NEUROMETABOLIC DISEASE

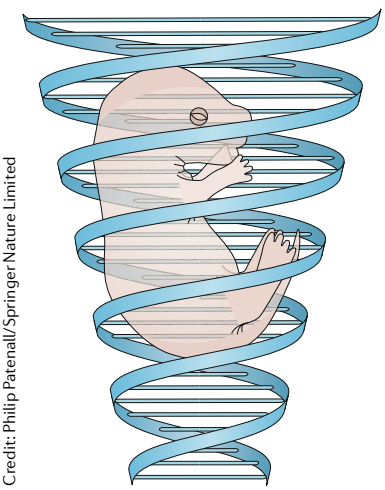
Fetal gene therapy could be feasible for neuronopathic Gaucher disease

> Fetal gene therapy may be both medically preferable and technologically feasible

Gene therapy can be delivered to a fetus in utero to treat neuronopathic Gaucher disease, according to a new mouse study led by Simon Waddington at the UCL Institute for Women's Health, London, UK. The findings, published in *Nature Medicine*, could open up new possibilities for early intervention in neurodevelopmental disorders.

Gaucher disease is a multisystem lysosomal storage disorder caused by mutations in the glucosylceramidase (*GBA*) gene. The condition manifests as a spectrum of disease depending on the nature of the mutation, from the severe, childhood-onset neuronopathic form to milder forms with a more gradual onset. The milder forms respond well to enzyme replacement therapy, but the childhood-onset form is currently untreatable.

Together with his colleague Ahad Rahim, Waddington had previously shown that systemic delivery of an adeno-associated virus 9 (AAV9) vector carrying a reporter gene to mouse fetuses resulted in widespread expression of the gene in the CNS. "My personal motivation was to search for the most difficult-to-treat diseases as a target for fetal gene therapy," explains Waddington. "We had conversations with lysosomal storage disease clinicians, and they suggested that we consider neuronopathic Gaucher disease."



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For the new study, Waddington, Rahim and co-workers used a *Gba*-mutant mouse model that recapitulated the neurodegenerative phenotype associated with childhood-onset neuronopathic Gaucher disease. The researchers injected an AAV9 vector containing the human *GBA* gene intracranially into fetuses at gestational day 16.

This intervention was found to halt neurodegeneration and reduce neuroinflammation in the affected mice, resulting in improved survival and motor function after birth. Injection of the vector into neonatal mice also ameliorated the neurodegenerative phenotype but was less effective than fetal injection.

"With both of these approaches, the mice still exhibited visceral disease because we had only performed gene therapy on their brains," says Waddington. "We therefore took these experiments to their logical conclusion — neonatal intravenous injection. Again, we saw amelioration of neuropathology, but the treatment also prevented visceral disease, including lung pathology, which is not even stopped by enzyme replacement therapy."

In collaboration with a team led by Jerry Chan in Singapore, Waddington and colleagues went on to explore whether a viral vector could be delivered directly to the fetal primate brain. An AAV9 vector containing a marker gene was injected into the lateral ventricles of fetal macaque brains at gestational day 58. By the time of birth, marker gene expression was widely distributed throughout the brains of the treated animals.

"Fetal gene therapy may be both medically preferable and technologically feasible in the treatment of lethal, early-onset genetic diseases, particularly those manifesting with neurodegeneration or neurodevelopmental anomalies," comments Waddington. "Potential hurdles include the choice of an appropriate disease target, effective genetic — and perhaps phenotypic — diagnosis in utero, and the fact that for all obstetric medicine, the mother's health must also be considered."

Waddington suggests spinal muscular atrophy (SMA) as another neurodegenerative disease that could be amenable to fetal gene therapy in the future. This condition can be diagnosed in utero and has been shown to respond to gene therapy administered in the first few months of life. For the moment, however, Waddington's team is focusing on optimizing gene therapy for Gaucher disease in preclinical models, with the ultimate aim of taking this approach forward into clinical trials.

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ORIGINAL ARTICLE Massaro, G. et al. Fetal gene therapy for neurodegenerative disease of infants. *Nat. Med.* https://doi.org/10.1038/s41591-018-0106-7 (2018)

FURTHER READING Rahim, A. A. et al. Intravenous administration of AAV2/9 to the fetal and neonatal mouse leads to differential targeting of CNS cell types and extensive transduction of the nervous system. *FASEB J.* **25**, 3535–3518 (2011) | Mattar, C. N. et al. Systemic gene delivery following intravenous administration of AAV9 to fetal and neonatal mice and late-gestation nonhuman primates. *FASEB J.* **29**, 3876–3888 (2015)