Fibrin Hydrogel-Based Delivery for Pancreatic Organoid Therapies

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INTRODUCTION

Background:

- 1.25 million Americans have Type 1 Diabetes (T1D), a condition where the body is unable to create insulin to regulate glucose[1]
- ***Current T1D treatments require stringent and intrusive monitoring of glucose and administering of insulin***
- Research has been conducted to create pancreatic organoids (group of cells functioning as an "organ-like" structure) to restore patient's insulin production

Needs Statement:

- Develop a highly immune compatible organoid therapy system for patients with impaired insulin production for recapitulation of pancreatic function without rejection.

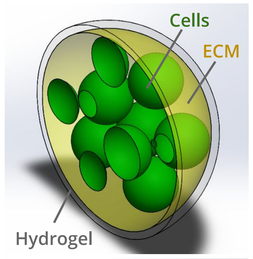
Proposed Solution:

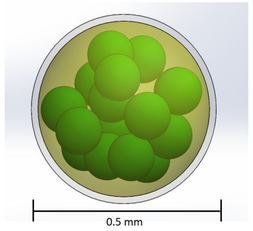
- Organoid Therapeutics has developed such an organoid therapy
  - *Said therapy currently lacks a protection/delivery mechanism*
- **Objective:** Create an immunomodulating coating that encourages organoid integration and ensures cell survival

We've developed a fibrin-based, immune-compatible organoid encapsulation method

DESIGN OF SOLUTION

Organoid Therapy Components





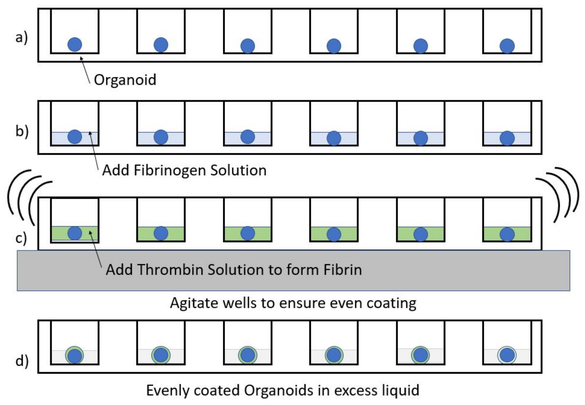
Organoid (Provided by Organoid Therapeutics)

- Beta-islet cells derived from induced pluripotent stem cells to mimic pancreatic functionality
- Extracellular Matrix (ECM) assists in beta-islet cell aggregation/organoid formation

Fibrin-based Hydrogel Coating

- Fibrin is a natural biopolymer that encourages blood vessel growth
- Produced when fibrinogen is enzymatically cleaved by thrombin
- Coating encapsulates and protect organoids during delivery
- Low immunogenicity: minimal immune response

Organoid Coating System: "*Powdered Doughnut Method*"



a) Organoids inside the wells
b) Fibrinogen solution added to the well binds to the cells
c) Thrombin cleaves the fibrinogen to form fibrin and is agitated
d) Agitation leads to even coating of fibrin around each organoid

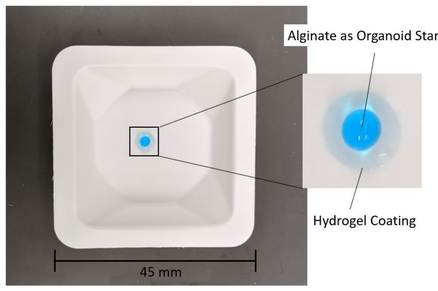
PROOF OF FEASIBILITY

Fibrin Properties Ideal for Organoid Protection

- Elastic and viscous properties
- If cross-linked, can withstand large amounts of stress
  - *Young's modulus = 14.5 ± 3.5 MPa*[2]
- Can stretch up to 3.3 times its original length
  - *Fracture strain = 332%*[2]

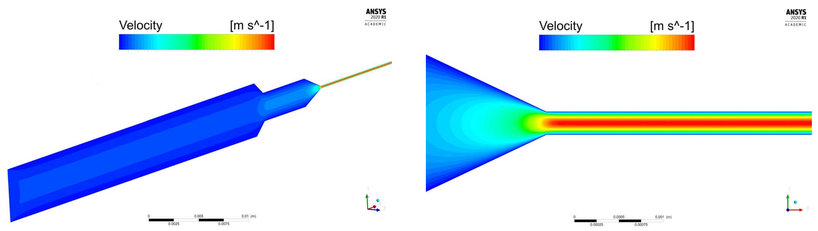
Coating Method Effectively Coats Organoids

- Anticipated coating tests on the following:
  1) Fabricated alginate beads
  2) Liver tissue spheroids
  3) Pancreatic organoids
- Results of preliminary alginate bead testing:



- Fabricated alginate beads (~ 0.5 mm in diameter)
- Fibrin hydrogel developed evenly around bead

Organoid Survivability During Injection



- Generalized velocity profiles shown above
- Calculated wall shear for varying needle gauge and flow conditions shown below

Wall Shear (Pa)									
		Inlet Flow Rate (m/s)							
		0.005	*0.01*	*0.015*	*0.02*	*0.025*	*0.03*	*0.035*	*0.04*
Needle Gauge	*24G*	136.7	273.4	410.2	546.9	683.6	820.3	957.1	1093.8
	26G	234.0	468.0	702.0	936.0	1170.0	1404.0	1638.0	1872.0
	27G	444.1	888.2	1332.3	1776.4	2220.4	2664.5	3108.6	3552.7
	28G	660.2	1320.4	1980.6	2640.8	3301.0	3961.2	4621.4	5281.6

- Fibrin elasticity withstands even the largest shear values

Future Testing:

- *Hypothesis: Hydrogel coating will be thinner around organoids*
  - Integrin binding will allow a thin coating of fibrinogen to adhere to the surface
- Finish coating tests with liver tissue and organoids
- Optimize needle gauge by performing live-dead assay on organoids after injection
- *In vivo* testing in mice over several months monitoring insulin levels to determine number of organoids per dose and frequency of dosages

REGULATORY PATHWAY & PATENTS

Regulatory Pathways[3]:

- Solution is classified as a "biologic"
- No official regulatory pathway exists for human cell-based therapeutics
  - Regulatory framework is described by the FDA
  - Similar recommendations as Class III medical devices (e.g. Premarket Approval)

Patent Information[4, 5, 6, 7, 8]:

- Fibrin hydrogel coating method is novel and patentable.
  - Fibrin not currently used to deliver organoids
  - Similar hydrogel encapsulation methods do not exist
- ECM-derived gels not used by competitors as encapsulation devices

COSTS & REIMBURSEMENT

Cost Breakdown per Dose*:

Total material cost per dose	$8,638
Total labor cost per dose	$1,246
50% overhead costs	$4,942
25% profit margin	$2,471
Total selling price for one dose	**$17,297**

** One Dose = 7000 organoids, does not include one time equipment costs*

Reimbursement[3]:

- No pancreatic organoid therapies currently on the market
- Islet cell transplantation is almost analogous
  - Covers the acquisition and delivery costs of the cells
  - Only covered by Medicare in the context of clinical trials

CONCLUSIONS

Organoid therapies could revolutionize T1D care

- Cost of organoid therapy is less than a lifetime of insulin costs ($17,300 per dose vs. $1.22 million)

Fibrin hydrogel encapsulation method is promising

- Favorable and tunable mechanical properties
- Easily scaled to match market demand with a localized distribution setup
- Potential application for other organoids

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[1] Gale, E.A.M. "Epidemiology of Type 1 Diabetes." Diapedia 2104085168 rev. no. 39, 2014.
[2] Litvinov, R. I., & Weisel, J. W. (2017). Fibrin mechanical properties and their structural origins. Matrix biology : journal of the International Society for Matrix Biology, 60-61, 110–123. https://doi.org/10.1016/j.matbio.2016.08.003
[3] FDA. (Dec 2017). Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Center for Devices and Radiological Health & Center for Biologics Evaluation and Research. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal
[4] Drohan, William N et al. (1995). Supplemented fibrin matrix delivery systems. US7229959B1. Washington, DC: U.S. Patent and Trademark Office.
[5] Feyeux, Maxime et. al. (2017). Neural tissue unit and use of such a unit for implantation into the nervous system of a mammal. US20200063099A1. Washington, DC: U.S. Patent and Trademark Office.
[6] Rubens, Fraser D. & Paul D. Bishop. (1993) Fibrin coated polymer surfaces. CA2133974C. Gatineau: Canadian Intellectual Property Office.
[7] Green, Chad et al. (2016). Loading system for an encapsulation device. US20160374900A1. Washington, DC: U.S. Patent and Trademark Office.
[8] Janssen, Robert. (2006). Gloves with hydrogel coating for damp hand donning and method of making same. US20060141186A1. Washington, DC: U.S. Patent and Trademark Office.