Ensuring a future for gene therapy for rare diseases

Hematopoietic stem-cell gene therapy has proven to be an effective treatment for several primary immunodeficiencies, and yet companies in this space are withdrawing from the EU market. Technological and regulatory innovations and a change to cost–benefit models are needed so that rare disease patients can receive these life-saving medicines.

Alessandro Aiuti, Francesca Pasinelli and Luigi Naldini

Autologous hematopoietic stem and progenitor cell gene therapy (HSPC-GT) has emerged as an effective treatment for several inherited diseases, including primary immunodeficiencies[1] (Fig. 1). However, the recent news that Orchard Therapeutics will discontinue investment in gene therapy programs for three rare primary immunodeficiencies, citing commercial reasons[2], represents a serious setback for the field, not just for these diseases but for all genetic disorders. Two of the programs that will be discontinued by Orchard, adenosine deaminase severe combined immunodeficiency (ADA-SCID) and Wiskott–Aldrich syndrome (WAS), were originally developed at the San Raffaele Telethon Institute for Gene Therapy (where A.A. and L.N. work).

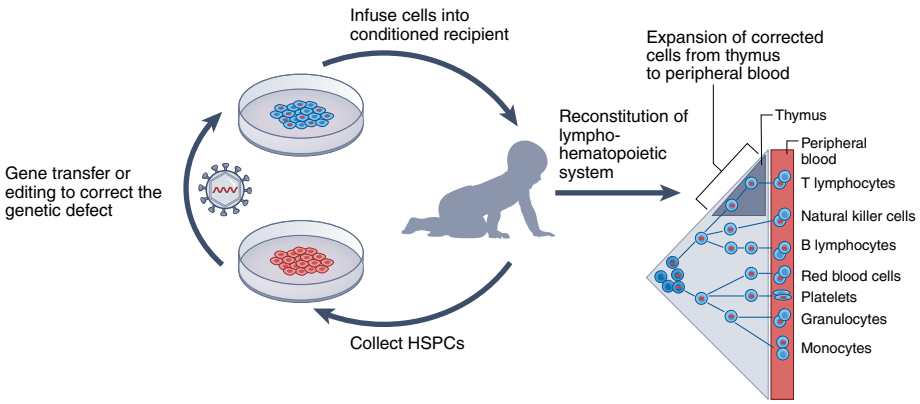

Fig. 1 | Hematopoietic stem and progenitor cell gene therapy. Hematopoietic stem and progenitor cells (HSPCs) are collected from the patient and gene-corrected ex vivo before being reinfused after administration of a conditioning regimen, leading to the expression of the transferred or edited gene in peripheral blood cells.

Effective therapies

Also known as inborn errors of immunity, primary immunodeficiencies are rare, monogenic diseases caused by mutations in genes involved in immune cell development, regulation and function and are characterized by recurrent infections, autoimmunity, lymphoproliferation, inflammatory manifestations, allergy and malignancies[3]. Treatment for the most severe forms consists of allogeneic hematopoietic stem-cell transplantation (allo-HSCT) from an immune-compatible donor. In the past decade, the development of alternative donor strategies, novel graft manipulation techniques, modified conditioning regimens, graft-versus-host disease prophylaxis and control of viral infections have greatly improved access to allo-HSCT and alleviated its morbidity, increasing overall survival[4–6]. Nevertheless, allogeneic procedures still carry a significant risk of potentially serious complications owing to acute and chronic graft-versus-host disease, graft failure and graft rejection, with higher mortality in patients with underlying infection, organ damage or older age.

HSPC-GT provides a promising alternative to allo-HSCT, as the use of autologous cells, with no need for a donor, makes the treatment available to every patient and abrogates risks related to immune mismatch. Lower-intensity conditioning regimens adopted in HSPC-GT induce partial replacement of the bone marrow HSPCs but are sufficient to provide substantial therapeutic benefit while alleviating the morbidity and mortality of the procedure. Importantly, the incidence of delayed leukemogenesis triggered by sporadic vector insertion near oncogenes, which emerged in early HSPC-GT trials, has been abated by new vector platforms. As more becomes known about the long-term safety and therapeutic benefit of HSPC-GT, its application could be broadened to encompass less severe conditions, for which allo-HSCT is not currently indicated but lifelong treatment, such as immunoglobulin infusions and frequent antimicrobial therapy, is required.

Primary immunodeficiencies are the first genetic diseases in which ex vivo HSPC-GT approaches were implemented and proved successful. HSPC-GT mediated by γ-retroviral vectors for ADA-SCID (Strimvelis, Orchard) was the first to achieve marketing authorization and reimbursement in the EU[7,8]. Although the number of patients treated since its commercialization has been relatively small, as expected for an ultra-rare disease, the registration allowed access to a reimbursed product to patients from various EU countries.
A recent meta-analysis showed that from 1995 to 2020, 224 patients with primary immunodeficiency, with 5 underlying diseases[9], each of whom lacked access to standard-of-care allo-HSCT (usually because of the absence of a matched sibling donor), were treated with HSPC-GT and showed a 5-year overall survival of >94%, reaching 100% in the case of ADA-SCID. The analyses showed stable reconstitution of hematopoiesis in most recipients, with superior engraftment and improved safety profile in patients receiving HSPCs

Table 1 | Gene therapy approaches for inborn errors of immunity

Status	Approach	Disease	Gene
EU approval	γ-retroviral vector	ADA-SCID	*ADA*
Clinical trials	Self-inactivating γ-retroviral vector; lentiviral vector	SCID-X1 (γ-chain deficiency)	*IL2RG*
	Lentiviral vector	ADA-SCID	*ADA*
	Lentiviral vector	Artemis deficiency	*DCLRE1C*
	Lentiviral vector	RAG1 deficiency	*RAG1*
	Lentiviral vector	Wiskott–Aldrich syndrome	*WAS*
	Lentiviral vector	X-linked chronic granulomatous disease ($gp91^{phox}$)	*CYBB*
	Lentiviral vector	$P47^{phox}$ chronic granulomatous disease	*NCF1*
	Lentiviral vector	Leukocyte adhesion deficiency type 1	*ITGB2*
	Lentiviral vector	Osteopetrosis	*TCIRG*
	Lentiviral vector	IPEX syndrome	*FOXP3*
Preclinical studies	Lentiviral vector	RAG2 deficiency	*RAG2*
	Lentiviral vector	ADA2 deficiency	*ADA2*
	Lentiviral vector	Familial hemophagocytic syndrome 2	*PRF1*
	Lentiviral vector	Familial hemophagocytic syndrome 3	*UNC13D*
	Lentiviral vector	X-linked lymphoproliferative syndrome	*SAP*
	Lentiviral vector; gene editing	X-linked agammaglobulinemia (XLA)	*BTK*
	Gene editing	SCID-X1	*IL2RG*
	Gene editing	CD3d deficiency	*CD3D*
	Gene editing	Wiskott–Aldrich syndrome	*WAS*
	Gene editing	X-linked chronic granulomatous disease	*CYBB*
	Gene editing	Severe congenital neutropenia	*ELANE*
	Gene editing	Hyper-IgM syndrome 1 (HIGM1)	*CD40L*
	Gene editing	STAT3-hyper IgE syndrome	*STAT3*
	Gene editing	CTLA4 insufficiency	*CTLA4*

ADA, adenosine deaminase; CGD, chronic granulomatous disease; DADA2, ADA2 deficiency; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LAD, leukocyte adhesion deficiency; LV, lentivirus; RAG1/2, recombination activating genes 1/2; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome; XLP, X-linked lymphoproliferative syndrome.

transduced by lentiviral as compared to γ-retroviral vectors.

Oncogenesis due to insertional mutagenesis has been confined to patients treated with early generation γ-retroviral vectors, and its incidence strongly varies with the disease type. Moreover, there is now a better understanding of the factors that may aggravate the genotoxic risk of vector integration, such as vector design, promoter choice and quality of manufactured cell product.

Disinvestment despite demand

At present, clinical trials of HSPC-GT using lentiviral vectors are ongoing in Europe and the USA for nine distinct primary immunodeficiencies[10–15] (Table 1). For the most advanced programs, there is robust evidence of safety and of long-term-stable and near-complete immune reconstitution in treated patients. Moreover, promising results have been obtained at the preclinical stage for at least 15 different innate and/or adaptive immune system defects, using gene-addition or gene-editing approaches. Despite these remarkable successes, there remain some concerns about the associated long-term risks. But no requirement for 100% efficacy or safety is either expected or achieved for other treatments, including allo-HSCT, which has long been the standard of care for severe primary immunodeficiencies.

The news of disinvestment in gene therapy for primary immunodeficiencies follows the announcement that Bluebird Bio, another biotech focused on HSPC-GT for severe genetic conditions, has closed operations in Europe due to challenges in achieving the requested reimbursement and market access for two ex vivo HSPC-GT for the treatment of β-thalassemia and a rare neurodegenerative disorder, X-linked adrenoleukodystrophy[16].

There are several potential reasons for the disinvestment in these gene therapies. Gene therapy medicinal products require high investment with elevated costs of development, manufacturing, logistics and demanding long-term follow-up of patients (Table 2). Manufacturing is particularly expensive for autologously sourced cell products, such as HSPC-GT, which are personalized medicines requiring manipulation in dedicated facilities, complex starting materials including viral vectors, and multiple non-routine quality tests for each individual product batch. Compensating for these costs and making profit from these treatments becomes challenging when targeting rare diseases, especially if aiming at a fast return on investment. Regulatory authorities in the EU and the USA require strict monitoring of patients and data collection in long-term follow-up studies as part of risk management measures, primarily to identify delayed oncogenesis from vector integration. This requirement is different for patients who have received conventional allo-HSCT or high-dose chemotherapy, who are monitored as part of normal routine clinical follow-up, despite their risk of developing long-term organ complications or therapy-related tumors[17].

Fragmented regulation

Another major hurdle comes from the burden and heterogeneity in the regulatory evaluation system and market access between different jurisdictions, especially between the EU and USA. Despite constant adjustment of guidelines and expectations from regulatory authorities, cell-based gene therapy products continue to challenge conventional approaches to standard drug development and commercialization. The current requirements to qualify an autologous cell-based gene therapy product according to established criteria of homogeneity, purity and potency sometimes requires demanding and expensive tests, which may exceed the information required to ensure the expected biological activity.

In the USA, funding and incentives support early clinical research, but the path to market authorization appears to be more demanding; none of the HSPC-GTs approved in the EU have yet received regulatory approval by the US Food and Drug Administration. In the EU, long negotiations with individual EU nations slow availability for patients, as do difficulties in accepting innovative models of reimbursement of the high costs of therapies

Table 2 | Critical issues and potential solutions for gene therapy

Critical issue	Potential solution
High production costs	Technological innovation, such as stable vector packaging cell lines and large-scale bioreactor production, closed system and optimized transduction, shortened manipulation and minimal batch testing prioritizing molecular methods
Bottlenecks and inconsistencies in regulatory approval	Update regulatory legislation along the entire development and registration path, support for platform-based approaches, use of master files
	Harmonization of regulatory requirements within the EU and with other jurisdictions
Inappropriate cost–benefit analyses	Close dialogue with key stakeholders throughout the process
	Collaboration between countries to harmonize market access and reimbursement
	Use of innovative tools to capture the long-term medical and social impact of gene therapies, so that new pricing approaches can be devised.
	Risk-sharing agreement between companies and payers to balance uncertainty on the durability at the time of market access
Affordability and sustainability	Public–private coordinated efforts to facilitate access
	Public funds for ultra-rare diseases to reimburse the treatment costs and to collect real-world evidence
	Manufacturing and administration of gene therapies for ultra-rare diseases under a nonprofit scheme supported by public national or supra-national funds
	Cross-border cooperation for patients with ultra-rare diseases

by health technology assessment bodies and governments. HSPC-GT for ADA-SCID was found to be cost effective by the Italian Drug Agency AIFA and the National Institute for Health and Care Excellence in the UK as compared to standard of care (allo-HSCT), and was made accessible to patients in five EU countries through the EU social security regulation, but there have been challenges in other countries, most likely due to budget concerns. For some other gene therapies, the price range proposed by the license holder did not meet health technology assessments in any of the EU countries where negotiations took place.

A long-term-effective treatment administered only once in a lifetime is not always perceived as cost saving because of current budgeting practices, where costs are often counted over a single year. This is despite the skyrocketing costs and burden of lifelong chronic treatment for rare diseases[18–21]. In addition, some health technology assessment bodies may opt to cover allo-HSCT, a less expensive procedure, rather than HSPC-GT, even though the risk of short- and long-term complications may be higher for the former.

Evidence generation

As well as providing immediate benefit for patients, HSPC gene therapy for primary immunodeficiencies provides an in-human model to gather more evidence about improved delivery and manufacturing strategies, including engraftment of engineered hematopoietic stem cells and expanding these ex vivo.

It is possible that gene therapy will be superseded by gene-editing methods, such as CRISPR–Cas9, but existing gene therapy approaches allow the accumulation of long-term safety and efficacy data on gene transfer approaches, providing a benchmark against which to assess the potential advantages and disadvantages of novel engineering strategies. Preliminary results of the first clinical testing of gene editing in human HSPCs are indeed promising[22], but more research is needed on the long-term resilience and safety of the engineered graft, preservation of long-term hematopoietic stem cell activity and consequences of p53-mediated responses to double-strand DNA breaks[23,24]. Comparators from gene transfer clinical trials will be invaluable for evaluating platform-specific adverse impacts from gene editing.

Prioritizing patients

There is substantial unmet clinical need for many severe and neglected genetic conditions. Patients are poorly served by a system whereby novel treatments become available at a slow rate and then may be withdrawn due to a perceived lack of commercial viability. Academia played a key role in the early development of gene transfer therapy and gene editing, with considerable funding from public agencies (including the EU Commission, US National Institutes of Health and California Institute of Regenerative Medicine) and nonprofit organizations (such as Fondazione Telethon, AFM/Telethon and the Wellcome Trust). Discontinuing gene therapy programs would not only leave patients without potentially lifesaving therapies but also waste precious know-how developed using taxpayer money and individual donations.

Continued access for patients to gene therapies is achievable (Table 2). Production costs should be reduced throughout the process by leveraging automated closed systems with reduced environmental requirements and decentralized on-site cell manufacturing, reduced cost of goods, optimized transduction, shortened manipulation time and minimal batch testing once the process has been validated. The burden of preclinical testing for a new product using previously validated vectors could be reduced by allowing reuse of information, common standards and platform approaches. A close dialogue is needed between all key stakeholders, including academia, patient associations, public and private funding agencies, pharmaceutical companies, contract manufacturing organizations, governmental and global health agencies, regulators, payers and health technology assessment bodies, in order to optimize roadmaps from early development to advanced clinical testing of any novel advanced therapy medicinal products, including gene therapy. Such a roadmap can use tools such as the IRDiRC Orphan Drug Development Guidebook[25], which includes business models to promote availability and affordability of these medicines.

Costs can and should be reduced, but benefits should also be more appropriately evaluated. Health technology assessment processes do not fully appreciate the benefit of once-in-a-lifetime transformative treatments for rare and ultra-rare diseases. Continuous evidence generation and real-world collection tools should be deployed to measure lifetime benefits for patients, so that new approaches to pricing models can be devised. Regulations should be streamlined, both within and outside the EU, to allow cross-border delivery and reimbursement of treatments.

There are objective limits to cost containment for gene therapies because of their complex development and production processes, and so they will continue to put significant pressure on payers and health systems. These treatments should eventually be made available to all who need them, or we risk a future where they are only available in a few rich countries or through private clinics. Additional public investment

in the manufacturing of gene therapies for ultra-rare diseases and administration under a nonprofit scheme could allow lower regulatory and production costs, without impacting safety.

Continued investment in this field should allow the development and rollout of effective gene therapies that reduce overall healthcare costs when compared to continuous lifelong treatment of symptoms. This would benefit all taxpayers, as well as the patients who are provided with a cure for their otherwise lethal diseases. ❐

Alessandro Aiuti[1,2], Francesca Pasinelli[3] and Luigi Naldini[1,2] ✉

[1]*San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milan, Italy.* [2]*Vita-Salute San Raffaele University, Milan, Italy.* [3]*Fondazione Telethon, Rome, Italy.* ✉*e-mail: naldini.luigi@hsr.it*

Published online: 15 August 2022
https://doi.org/10.1038/s41591-022-01934-9

References

1. Ferrari, G., Thrasher, A. J. & Aiuti, A. *Nat. Rev. Genet.* **22**, 216–234 (2020).
2. Orchard Therapeutics. Press release (March); https://ir.orchard-tx.com/node/8771/pdf (2022).
3. Notarangelo, L. D., Bacchetta, R., Casanova, J.-L. & Su, H. C. *Sci. Immunol.* **5**, eabb1662 (2020).
4. Castagnoli, R., Delmonte, O. M., Calzoni, E. & Notarangelo, L. D. *Front. Pediatr.* **7**, 295 (2019).
5. Pai, S.-Y. et al. *N. Engl. J. Med.* **371**, 434–446 (2014).
6. Lankester, A. C. et al. *J. Allergy. Clin. Immunol.* **149**, 1744–1754.e8 (2021).
7. Aiuti, A., Roncarolo, M. G. & Naldini, L. *EMBO Mol. Med.* **9**, 737–740 (2017).
8. Fischer, A. & Hacein-Bey-Abina, S. *J. Exp. Med.* **217**, e20190607 (2019).
9. Tucci, F., Galimberti, S., Naldini, L., Valsecchi, M. G. & Aiuti, A. *Nat. Comm.* **13**, 1315 (2022).
10. Cicalese, M. P. et al. *Blood* **128**, 45–54 (2016).
11. Kohn, D. B. et al. *N. Engl. J. Med.* **384**, 2002–2013 (2021).
12. Kohn, D. B. et al. *Nat. Med.* **26**, 200–206 (2020).
13. Ferrua, F. et al. *Lancet. Haematol.* **6**, e239–e253 (2019).
14. Magnani, A. *Nat. Med. et al.* **28**, 71–80 (2022).
15. Mamcarz, E. et al. *N. Engl. J. Med.* **380**, 1525–1534 (2019).
16. Bluebird Bio. Press release (August); https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-reports-second-quarter-financial-results-and (2021).
17. Tichelli, A. et al. *JAMA Oncol.* **5**, 229–235 (2019).
18. Sun, D. et al. *JAMA Pediatr.* **176**, 176–184 (2022).
19. Schoser, B. et al. *Pharmacoecon Open* **3**, 479–493 (2019).
20. Wang, Y. et al. *J. Med. Econ.* **23**, 1503–1515 (2020).
21. Simoens, S., De Groote, K. & Boersma, C. *Front. Pharmacol.* **13**, 771966 (2022).
22. Frangoul, H., Ho, T. H. & Corbacioglu, S. *N. Engl. J. Med.* **384**, e91 (2021).
23. Schiroli, G. et al. *Cell Stem Cell* **24**, 551–565.e8 (2019).
24. Ferrari, S. et al. *Nat. Biotechnol.* **38**, 1298–1308 (2020).
25. Jonker, A. H. et al. *Nat. Rev. Drug Discov.* **19**, 495–496 (2020).

Acknowledgements

Work in the labs of L.N. and A.A. is supported by grants from Fondazione Telethon, the EU Horizon 2020 Program, the Italian Ministry of Health, the Italian Ministry of University and Research, the Louis-Jeantet Foundation through the Jeantet-Collen Prize for Translational Medicine 2019 (to L.N.) and the Else Kröner Fresenius Foundation through the Kröner-Fresenius Prize for Medical Research 2020 (to A.A). The authors thank Michela Gabaldo, Aida Paniccia, Sara Maffioletti and Francesca Pampinella for helpful comments and support.

Author contributions

All authors contributed to writing this Comment.

Competing interests

A.A. is PI of clinical trials sponsored by Orchard Therapeutics, which licensed gene therapy products for ADA-SCID, WAS, metachromatic leukodystrophy (MLD), β-thalassemia and mucopolysaccharidosis type I (MPS-I) originally developed at SR-Tiget. A.A. is a member of the Committee for Advanced Therapies (CAT) and his views are personal and may not be understood or quoted as being made on behalf of the European Medicines Agency (EMA). L.N. is an inventor on pending and issued patents on LV technology and gene editing filed by the Salk Institute, Cell Genesys, Telethon Foundation and/or San Raffaele Scientific Institute. L.N. is a founder of, owns equity in, and is a consultant and member of the scientific advisory board of Genenta Science, a biotechnology company aiming at developing cancer gene therapy by tumor-infiltrating monocytes, and Genespire, a biotechnology startup developing lentiviral-vector-based liver gene transfer and hematopoietic cell gene editing. F.P. has no competing interests.