Correcting FVII Deficiency Using Coagulation Factors Produced In Vivo by Encapsulated Engineered Allogeneic Cells

Guillaume Carmona, Lauren Barney, Jared Sewell, Kevin Lai, Janet Huang, Christine Carroll, Chris Sparages, Michele McAulliffe, Richard Heidebrecht, Deya Corzo, Devyn Smith, David Peritt and Rogerio Vivaldi
Sigilon Therapeutics, Cambridge, MA, United States

Introduction

- Factor VII Deficiency is an autosomal, recessive rare bleeding disorder
- Current therapy is primarily on demand due to short half-life of the activated factor
- There are no ongoing clinical trials for novel therapies for this disease (as of 1/2020)
- We are proposing an innovative approach using cell therapy with shielded, genetically modified human allogeneic cells that can deliver long-term, sustained human FVII zymogen (hFVII) production in vivo
- Delivery of the precursor (zymogen) form of FVII vs the activated form will also allow for longer availability in circulation

Methods and Results

Figure 1. Construct Optimization for hFVII Zymogen Production

- We generated a range of constructs that express hFVII
- Each was used to transfet the chosen human cell line in order to assess the level of hFVII protein expression in vitro
- The protein levels were assessed using ELISA

Figure 2. Final hFVII Construct in SIG-009

- Spheres containing cells genetically modified with different FVII-expressing constructs were administered IP in NSG mice
- Blood samples were collected 14 days after administration
- hFVII antigen levels in mouse plasma were measured by ELISA
- N=3 per group; bars show mean+SEM

Figure 3. Inner Matrix Optimization for Optimal hFVII Zymogen Protein Levels

- Spheres containing different levels of the matrix modifier were administered IP in NSG mice
- Blood samples were collected 14 days after administration
- hFVII antigen levels in mouse plasma were measured by ELISA
- N=3 per group; bars show mean+SEM

Figure 4. SIG-009: Cell Line Modified with a Non-Viral Vector to Express hFVII Zymogen, Encapsulated within Alginate Spheres

- inner compartment: genetically modified cells
- alginate matrix
- outer layer: small molecule modified and unmodified alginates

Figure 5. hFVII Injected IP in NSG Mice Has Similar Bioavailability as hFVII injected IV

- hFVII recombinant protein was injected IV or IP in NSG mice
- Blood samples were collected over time
- hFVII antigen level in mouse plasma were determined by ELISA
- Bioavailability was determined using AUC (inset table)

Figure 6. hFVII Zymogen Produced by SIG-009 Rescues Clotting Activity of FVII-Deficient Human Plasma

- SIG-009 or empty spheres were incubated in the conditioned medium for 16 hours
- A fraction of the medium was collected and added to the human plasma obtained from FVII-deficient patients
- Clotting activity was measured using FVII chromogenic assay

Conclusions

- SIG-009 can deliver dose-dependent plasma levels of hFVII zymogen in vivo
- SIG-009 could reduce the risk of acute bleeds, particularly highly dangerous intracranial bleeds, by delivery of sustained levels of hFVII zymogen
- Our technology platform allows for re-dosing if needed, and has the potential for use in pediatric patients without concerns for decreased efficacy due to changes in the size of the liver

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