Optimization of Shielded Encapsulated Cell Therapy for Hemophilia and Beyond

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Introduction

- Cell therapy is an attractive option for treatment of various chronic diseases due to the ability to modify the cell genome to express therapeutic molecules.
- Many biomaterials (e.g., alginate hydrogels) can be used to physically shield the allogeneic cells from the recipient’s immune system. These barriers are effective at protecting the cells, but they themselves can elicit a foreign body response resulting in pericapsular fibrotic overgrowth (PFO).
- PFO blocks the nutrients from coming in and the therapeutic protein from coming out resulting in a significant challenge to durability, and thus, utility, of this type of therapy.
- Recently, a group of molecules were identified that significantly minimize the PFO in rodents and NHPs when conjugated to alginate biomaterials, allowing the encapsulated cells to remain functional long-term.¹

Methods and Results

Figure 1. Two-Compartment Sphere Development

- For the encapsulation technology to be broadly applicable, the spheres needed to be modified for encapsulation of cells capable of expressing a variety of therapeutic proteins.
- The optimal cell line is an adherent, epithelial cell line which has different matrix and cell-contact requirements compared to islets.

Figure 2. Inner Compartment Cell Density Optimization

- A constant total volume of spheres containing different numbers of genetically modified cells were administered IP in nude mice.
- Blood samples were collected 14 days after administration.
- FVIII antigen levels in mouse plasma were measured by ELISA.
- N=3 per group; bars show mean + SEM

Figure 3. Inner Compartment Material Optimization

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

Figure 4. Outer Layer Optimization

- Alginate polymers were prepared with varying levels of small molecule conjugation (0, A-H).
- Blood samples were collected 14 days after administration.
- FVIII antigen levels in mouse plasma were measured by ELISA.
- Significant PFO

Figure 5. Final Product: Human Cell Line Modified with a Non-Viral Vector to Express Therapeutic Protein, Encapsulated within Alginate Spheres

- Brightfield microscope image of a sphere with genetically modified cells.
- The spheres are sufficiently porous to allow gasses, nutrients, and secreted proteins to freely diffuse

Figure 6. Platform in Action: SIG-001 Corrects the Tail Bleeding Phenotype in vivo in Hemophilia A Mice²

- SIG-001 was placed in the IP space of male FVIII Hemophilia A (HA) mice via laparotomy (SIG-001, n=8).
- Control groups included male wild-type mice (wild type, n=7), and FVIII HA mice with spheres containing unmodified cells (control, n=8).
- Mice were observed daily and the bleeding time assay was conducted on day 7.

Conclusions

- We have developed an innovative platform that can be used across a broad range of chronic diseases.
- The novel structure and material components minimize the PFO while maximizing health and protein production of the cells and allow for potential long-term applications of the platform.
- Preclinical proof of concept shown for hemophilia A, FVII deficiency, MPS I and Fabry.
- First-in-human clinical trial in hemophilia A to open in 2020

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