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Correcting Bleeding Disorders Using Blood Clotting Factors Produced in vivo by Encapsulated Engineered Allogeneic Human Cells

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Abstract

Introduction: Factor replacement therapy for hemophilia requires frequent intravenous infusions yet are unable to address long-term complications due to suboptimal therapy adherence, non-ideal factor kinetics and generation of inhibitors. To overcome these drawbacks, alternative modalities such as gene and cell therapies are being investigated. Using AfibromerTM spheres made of a blend of alginates and containing a novel antifibrotic component, we have developed several candidate Shielded Living TherapeuticsTM products, in which ex vivo gene modified allogeneic human cells producing high levels of blood clotting factors are shielded from immune rejection by the host, enabling sustained in vivo factor production. Objective: To evaluate in vivo whether sustained delivery of blood clotting factors by implantation of AfibromerTM spheres and containing genetically engineered human cells producing hFVIII, hFIX or hFVII is dose adjustable and durable. Methods: Various doses of AfibromerTMspheres containing engineered human cells were administered intraperitoneally (IP) to murine wild-type (WT) and KO disease models. Factor production was evaluated via a combination of ELISA, activity and bleeding assays. ResultsAfibromerTM spheres containing engineered human cells optimized for hFVIII, hFIX and hFVII protein production were placed IP in WT mice. This resulted in sustained therapeutic levels of the respective blood clotting factors. Spheres producing hFVIII were tested long-term (up to 6 months) and showed stable factor production and good cell viability upon explant analysis of the spheres. Additional studies in hemophilia A KO 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. ConclusionsTaken together, these data demonstrate that administration of Afibromer™ spheres containing human cells engineered to express a blood clotting factor can result in sustained factor production and efficacious correction of the bleeding phenotype in murine preclinical models of hemophilia A. The sustained factor secretion achieved after a single IP implantation creates a viable alternative to traditional factor administration or gene therapy, with several important advantages. We aim to develop a new category of medicines for severe chronic diseases including bleeding disorders such as hemophilia A, and to advance its development into clinical testing in this indication.