The recently developed novel methodology of direct intraosseous (IO) delivery of LVs can efficiently transduce bone marrow cells, generating high levels of transgene expression in HSCs" Miao (2016).

Abstract:

Current treatment of hemophilia A (HemA) patients with repeated infusions of factor VIII (FVIII; abbreviated as F8 in constructs) is costly, inconvenient, and incompletely effective. In addition, approximately 25 % of treated patients develop anti-factor VIII immune responses.

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Gene therapy that can achieve long-term phenotypic correction without the complication of anti-factor VIII antibody formation is highly desired. Lentiviral vector (LV)-mediated gene transfer into hematopoietic stem cells (HSCs) results in stable integration of FVIII gene into the host genome, leading to persistent therapeutic effect. However, ex vivo HSC gene therapy requires pre-conditioning which is highly undesirable for hemophilia patients. The recently developed novel methodology of direct intraosseous (IO) delivery of LVs can efficiently transduce bone marrow cells, generating high levels of transgene expression in HSCs. IO delivery of E-F8-LV utilizing a ubiquitous EF1α promoter generated initially therapeutic levels of FVIII, however, robust anti-FVIII antibody responses ensued neutralized functional FVIII activity in the circulation. In contrast, a single IO delivery of G-FVIII-LV utilizing a megakaryocytic-specific GP1bα promoter achieved platelet-specific FVIII expression, leading to persistent, partial correction of HemA in treated animals. Most interestingly, comparable therapeutic benefit with G-F8-LV was obtained in HemA mice with pre-existing anti-FVIII inhibitors. Platelets is an ideal IO delivery vehicle since FVIII stored in α-granules of platelets is protected from high-titer anti-FVIII antibodies; and that even relatively small numbers of activated platelets that locally excrete FVIII may be sufficient to promote efficient clot formation during bleeding. Additionally, combination of pharmacological agents improved transduction of LVs and persistence of transduced cells and transgene expression. Overall, a single IO infusion of G-F8-LV can generate long-term stable expression of hFVIII in platelets and correct hemophilia phenotype for long term. This approach has high potential to permanently treat FVIII deficiency with and without pre-existing anti-FVIII antibodies.

Full Text

Reference:

Miao, C.H. (2016) Hemophilia A gene therapy via intraosseous delivery of factor VIII-lentiviral vectors. Thrombosis Journal. 2016 Oct 4;14(Suppl 1), p.41. eCollection 2016.

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