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.

P601

Correcting bleeding disorders using blood clotting factors produced *in vivo* by shielded engineered allogeneic cells

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Current haemophilia therapies require frequent protein infusions yet are unable to address long-term complications due to prolonged trough periods with suboptimal factor levels. To overcome these drawbacks, alternative modalities such as gene and cell therapies are being investigated. Spheres made with AfibromerTM biomaterials shield engineered human cells from immune rejection while preventing the fibrotic foreign body response around the spheres, enabling sustained, therapeutic factor levels. To evaluate whether sustained delivery of blood clotting factors by implantation of spheres containing engineered human cells producing hFVIII, hFIX or hFVII is dose adjustable and durable, various sphere doses were administered intraperitoneally (IP) to murine wild-type and knockout disease models. Factor production was evaluated via a combination of plasma protein levels, factor activity and bleeding (activity) assays. Administration to wild-type mice resulted in sustained plasma levels of blood clotting factors. Studies of FVIII-producing spheres in haemophilia A knockout-mice resulted in dose-dependent levels of functional hFVIII in plasma, with a corresponding correction of bleeding time and blood loss in a tail bleeding model. Taken together, these data demonstrate that administration of spheres made with Afibromer™ biomaterials shielding engineered human cells results in sustained factor production and efficacious correction of the bleeding phenotype in murine preclinical models. The sustained factor levels achieved after a single IP implantation create a viable alternative to traditional factor infusion or investigational gene therapies, with several important advantages. We aim to pursue first clinical studies in Haemophilia A patients and to develop Shielded Living TherapeuticsTM products for other chronic bleeding disorders.

P602

Combination of exosomes and near-infrared responsive gold nanoparticles: new selective and specific therapeutic vehicle

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Exosomes are extracellular vesicles (50 -150 nm of diameter) considered key elements for the intercellular communication. Although they are proposed to be ideal vehicles for the targeting of novel therapies, very little is known about the selectiveness and specificity of the transference processes involving exosomes released from different cells. PEGylated Hollow gold nanoparticles (PEG-HGNs) are near-infrared (NIR) responsive nanoparticles (NPs) which are able to generate localized heat by the use of NIR light leading to cell death when applying optical hyperthermia. In this study, we demonstrate the selectivity of in vitro exosomal transfer between certain cell types and how this phenomenon can be exploited to develop new specific vectors for advanced therapies. Firstly, PEG-HGNs were successfully incorporated in the exosome biogenesis pathway of placental stem cells (MSCs) and they were released as PEG-HGNs-loaded exosomes (PEG-HGNs_MSCs_EXOs). Exosomes were characterized by confocal microscopy, western blot, nanosight, zeta potential and electronic microscopy. Afterwards, time lapse microscopy and atomic emission spectroscopy demonstrated the selective transfer of the secreted exosomes only to the cell type of origin when studying different cell types including cancer, metastatic, stem or immunological cells. Finally, the preferential uptake to selectively induce cell death by light-induced hyperthermia was demonstrated. This work highlights the potential of exosomes as advanced therapeutic vectors and provides a better understanding to design selective therapies for different diseases.

P603

Lentiviral vectors pseudotyped with murine syncytins efficiently transduce B cells *in vitro* and *in vivo*

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Our laboratory is interested in the use of lentiviral vectors (LV) for in vivo gene delivery and explores various envelope pseudotypes for this purpose. Syncytins are fusogenic glycoproteins produced from endogenous retroviral sequences integrated in the genome of vertebrates 25–45 millions years ago. Syncytins are involved in many biological processes involving cell fusion. We report the possibility to pseudotype LV with murine syncytins A or B (LV-SynA and LV-SynB) and demonstrate that these particles are infectious in the presence of Vectofusin-1, a transduction adjuvant peptide, achieving titers of 1.4 ± 1.2 E+07 IG/mL (n=14). LV-SynA or LV-SynB enable high levels of transduction of B cells in vitro as shown with A20IIA murine B lymphoma cells and with murine spleen primary CD19+ B220+CD3-B cells (respectively $88 \pm 10\%$ and $89 \pm 4\%$ transgene positive cells). Both immature and mature murine bone marrow B cell subsets are efficiently transduced.