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GENE THERAPY

Lentiviral gene therapy of murine hematopoietic stem cells ameliorates the Pompe disease phenotype

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Pompe disease (acid α-glucosidase deficiency) is a lysosomal glycogen storage disorder characterized in its most severe early-onset form by rapidly progressive muscle weakness and mortality within the first year of life due to cardiac and respiratory failure. Enzyme replacement therapy prolongs the life of affected infants and supports the condition of older children and adults but entails lifelong treatment and can be counteracted by immune responses to the recombinant enzyme. We have explored the potential of lentiviral vector–mediated expression of human acid α-glucosidase in hematopoietic stem cells (HSCs) in a Pompe mouse model. After mild conditioning, transplantation of genetically engineered HSCs resulted in stable chimerism of approximately 35% hematopoietic cells that overexpress acid α-glucosidase and in major clearance of glycogen in heart, diaphragm, spleen, and liver. Cardiac remodeling was reversed, and respiratory function, skeletal muscle strength, and motor performance improved. Overexpression of acid α-glucosidase did not affect overall hematopoietic cell function and led to immune tolerance as shown by challenge with the human recombinant protein. On the basis of the prominent and sustained therapeutic efficacy without adverse events in mice we conclude that ex vivo HSC gene therapy is a treatment option worthwhile to pursue.

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