

Access to gene therapy for rare diseases when commercialization is not fit for purpose

Aiuti et al. recently highlighted that, despite promising preclinical and clinical efficacy data, hematopoietic stem-cell gene therapies for inherited diseases have not been widely adopted into clinical practice¹. Ultra-rare diseases such as inborn errors of metabolism and inborn errors of immunity are, as their names suggest, individually rare diseases, affecting <1 in 50,000 people. However, such diseases have a profound impact on the lives of many individuals because of reduced life expectancy or chronic progressive morbidity.

As Aiuti et al. discuss, there are no effective curative treatments available for most inborn errors of metabolism². Allogeneic hematopoietic stem-cell transplantation (alloHSCT) is considered a curative treatment for an increasing number of inborn errors of immunity; however, its use requires a suitable donor and, in spite of recent progress, carries significant risks of mortality and morbidity, mainly due to graft failure and graft-versus-host disease^{1,3}. In this context, rare inherited diseases represent significant unmet clinical need for which gene therapy could potentially offer a lifelong curative option⁴.

Despite promising efficacy data, the development of genetically modified cellular products for rare diseases presents a unique set of challenges due to the small numbers of patients affected with each disease, the cost and complexity of manufacturing, and the requirement for each individual product to undergo quality controls and regulatory assessments, making sustainable access to these therapies challenging from a typical commercial perspective. Although more than 15 different immune disorders have inspired the development of gene therapy approaches leading to either promising preclinical or long-term clinical efficacy data, so far only one therapy, Strimvelis for adenosine-deaminase-deficient severe combined immune deficiency (ADA-SCID)⁵, has achieved marketing authorization in Europe. Unfortunately, the product's commercial sponsor recently withdrew from the program⁶, and other industrial partners have also stepped away from this area after significant investments and generation of data to support licensing.

Autologous gene therapy, in which the patient's own hematopoietic stem cells are genetically corrected using viral vectors or gene-editing technologies, have shown great potential⁷, yet have not been widely adopted into clinical practice. Indeed, discontinuation of commercial involvement has occurred despite demand for these transformative treatments¹. It is becoming increasingly apparent that for patients with a rare or ultra-rare disease to benefit from cutting-edge personalized therapies, the current for-profit model of marketing authorization and commercialization is not economically fit for purpose.

Achieving sustainable and affordable access to life-changing gene therapies will require an evolution of the current model. To find solutions to these challenges, we and others established an initiative called AGORA (Access to Gene Therapies for Rare Diseases) comprising clinical academics, scientists and patient organizations. The first meeting of AGORA was held in September 2022 in London to discuss the challenges facing the field. The meeting brought together more than 50 stakeholders from across Europe, including researchers, funders, clinicians, regulatory agencies and industry partners. Several sessions over the course of the meeting highlighted the challenges facing the field from a multidisciplinary perspective. Our short-term aim is to act as a central body for academic

medical centers and not-for-profit organizations, providing support for them in seeking regulatory approval for proven-effective advanced therapy medicinal products in rare diseases, as well as to harmonize pan-European national activities.

Ultimately, the aim is to explore the creation of an independent, sustainable, not-for-profit entity that can support marketing authorization, delivery and access to therapies that are not commercially sustainable and therefore would be unavailable to patients. The scientific developers present at the inaugural meeting highlighted that the burden of evidence required by regulatory agencies, competent authorities and health technology assessment committees is heavy and may be disproportionate for gene therapies as compared to alloHSCT.

Costs for alloHSCT are substantially lower than those for novel gene therapy approaches¹. Sharing of existing preclinical and clinical validation, safety and efficacy data through a data repository could provide reassurance to regulators about the low risk of these therapies and reduce the financial burden by minimizing costly replicative studies and supporting marketing authorization.

Patient views were represented by the International Patients Organization for Primary Immunodeficiencies, the Chronic Granulomatous Disease Society and the Wiskott-Aldrich Foundation, all of which have members directly affected by the withdrawal of commercial sponsors from this field. They vividly described how initial excitement around transformative gene therapies has changed to disappointment and frustration at the lack of accessible products. They outlined the dilemmas facing patients and reiterated the need for developers, regulators and health technology assessors to consider clinical outcomes that are important to patients and families. Patient involvement in every aspect of the process, from trial design to accessibility and reimbursement strategies, is imperative.

Representatives from the European Medicines Agency (EMA) and national regulatory agencies were cognizant of the challenges facing both academic developers and pharma companies in delivering gene therapy to patients in need, but they stressed that their primary role is to ensure safety. The EMA highlighted its upcoming academic support pilot that will serve as a novel model to enable products developed in academia and small and medium-sized enterprises to reach marketing authorization⁸. Commercial stakeholders and funders emphasized the high costs involved in bringing gene therapy products to market. Nevertheless, more transparency about these costs is required in order to reach fair prices for such products⁹. Charitable and national or European-level funding can enable a product to reach early-phase clinical trials, but after these milestones are reached, commercial partners are usually required to obtain marketing authorization, which has proven challenging and unsustainable with rare diseases.

The meeting identified several actionable targets. To reduce costs, we propose creating a harmonized infrastructure with respect to production processes, including platform technology covering related diseases, a standardized regulatory approach across nations, and data sharing to de-risk and streamline safety assays. AGORA could serve as a central repository for such data and act as an independent international body that could provide sponsorship for clinical trials. Once established as a legal entity, and on the back

of significant global interest, we will initiate a pilot project, working with European institutions, to explore how to achieve our aims using an exemplar rare disease. We envisage that public and private partnerships involving several stakeholders across different nations will be needed to finance our efforts. The challenges facing our newly formed consortium are significant, but decades of research, huge financial investments and, most importantly, the lives of thousands of patients are at stake. AGORA has come together to find workable solutions to enable sustainable access to treatments. Our consortium sets out to achieve exactly what Aiuti et al. highlight in their article — to ensure a future for gene therapy for rare diseases.

Thomas Fox 1, Juan Bueren 2, Fabio Candotti 3, Alain Fischer 4, Alessandro Aiuti 5, Arjan Lankester 6, The AGORA Initiative* & Claire Booth 1

1UCL Great Ormond Street Institute of Child Health, London, UK. 2Biomedical Innovation Unit, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Centro Investigación Biomédica en Red de Enfermedades Raras (CIBERER) and IIS Fundación Jiménez Díaz, Madrid, Spain. 3 Division of Immunology and Allergy, University Hospital of Lausanne and Lausanne University, Lausanne, Switzerland. 4 Imagine Institute, Paris, France. 5 San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy. 6 Willem-Alexander Children's Hospital, Department of Pediatrics, Stem Cell Transplantation Program, Leiden University Medical Center, Leiden, The Netherlands.

e-mail: c.booth@ucl.ac.uk

References

1. Aiuti, A. et al. *Nat. Med* 28, 1985–1988 (2022).
2. Gentner, B. et al. *N. Engl. J. Med.* 385, 1929–1940 (2021).
3. Cicalese, M. P. et al. *Pediatr. Allergy Immunol.* 31 (Suppl. 24), 5–7 (2020).
4. Amaral, M. D. *Curr. Opin. Pharmacol.* 63, 102201 (2022).
5. Ferrua, F. et al. *Hum. Gene Ther.* 28, 972–981 (2017).
6. Orchard Therapeutics. <https://go.nature.com/3Y8ruFG> (2022).
7. Naldini, L. *EMBO Mol. Med.* 11, e9958 (2019).
8. European Medicines Agency. <https://go.nature.com/3jAE3dE> (2022).
9. Fischer, A. et al. *Nat. Med.* 25, 1813–1814 (2019).

The AGORA Initiative Michael Albert 7, Maria Ester Bernardo 5, Marina Cavazzana 4,8, Stephan Ehl 9, Benedicte Neven 8, Johan Prevot 10, Axel Schambach 11, Julian Sevilla 12,13, Adrian Thrasher 1 & Rob Wynn 14,7 Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians- Universität München, Munich, Germany. 8 Hospital Necker–Enfants Malades, Assistance Publique–Hôpitaux de Paris, INSERM, Paris, France. 9 Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Faculty of Medicine, Medical Center–University of Freiburg, Freiburg, Germany. 10 International Patient Organisation for Primary Immunodeficiencies (IPOPI), Brussels, Belgium. 11 Institute of Experimental

Hematology, Hannover Medical School, Hannover, Germany. 12Onco-Hematology Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain. 13Fundación Investigación Biomédica Hospital Infantil Niño Jesús (FIBHINJ), Madrid, Spain. 14Blood and Marrow Transplant Unit, Royal Manchester Children's Hospital, Manchester, UK.