Mission possible: gene therapy for inherited metabolic diseases

Authors: Julien Baruteau[1,2,3‡] Nandaki Keshavan[1,2], Charles P. Venditti[4]

[1] Great Ormond Street Institute of Child Health, University College London, London, UK, [2] Great Ormond Street Hospital for Children NHS Trust, London, UK, [3] National Institute of Health Research Great Ormond Street Biomedical Research Centre, London WC1N 1EH, UK, [4] Metabolic Medicine Branch, National Human Genome Research Institute, National Institutes of Health (NIH), Bethesda, Maryland, USA.

[‡] Corresponding author. J.baruteau@ucl.ac.uk

Since the description of Inborn Errors of Metabolism as a novel field of medicine by Archibald Garrod in 1908 [1], various breakthroughs in management and therapeutic milestones have been achieved: specific diets, newborn screening and enzyme replacement therapy to name a few (Figure 1). Genomic assays, including exome, genome and RNA sequencing, have led to the identification of a rapidly growing number of new inborn errors of metabolism and many new patients in recent years.

Gene therapy centred around gene addition and editing therapy has emerged in parallel, with the technological progress in engineering nucleic acids, nucleases, and viruses. Seminal early milestones have raised a huge hope for inherited metabolic diseases (IMDs) with little or no therapeutic benefit under standard of care [2,3]. Complex biotechnologies such as gene addition mediated by adeno-associated viral vectors (AAV) and integrating vectors that rely upon lentiviral and CRISPR-Cas9 mediated gene editing platforms are now the basis of approved drug products for monogenic diseases [4-6]. Application of gene therapy has been studied in many rare IMDs. Proof-of-concept data using varied technologies, nucleic acids, and delivery platforms to achieve gene replacement, integration, and editing, especially in the liver and the central nervous system, have served to enable a wide range of exciting new therapies for genetic and metabolic disorders. Whilst first-in-man clinical trials expand, the challenges for this rapidly evolving field include the development of safer and more efficient vectors, more accessible technologies, and the development of new regulatory paradigms to expedite approvals. Today, a one-size-fits-all strategy remains elusive for most disorders given that even within a rare IEM patient population, phenotypic heterogeneity, variable disease progression and uncertainties surrounding the natural history can further complicate the risk-benefit balance for clinical trials.

This themed issue of *Journal of Inherited Metabolic Disease* reviews state-of-the-art of gene therapy technologies applied to various inborn metabolic diseases. It provides updates on clinical successes, limitations and future directions whilst considering specificities for liver and fetal applications. The special issue starts with two reviews concerning liver-directed gene therapy. Baruteau *et al* present an overview of the progress, challenges and perspectives for the main liver inherited metabolic diseases from a clinical perspective REF. Chuecos and Lagor introduce adeno-associated viral vectors (AAV), which represent currently the leading liver-targeting gene therapy technology, with a particular focus on AAV physiology, AAV transduction including sex differences and an updated review of AAV clinical trials for liver inherited metabolic diseases and their contribution to the field of gene therapy

[7]. Pontoizeau *et al* provide an additional proof-of-concept of neonatal gene therapy for maple syrup urine disease [8]. Duff *et al* review the specificities, development and perspectives of gene therapy for urea cycle defects [9]. Chandler and Venditti summarise the preclinical studies and clinical trials of genetic therapies developed for methylmalonic and propionic acidaemias and lessons learned over the years [10]. Martinez *et al* provide an update on proof-of-concept in animal models and clinical trials of gene therapy for phenylketonuria, including recent innovative preclinical approaches of introducing an acquired competitive advantage of genetically modified hepatocytes [11]. Koeberl *et al* review gene therapy advances for glycogen storage diseases (GSD) from preclinical to clinical studies, with a particular focus on GSDI, II and III [12]. Sellier *et al* report a muscle-specific, liver-detargeted AAV gene therapy to treat a neonatal and adult Pompe mouse model [13]. Rossi and Brunetti-Pierri review the development of *ex vivo* and *in vivo* gene therapy approaches for mucopolysaccharidosis (MPS) with detailed sections for MPSI, MPSII, MPSIII, MPSIV and MPSVI [14]. Keshavan *et al* provide a perspective on the development of gene therapy for primary mitochondrial diseases REF. Ng *et al* show the epic journey to develop gene therapy approaches for inherited neurotransmitter defects culminating with the recent approval of eladocagene exuparvovec (Upstaza™) for aromatic L-amino acid decarboxylase (AADC) deficiency in late 2022 REF. To conclude this special issue, Waddington *et al* present a magistral review of fetal gene therapy and its complex implications from preclinical evidence to translation, safety, and ethics for both the fetus and the mother [15].

In conclusion, numerous proof-of-concept studies have investigated different gene therapy technologies in preclinical models of IMDs. The wider translation of these promising therapeutic strategies to patients, and overcoming their inherent limitations, remains the bottleneck. Supported by improved knowledge gathered from numerous ongoing clinical trials for inborn errors of metabolism, the translation of innovative gene therapy for rare diseases, which remains a long and arduous journey, is gradually reaching patients, and is uplifted by the hope of a brighter outcome and a much-improved quality of life.

References

1 Rosenberg, L. E. Legacies of Garrod's brilliance. One hundred years--and counting. *J Inherit Metab Dis* **31**, 574-579, doi:10.1007/s10545-008-0985-8 (2008).

2 Cartier, N. *et al.* Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science* **326**, 818-823, doi:10.1126/science.1171242 (2009).

3 Hwu, W. L. *et al.* Gene therapy for aromatic L-amino acid decarboxylase deficiency. *Sci Transl Med* **4**, 134ra161, doi:10.1126/scitranslmed.3003640 (2012).

4 Wong, C. UK first to approve CRISPR treatment for diseases: what you need to know. *Nature* **623**, 676-677, doi:10.1038/d41586-023-03590-6 (2023).

5 Mullard, A. FDA approves first haemophilia B gene therapy. *Nat Rev Drug Discov* **22**, 7, doi:10.1038/d41573-022-00199-8 (2023).

6 First gene therapy for adrenoleukodystrophy. *Nat Biotechnol* **39**, 1319, doi:10.1038/s41587-021-01127-8 (2021).

7 Chuecos, M. A. & Lagor, W. R. Liver directed adeno-associated viral vectors to treat metabolic disease. *J Inherit Metab Dis*, doi:10.1002/jimd.12637 (2023).

8 Pontoizeau, C. *et al.* Successful treatment of severe MSUD in Bckdhb(-/-) mice with neonatal AAV gene therapy. *J Inherit Metab Dis*, doi:10.1002/jimd.12604 (2023).

9 Duff, C., Alexander, I. E. & Baruteau, J. Gene therapy for urea cycle defects: An update from historical perspectives to future prospects. *J Inherit Metab Dis*, doi:10.1002/jimd.12609 (2023).

10 Chandler, R. J. & Venditti, C. P. Gene therapy for organic acidemias: Lessons learned from methylmalonic and propionic acidemia. *J Inherit Metab Dis*, doi:10.1002/jimd.12665 (2023).

11 Martinez, M., Harding, C. O., Schwank, G. & Thony, B. State-of-the-art 2023 on gene therapy for phenylketonuria. *J Inherit Metab Dis*, doi:10.1002/jimd.12651 (2023).

12 Koeberl, D. D. *et al.* Gene therapy for glycogen storage diseases. *J Inherit Metab Dis*, doi:10.1002/jimd.12654 (2023).

13 Sellier, P. *et al.* Muscle-specific, liver-detargeted adeno-associated virus gene therapy rescues Pompe phenotype in adult and neonate Gaa(-/-) mice. *J Inherit Metab Dis*, doi:10.1002/jimd.12625 (2023).

14 Rossi, A. & Brunetti-Pierri, N. Gene therapies for mucopolysaccharidoses. *J Inherit Metab Dis*, doi:10.1002/jimd.12626 (2023).

15 Waddington, S. N. *et al.* Fetal gene therapy. *J Inherit Metab Dis*, doi:10.1002/jimd.12659 (2023).

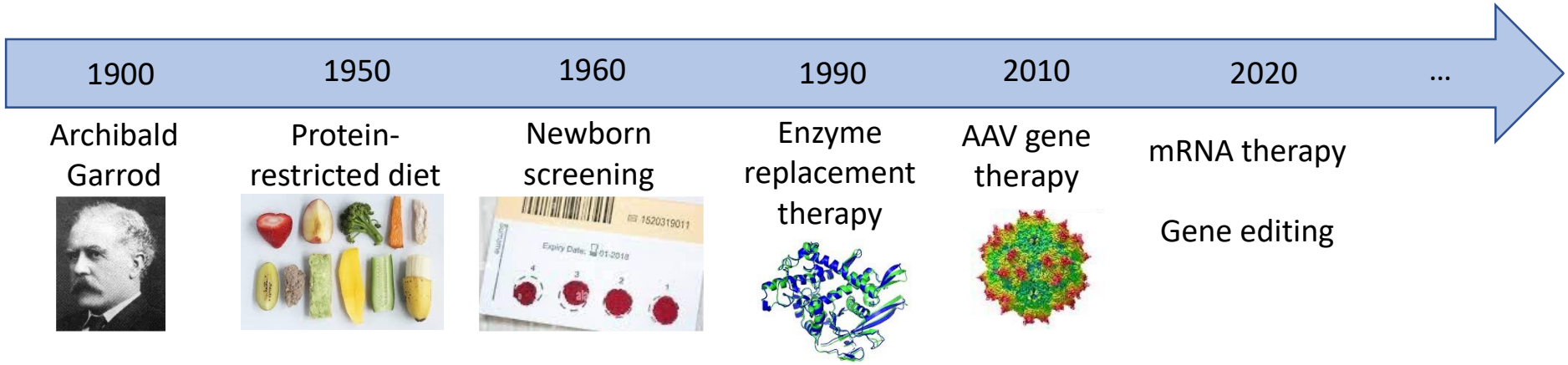

Figure 1: Historical perspective in Inherited Metabolic Medicine. In 1908, Archibald Garrod described the concept of inborn errors of metabolism. In the 1950s and 1960s, phenylalanine-restricted diet and newborn screening were pioneered for the management of patients with phenylketonuria. Enzyme replacement therapy was initially translated in the 1990s for patients with lysosomal storage disases. AAV gene therapy was developed for patients with inherited metabolic diseases in 2000-2010s. The 2020s have witnessed the initiation of mRNA therapy and development of gene editing strategies in first-in-man trials for inherited metabolic diseases.