



Transient Increase in Intrahepatic Pressure Mediates Successful Treatment of the Gunn Rat with Reduced Doses of Lentiviral Vector

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Titre Transient Increase in Intrahepatic Pressure Mediates Successful Treatment of the Gunn Rat with Reduced Doses of Lentiviral Vector

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Résumé en anglais
Lentiviral vectors can stably transduce hepatocytes and are promising tools for gene therapy of hepatic diseases. Although hepatocytes are accessible to blood-borne viral vectors through fenestrations of the hepatic endothelium, improved liver transduction after delivery of vectors to the blood stream is needed. As the normal endothelial fenestration and lentiviral vectors are similar in size (150 nm), we hypothesized that a transient increase in hepatic blood pressure may enhance in vivo gene transfer to hepatocytes. We designed a simple surgical procedure, by which the liver is temporarily excluded from blood flow. Lentiviral vectors were injected in a large volume to increase intrahepatic pressure. We demonstrated that in the Gunn rat, a model of Crigler-Najjar disease, the administration of low vector doses (corresponding to a multiplicity of infection of 0.2) by this procedure resulted in therapeutic correction of hyperbilirubinemia, without toxicity. The correction was sustained for 10 months (end of study). The same vector amounts yielded only partial correction after intraportal delivery. We believe that this new and clinically applicable strategy may broaden the range of genetic liver diseases accessible to gene therapy.

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