A Scaled and Semi-Automated Cell Encapsulation Process for a Shielded Cell-Based Platform for Chronic Diseases

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Introduction

Historically, allogeneic cell-based therapies have faced two major challenges:
- Implantation of allogeneic or xenogeneic-derived cells are quickly rejected by the patient’s immune system
- When these cells are protected from the immune system by encapsulation in biomaterials, the biomaterials themselves activate a foreign body response resulting in pericapsular fibrotic overgrowth (PFO) formation.

We have previously described our innovative modular platform designed to (a) support genetically engineered allogeneic cells (which produce therapeutic proteins) and (b) shield them from the host’s immune system (Barney ASGCT 2020).

Manual Encapsulation Method

- The manual encapsulation method was modified from published methods (Vegas et al., Nature Biotechnology 34 [3] 343-352) to generate two-compartment spheres using a coaxial needle.
- Pump extrudes inner and outer alginate solutions of a predetermined rate.
- High voltage is applied to the needle tip to accelerate droplet formation rate of tip.
- Droplets are extruded through coaxial needle.
- Voltage can drift during a run which affects sphere formation rate unless manual adjustments are consistently made throughout the process to produce a batch with consistent size.

The manual system is limited to low batch volumes and requires manual input to maintain control over the droplet rate and resulting sphere size. An automated and scaled method was required to supply the first-in-human clinical trial for our lead candidate SIG 001 for hemophilia A (SIG-001-121, Shaprio ASH 2020, NCT04544162).

Semi-Automated Encapsulation Method Development

- A semi-automated method was developed to automate manufacturing and increase batch scale.
- The manual encapsulation method was modified to create a semi-automated batch encapsulation platform, which consists of:
  - A dual syringe pump to extrude the inner and outer polymer solutions through tubing into the coaxial needle
  - A crosslinking bath with custom sterilizable bath cover to hold the needle, sensors, and grounding pin for aseptic assurance and position control
  - Optical sensors to measure droplet rate and automatic voltage adjustment using a custom controller (not shown)

- With this system, the batch scale and droplet rate were increased four-fold compared to the manual process, while maintaining the same total process time.
- The control of the droplet rate and resulting sphere size was automated, resulting in a narrow distribution of sphere diameter and morphology within a batch.

Conclusion

- The increased sphere formation rate achievable in this system allowed an order of magnitude increase in the volume of spheres, which can be produced while maintaining a short residence time in the cross-linking bath. Without impact to sphere quality.
- The semi-automated manufacturing method described here is being used for the ongoing first-in-human clinical trial of SIG-001 in hemophilia A.
- There is ongoing work to further scale and automate the manufacturing process for future manufacturing for the hemophilia A program, and for our pipeline programs in other rare blood disorders, lysosomal disorders, type 1 diabetes, and other serious chronic illnesses.

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