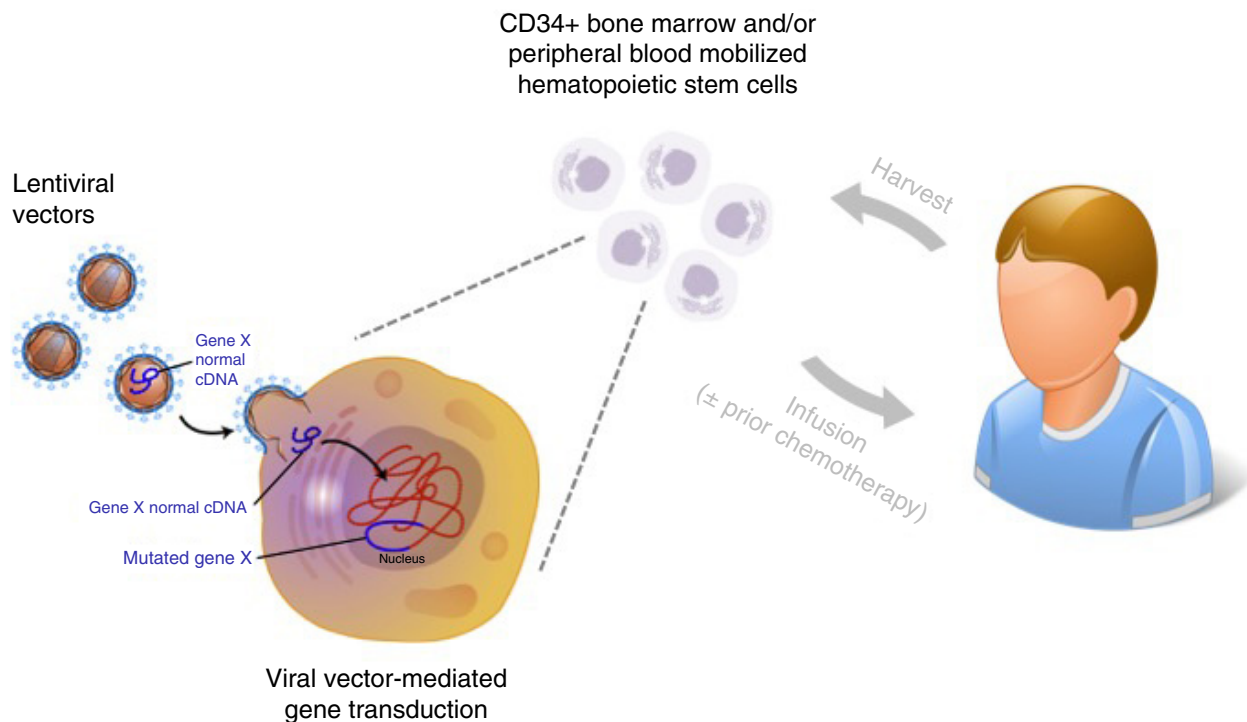
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## Introduction

Primary immunodeficiency diseases (PIDs) are a heterogeneous group of mostly rare genetic diseases comprising over 250 different clinical entities and resulting from a vast variety of aberrations affecting the biological pathways of development and differentiation of the immune system<sup>1</sup>. The most severe forms of PIDs are characterized by recurrent and life-threatening infections, the risk of which can be obviated only with the reconstitution of a normally functioning immune system. Since the late 1960s, allogeneic hematopoietic stem cell transplantation (HSCT) has been successfully used to treat severe PIDs and it still represents the treatment of choice. While its results have been improving steadily over the past few decades, HSCT remains an intensive procedure burdened by significant morbidity and mortality, especially when affected patients cannot benefit from HLA-identical sibling donors<sup>2</sup>. Based on the notion that genetic correction of autologous hematopoietic stem cells (HSCs) could provide a safer alternative for any patient from whom HSCs can be obtained, gene therapy approaches for PIDs were developed starting in the mid-1980s and were initially based on the use of gene transfer vectors derived from murine gamma-retroviruses<sup>3</sup>. These pioneer clinical protocols made their entry into the clinical arena in the early 1990s and focused on patients affected with adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID) who derived limited benefit from the genetic correction of either their peripheral blood lymphocytes or

CD34+ hematopoietic progenitors<sup>4-7</sup>. Following technical progress led to the identification of effective combinations of cytokines and growth factors (e.g. interleukin [IL]-3, IL-6, stem cell factor [SCF], thrombopoietin, and fms-like tyrosine kinase [Flt]-3 ligand) that, together with culture supports such as fibronectin, resulted in major improvements in the ability to introduce genes into HSCs<sup>8,9</sup>. These improvements precluded to the first unambiguous successful clinical applications of gene therapy in patients affected with X-linked SCID (SCIDX-1), ADA-SCID, and Wiskott-Aldrich syndrome (WAS)<sup>10-13</sup> (Figure 1). Unfortunately, with the initial clear clinical benefits, the first serious complications of gene therapy also occurred. In a significant number of patients treated using murine gamma-retroviral vectors, insertional oncogenesis events driven by the presence of the powerful viral enhancer elements resulted in acute leukemias that, in some cases, have had fatal outcomes<sup>14-16</sup>. These serious adverse events have sparked a revision of the assessment of risks and benefits of integrating gene transfer as therapy for PIDs and prompted the development and application of new generations of viral vectors with increased safety characteristics.

This commentary will summarize the results of the current clinical trials that are making use of such newer vectors with the goal of continuing the expansion of successful applications of gene therapy for PIDs, while increasing the safety of clinical investigations.



**Figure 1. Schematic representation of a typical gene therapy procedure for primary immunodeficiency diseases (PIDs).** CD34+ hematopoietic progenitors are obtained through bone marrow harvest or peripheral blood apheresis after pharmacological mobilization. Cells are then cultured *in vitro* with cytokines and growth factors (e.g. SCF, TPO, and Flt-3 ligand) and exposed to viral vectors. Finally, transduced cells are collected and reinfused to the patient through a peripheral vein. If the gene therapy protocol involves myeloablative chemotherapy, the cytoreductive agent is administered ~24 hours before the infusion of gene-corrected cells. (Graphics modified from original illustrations by Derryl Leja, NHGRI, Image Gallery, [www.genome.gov](http://www.genome.gov)).

## Improving the safety of gene therapy for primary immunodeficiencies

### X-linked severe combined immunodeficiency

This form of SCID is caused by mutations affecting the expression of the common gamma chain ( $\gamma_c$ ) of the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21<sup>17,18</sup> and, similar to other SCID diseases, is characterized by combined impairment of T- and B-cell immunity and early susceptibility to overwhelming infections. Clinical gene therapy trials using murine gamma-retroviral vectors expressing  $\gamma_c$  were developed in the mid 1990s as an alternative therapeutic option to HSCT and, in the early 2000s, yielded the first convincing results that gene therapy could provide a cure for human genetic diseases<sup>10,12</sup>. Unfortunately, five out of the 20 SCIDX-1 patients treated in these trials developed T-cell leukemia between 2 and 5 years after gene therapy. In all cases, evidence pointed to the integration of the  $\gamma_c$  retroviral vector in the vicinity of oncogenes (*LMO2* or *CCND2*) as the promoting factor due to the presence of a powerful enhancer element within the retroviral construct that is accepted to have caused aberrant oncogene activation and consequent leukemogenesis<sup>14,15</sup>.

Investigators in the field reacted to these adverse events by developing safer  $\gamma_c$  gene transfer vector alternatives. A gamma-retroviral vector devoid of enhancer sequences was demonstrated to be effective in the mouse model of SCIDX-1<sup>19</sup> and then brought to the clinic in a consortium study including centers in Paris, Boston, Cincinnati, Los Angeles, and London. Recently published data show that seven out of eight evaluable patients achieved significant numbers of corrected, diverse, and functional circulating T-lymphocytes with temporal kinetics that did not differ from earlier  $\gamma_c$  gene therapy trials. In contrast to T cells, there was not significant correction of the B-cell compartment, with all patients remaining on immunoglobulin replacement therapy. Importantly, at 12–39 months post-gene therapy, no clonal expansions were detected and analysis of retroviral integration sites showed significantly less clustering near *LMO-2*, *EVII*, or other lymphoid oncogenes compared to the earlier  $\gamma_c$  gene therapy trials<sup>20</sup>. If confirmed after extended follow-up, these findings would indicate that the use of enhancer-deleted retroviral vectors can result in similar restoration of immune function for SCIDX-1 patients compared to first-generation gamma-retroviral vectors, while affording superior safety.

As another alternative to gamma-retroviral vectors for gene therapy of SCIDX-1 and other PIDs, investigators turned to gene transfer constructs based on human immunodeficiency virus type 1 (HIV-1) that are accepted as integrating vectors with lower potential to cause activation of oncogenes located near their genomic integration sites<sup>21</sup>. A  $\gamma_c$ -expressing lentiviral vector based on HIV-1 has been developed<sup>22</sup> and is being used in a two-site clinical trial open at the St. Jude Children's Research Center in Memphis, where typical SCIDX-1 patients will be enrolled, and at the National Institutes of Health, where atypical, older patients are treated. The latter arm of the trial uses non-myeloablative conditioning to improve the efficacy of engraftment of gene-corrected cells and has enrolled five patients with encouraging preliminary results of reconstitution of B-lymphocyte function in two patients at >2.5 years post-treatment<sup>23</sup>. Whether or not lentiviral-mediated gene therapy for SCIDX-1 represents a safe and effective alternative will need to be established based on extended patient accrual and follow-up.

### Wiskott-Aldrich syndrome

WAS is an X-linked disorder with a spectrum of clinical presentations ranging from isolated mild thrombocytopenia to life-threatening bleeding episodes, severe eczema, recurrent infections, autoimmune disorders, and high incidence of lymphomas. Functional abnormalities affect all major lymphoid and myeloid cell populations and contribute to the heterogeneous and medically challenging clinical presentation of affected patients<sup>24</sup>. HSCT can be curative for WAS, but its outcome is unsatisfactory when HLA-identical donors are not available<sup>2,25</sup>, which supported the development of gene therapy for this disease.

The first clinical gene therapy trial for WAS was carried out in Germany and used a gamma-retroviral vector to correct CD34+ cells from ten WAS patients, nine of whom showed significant increase of platelet counts and restoration of immune responses. Unfortunately, seven patients developed acute leukemia likely due to vector-mediated activation of the *LMO2*, *MDS1*, or *MNI* genes<sup>16</sup>. Therefore, gamma-retroviral vector-mediated gene therapy of WAS appears to carry an unacceptably high level of risk of insertional oncogenesis. Providing an alternative to the use of murine gamma-retroviral vectors, WAS gene transfer constructs based on HIV-1 had also become available<sup>26</sup>, which allowed for their application to two clinical trials, the initial results of which have been recently published. In the first trial, Italian investigators showed improvement of platelet counts, immune function, and clinical manifestations of the disease in three patients at  $\geq 1$  year after gene therapy. Importantly, comparison of retroviral and lentiviral vector integration sites in samples from the German and Italian studies showed lack of overrepresentation of sites targeting oncogenes in the Italian patient group, while demonstrating early enrichment of oncogenic targets in patients from the German trial<sup>27</sup>. In the second trial, six out of seven patients treated in London and Paris also showed improvement of immune function and clinical manifestations 6–42 months after treatment, during which no vector-mediated clonal expansions were noted<sup>28</sup>. Of note, for reasons that are not yet clear, neither trial resulted in reconstitution of normal platelet numbers, although bleeding episodes significantly reduced in number and severity, and treated patients became independent from transfusion and need for thrombopoiesis stimulator factors<sup>27,28</sup>. More recently, a trial using the same lentiviral vector used in the Italian and French sites described above has launched in Boston, MA, USA and has enrolled four patients as of December 2015 with similar results<sup>29</sup>. Based on these observations, it can be concluded that lentiviral-mediated gene therapy for WAS is feasible and can result in significant benefit for treated patients. Clearly, however, long-term observation is warranted to confirm the superior safety of lentiviral gene transfer as an alternative treatment option for this disease.

### Chronic granulomatous disease

Gene therapy has long been considered an attractive alternative therapeutic option for X-linked chronic granulomatous disease (CGD), a genetic defect affecting the expression of the gp91phox molecule and characterized by impaired superoxide production in phagocytic cells with consequent susceptibility to life-threatening abscesses and/or granuloma formations in the skin, liver, lungs, or bone of affected patients<sup>30</sup>. Early clinical trials were performed in the late 1990s with limited success due to low engraftment of gene-corrected hematopoietic progenitor cells and often only transitory

functional correction of 0.5–1% of peripheral blood granulocytes<sup>31–35</sup>. A trial performed in Germany in 2004 using a gamma-retroviral vector expressing gp91phox under the transcriptional control of the spleen focus-forming virus long terminal repeat (LTR) appeared to have achieved superior results in two CGD patients when around 15% of neutrophils were found to be functionally corrected early after treatment. This fraction increased due to insertional activation of the *PRDM16* and *MDS1/EVII* genes in clonal cell populations that expanded with time. Unfortunately, both patients eventually presented with myelodysplasia that was likely caused by the activation of the *EVII* gene and that resulted in lethal complications<sup>36–38</sup>. The same clonal expansion was observed in two children with CGD treated in Switzerland with the same protocol with significant correction of functional neutrophils and eradication of fungal infections. In one of these two cases, the clonal expansion was also followed by the occurrence of myelodysplasia and both patients were rescued with allogeneic stem cell transplantation<sup>39,40</sup>.

Similar to what ensued after the cases of leukemogenesis in the SCIDX-1 and WAS trials, an enhancer element-devoid gamma-retroviral vector and a lentiviral vector expressing gp91phox have been developed for safer gene therapy approaches for CGD<sup>41,42</sup> and multicenter clinical trials are planned in Europe and the USA to determine their efficacy. In addition to the needed improvements in safety, gene therapy approaches for CGD are confronting the as-yet-unexplained difficulty in achieving long-term engraftment of significant levels of transduced cells. The lack of a strong selective advantage of gene-corrected populations in this disease may imply that higher levels of HSC transduction and engraftment will be needed to obtain clinical benefit. In this respect, the gene therapy field is likely to borrow from the experience of HSCT in CGD to identify preparative conditioning regimens that are effective and well tolerated<sup>43</sup>. Finally, with the aim of avoiding possible toxic effects of gp91phox expression in hematopoietic progenitors, the newer constructs for gene therapy of CGD carry myeloid-specific promoters and/or allow for microRNA-mediated post-transcriptional downregulation of expression in hematopoietic stem/progenitor cells<sup>42,44</sup>.

### Adenosine deaminase deficiency

This form of SCID is caused by genetic defects of ADA and presents with extreme reduction of lymphocyte numbers and impairment of immune functions that can lead to early death from infections<sup>45</sup>. HSCT and enzyme replacement therapy (ERT) are available forms of treatment for this disease, but each has drawbacks that limit their efficacy<sup>46,47</sup>. As mentioned above, in the mid-1980s, ADA deficiency was identified as an ideal candidate disorder for trials of gene therapy. A series of clinical trials tested gamma-retroviral vector-mediated ADA gene transfer into patients' peripheral blood T lymphocytes<sup>4,5,48–51</sup>, bone marrow, or cord blood HSCs<sup>6,7,52</sup> as an alternative treatment option to HSCT and ERT, but failed to result in self-standing improvements of the disease in treated patients.

The turning point was when the experimental protocols were changed to include administration of mild myeloreductive chemotherapy with busulfan (e.g. 4 mg/kg) or melphalan (140 mg/m<sup>2</sup>), and the withholding of ERT, as steps aimed at increasing the initial advantage of gene-corrected HSCs. As shown initially by

Aiuti and collaborators in Italy, this approach was revealed to be extremely effective in achieving immune reconstitution (increases in T-cell counts, normalization of T-cell function, and restoration of responses to vaccinations) in the majority of ten treated patients who remained off ERT in the long term<sup>11,53</sup>.

These encouraging results were confirmed in a similar gene therapy trial conducted in the UK, in which four out of six treated patients showed increases in T-cell and B-cell numbers, with normalization of *in vitro* lymphocyte responses and adequate immunoglobulin production in three subjects<sup>54,55</sup>.

Our own investigations performed at the Children's Hospital Los Angeles, University of California Los Angeles, and the National Institutes of Health compared the immune reconstitution observed in four patients treated without prior administration of chemotherapy and while on ERT to that of six patients whose treatment strategy involved low-dose busulfan chemotherapy (75–90 mg/m<sup>2</sup>) and withdrawal of ERT. The results demonstrated that the use of reduced-intensity conditioning favored engraftment of gene-modified stem cells and the generation of ADA-expressing lymphocytes and consequent immune reconstitution<sup>56</sup>.

It is important to note that the immune recovery observed in ADA-SCID patients after gene therapy with gamma-retroviral vectors occurred in the absence of insertional oncogenesis events, which distinguishes the experience in this disease from the other PIDs discussed above. The reasons underlying this contrast remain unclear, but they may reflect biological differences between ADA,  $\gamma_c$ , and the WAS protein and their possible contributing roles in leukemogenesis. Regardless of the current safety record of gamma-retroviral vector-mediated gene therapy for ADA-SCID, compelling reasons existed to generate a newer, more efficient, and safer ADA vector, which was accomplished with the development of a lentiviral construct<sup>57</sup> that is being tested in the UK and USA with very encouraging preliminary results<sup>58</sup>.

### Future prospects and challenges

Preclinical development is underway for several other forms of PID that would benefit from gene therapy approaches (Table 1). Promising results have been obtained using lentiviral vectors to correct SCID due to RAG1, RAG2, and Artemis deficiencies in mouse and xenotransplant models<sup>59–65</sup> and are expected to translate into clinical experiments in the near future. Gene therapy for PIDs such as purine nucleoside phosphorylase (PNP) deficiency, Janus kinase (JAK)-3-deficient SCID, and leukocyte adhesion deficiency type 1 (LAD-1) was considered and/or unsuccessfully carried out before technological advances established the current levels of feasibility of clinical gene transfer<sup>66–68</sup>. Better outcomes would be expected if these experiments were to be re-attempted at present times. For several other forms of PIDs, the tissue-restricted or finely regulated characteristics of expression of the causal genes represent significant challenges and will require additional technical progress. It is hoped that the expanding application of “gene editing” strategies (e.g. zinc-finger nucleases [ZFNs], transcription activator-like effector nucleases [TALENs], and clustered regularly interspaced short palindromic repeats [CRISPR]/CRISPR-associated endonuclease [Cas-9] technology) will ultimately provide



**Table 1. Ongoing pre-clinical experimentations of gene therapy for primary immunodeficiency diseases.**

	Challenges	Models*	Status
<b>SCIDs</b>			
Artemis deficiency	Ectopic expression toxicity?	KO mouse	<i>In vivo</i> gene correction <sup>63,64</sup>
CD3 $\gamma$ deficiency	Regulated gene expression	KO mouse	<i>In vitro</i> gene correction <sup>74</sup>
JAK3-SCID	Biochemical effects of JAK3 overexpression	KO mouse	<i>In vitro</i> and <i>in vivo</i> gene correction; failed clinical attempt <sup>68,75-79</sup>
RAG-1 deficiency	Balance efficacy/toxicity	KO mouse Xenotransplant	<i>In vivo</i> gene correction <sup>59,61,62,65,80</sup>
RAG-2 deficiency	High gene expression necessary	KO mouse	<i>In vivo</i> gene correction <sup>60,81</sup>
Reticular dysgenesis	Expression in myeloid lineages	KO zebrafish iPSCs	<i>In vitro</i> and <i>in vivo</i> gene correction <sup>82</sup>
<b>Combined immunodeficiencies</b>			
PNP deficiency	Non-immunological clinical complications	KO mouse	<i>In vitro</i> and <i>in vivo</i> gene correction <sup>66,83</sup>
ZAP70 deficiency	Restricted gene expression	KO mouse	<i>In vitro</i> and <i>in vivo</i> gene correction <sup>84-88</sup>
MHC class II deficiency	Regulated gene expression	KO mouse	<i>In vitro</i> gene correction <sup>89</sup>
<b>Antibody defects</b>			
XLA	Restricted gene expression	KO mouse Xid mouse	<i>In vivo</i> gene correction <sup>90-93</sup>
X-HIM	Regulated gene expression	KO mouse	<i>In vitro</i> and <i>in vivo</i> gene correction <sup>94-96</sup>
<b>Immune dysregulation syndromes</b>			
Perforin deficiency	Restricted gene expression	KO mouse	<i>In vivo</i> gene correction <sup>97</sup>
XLP	Regulated gene expression	KO mouse	<i>In vivo</i> gene correction <sup>98</sup>
<b>Innate immune defects</b>			
LAD-1	Restricted gene expression No selective advantage	KO mouse CLAD dog	<i>In vitro</i> and <i>in vivo</i> gene correction; failed clinical attempt <sup>67,99-107</sup>

\*In addition to biological patient samples.

JAK3, Janus kinase 3; LAD-1, leukocyte adhesion deficiency type 1; PNP, purine nucleoside phosphorylase; RAG, recombination activating gene; X-HIM, X-linked hyper-IgM syndrome; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative syndrome; ZAP70, zeta-chain-associated protein kinase 70; KO, knockout; iPSCs, induced pluripotent stem cells.

the ability of performing precise genetic correction of PID-causing mutations, while respecting the physiological machineries of gene expression regulation and avoiding the problems of ectopic gene expression that are inherent in current “gene addition” approaches. Important proofs-of-concept have already been obtained using ZFN technology, including the repair of  $\gamma$ c mutations in *in vitro* and *in vivo* xenotransplant models<sup>69,70</sup> and the site-directed addition of the gp91phox complementary DNA (cDNA) in induced pluripotent stem cells (iPSCs)<sup>71</sup>.

While there are excellent prospects for the safer implementation of gene therapy for an increasing number of PIDs, it is difficult to ignore that clinical gene transfer remains a laborious procedure restricted to a very small number of highly specialized academic centers worldwide. For PIDs like ADA-SCID, SCIDX-1, and WAS, the current results make gene therapy a realistic therapeutic alternative

that can be considered as part of the clinical management plan. Access to this therapeutic modality, however, is far from simple owing to financial and geographical considerations. As a possible solution, strategies are being developed that would allow hematopoietic progenitors to be collected at the patient’s local institution and sent to gene therapy centers where the gene transfer procedure would be performed. Cryopreserved, gene-corrected samples would then be sent back for infusion. The involvement of pharmaceutical and biotechnology companies would make these objectives easier to achieve, and it is encouraging that corporate interest in supporting clinical gene therapy trials for PIDs is increasing.

Thirty years after proof-of-principle experiments demonstrating the first corrections of genetic disease phenotypes *in vitro*<sup>72,73</sup>, gene transfer is fulfilling its promise by achieving convincing curative potential for a variety of human disorders. Since the very beginning

of the field of human gene therapy, PIDs have played a major role in driving the evolution and implementation of the initial theoretical strategies of this discipline. Cutting-edge activity continues to characterize this area of gene therapy and will undoubtedly foster further applications against human diseases.

### Abbreviations

ADA: adenosine deaminase  
 CGD: chronic granulomatous disease  
 ERT: enzyme replacement therapy  
 Flt-3: fms-like tyrosine kinase  
 gc: gamma chain  
 HSC: hematopoietic stem cell  
 HSCT: hematopoietic stem cell transplantation  
 HIV-1: human immunodeficiency virus type 1  
 IL: interleukin  
 iPSCs: induced pluripotent stem cells  
 JAK: Janus kinase  
 LAD: leukocyte adhesion deficiency

PIDs: primary immunodeficiency diseases  
 RAG: recombination activating gene  
 SCF: stem cell factor  
 SCID: severe combined immunodeficiency  
 SCIDX-1: X-linked severe combined immunodeficiency  
 WAS: Wiskott-Aldrich syndrome  
 ZFNs: zinc-finger nucleases

### Competing interests

The author has no competing interests to declare.

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