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Combined gene and cell therapy for the treatment of Hemophilia A within an implantable therapeutic device [Abstract]

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Application of combined gene and cell therapy within an implantable therapeutic device for the treatment of severe haemophilia A

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Hemophilia A (HA) is a rare bleeding disorder caused by absence or dysfunction of FVIII protein. New regenerative medicine approaches to treat HA require insights into cell compartments capable of producing FVIII. We and others previously demonstrated that FVIII is produced specifically in endothelial cells. The aim of our work is to develop a novel ex vivo cell-based therapy using a medical device (Cell Pouch™, Sernova) leading to an improvement in patient quality of life. We isolated blood outgrowth endothelial cells (BOECs) from healthy and patients' blood. HA BOECs were transduced with a lentiviral vector carrying the B domain deleted form of FVIII under the Vascular Endothelial Cadherin promoter (LV-VEC.hFVIII) and were characterized for endothelial phenotype and for the number of integrated LV copies/cell (~3). We observed that FVIII was expressed by 80% of LV-VEC.hFVIII transduced cells and was efficiently secreted in the supernatant. Ten million LV-VEC.hFVIII-BOECs were transplanted intraperitoneally in association with cytodex® 3 microcarrier beads in NOD/SCID gamma-null HA mice (NSG-HA) (n=6). BOECs survived and secreted FVIII at therapeutic levels (12%) up to 18 weeks and ameliorate the bleeding phenotype of HA mice. Finally, LV-transduced HA BOECs were transplanted into a prevascularized subcutaneous, scalable medical device (Cell Pouch™), optimized for sustained secretion of therapeutic FVIII in NSG-HA mice, showing BOEC engrafted and activity up to 16 weeks post-transplant. These results pave the way for future human clinical testing in HA patients by transplantation of GMP produced autologous gene corrected BOECs with no sign of tumorigenicity within this device.