

Gene therapy could correct blood stem cells inside, rather than outside, the body

Experiments in mice reveal an early postnatal window of opportunity for the effective transfer of genes to blood-cell-producing haematopoietic stem cells by injecting mice with gene-carrying lentiviral vectors. This approach showed therapeutic benefit in three mouse models of severe diseases, and could expand the applicability of haematopoietic stem-cell gene therapy in the clinic.

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At a glance

The study: Can *in vivo* lentiviral gene therapy target blood stem cells in neonatal mice?

The models: Three mouse models of diseases, including one of bone-marrow failure syndrome.

Key findings: *In vivo* lentiviral gene therapy showed therapeutic benefit in all three models.

Next steps: Translate to non-human primates and explore clinical potential.

The unmet medical need

In lentiviral *ex vivo* gene therapy, blood-making cells called haematopoietic stem and progenitor cells (HSPCs) are taken from a person with a genetic disease, genetically modified using engineered lentiviral vectors (LVs) and then reintroduced into the individual. Such *ex vivo* LV-mediated gene therapies have revolutionized the treatment of severe genetic diseases¹, with some therapies already market-approved and others in the pipeline^{2,3}. However, *ex vivo* manipulation of HSPCs, and the risks associated with the 'conditioning' that makes space in the bone marrow for the engraftment of corrected HSPCs still pose challenges⁴. Moreover, the costs associated with manufacturing and characterizing personalized therapies limit accessibility to such treatments. Fanconi anaemia is a rare inherited bone-marrow-failure syndrome that is associated with defects in DNA repair and causes a substantial decrease in HSPCs at an early age. Transplantation of healthy donor HSPCs is the standard treatment for bone-marrow failure but has adverse effects. *Ex vivo* LV-mediated gene therapy has been shown to correct bone-marrow failure in individuals who have a sufficient reservoir of HSPCs, even without conditioning⁵. Here, we test *in vivo* LV gene therapy in mouse models of Fanconi anaemia and other severe genetic diseases.

The study and its findings

We discovered high numbers of circulating haematopoietic stem cells (HSCs) in newborn mice, migrating from the liver (where fetal HSCs reside) to the maturing bone marrow. We saw this period as an opportunity to target the early-stage HSCs

with LVs injected into the bloodstream (Fig. 1a). Moreover, by applying a clinical HSC-mobilization regimen in young mice, we showed that this window can be extended for 14 days into the mouse juvenile period. Notably, the targeted HSCs engrafted in conditioned mice and could differentiate into different blood lineages, demonstrating that targeted HSCs can repopulate the haematopoietic system in the long term.

Next, we tested this approach in mouse models of three severe diseases: autosomal recessive osteopetrosis, adenosine deaminase deficiency leading to severe combined immunodeficiency and Fanconi anaemia. In all three models, our gene-therapy approach showed therapeutic benefit; in the model of Fanconi anaemia, corrected cells showed progressive expansion and normalized blood parameters (Fig. 1b).

This study lays the groundwork for broadening the scope and accessibility of gene therapy. In particular, in individuals with Fanconi anaemia, an *in vivo* gene-therapy approach could not only eliminate the need to manipulate these fragile cells, but also broaden the application of gene therapy to individuals with a limited pool of HSCs.

Outlook for the future

- We found high numbers of circulating HSCs in human neonates. We therefore plan to assess the efficiency of our approach in neonate non-human primates.
- Despite showing therapeutic benefit in three disease models, gene-transfer efficiency was lower *in vivo* than *ex vivo*. We plan to increase efficiency through innovative strategies such as lentiviral vector retargeting.
- Our results pave the way for targeting other tissues affected by Fanconi anaemia, such as the mucosa, to reduce the risk of head and neck cancer. Moreover, our results could apply to other blood and bone-marrow-failure conditions.

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EXPERT OPINION

This study presents a wonderful idea of taking advantage of a susceptible period for targeting gene therapy to HSCs *in vivo*. The authors provide strong proof of concept that potentially clinically relevant levels of gene transfer can be achieved, and show

that at least one disease model (Fanconi anaemia) can be effectively treated using this approach.” (CC BY 4.0)

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FIGURE

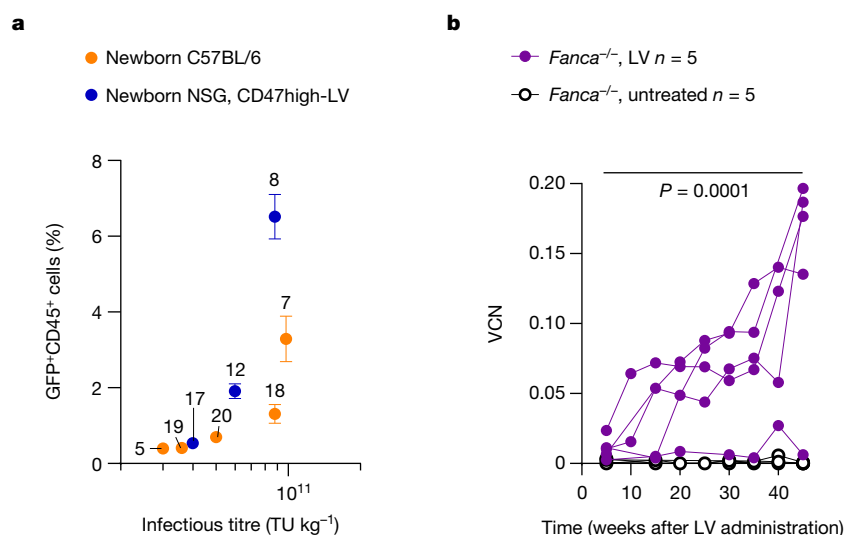


Figure 1 | Lentiviral vectors transfer healthy genes to blood stem cells in neonatal mice. A gene-therapy approach using lentiviral vectors (LVs) was tested in neonatal mice to transfer genes into blood stem cells (haematopoietic stem cells), that were travelling from the liver to the bone marrow. **a**, Newborn mice were treated with different doses of LV – expressed as transducing units (viral vectors) per kilogram of body weight (TU kg⁻¹) – carrying the gene encoding a green fluorescent protein (GFP). The graph shows the percentage of cells expressing GFP among circulating CD45⁺ blood cells. C57BL/6 mice are immunocompetent mice that do not sense the human CD47 protein present on LV particles; whereas a strain of immunocompromised mice called NSG does. NSG mice express a CD47 receptor variant that interacts with the human protein CD47, this functions as a ‘don’t eat me’ signal that is included on CD47high-LV to prevent uptake by immune cells. Sample sizes are indicated. **b**, In a mouse model of the disease Fanconi anaemia (*Fanca*^{-/-} mice), newborn animals were either treated with LVs or left untreated. Numbers of copies of LV genetic material (vector copies per diploid genome, VCN) in the circulating blood of these mice are shown. Milani, M. *et al.* *Nature* (CC BY-NC-ND 4.0).

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FROM THE EDITOR

This work sheds light on how gene therapies can be delivered *in vivo* to achieve therapeutic efficacy for several debilitating diseases. In the haematopoietic systems of mice, the authors identified a neonatal time window of permissiveness for gene therapy (with preliminary evidence of similar haematopoietic states in newborn humans). These findings are likely to promote further debate about optimal timings of therapeutic interventions in children, to balance ethical and medical considerations.

Darren Burgess, Senior Editor, *Nature*