Pancreas on a Chip: Islet Cell Matrix

BMEN 5151

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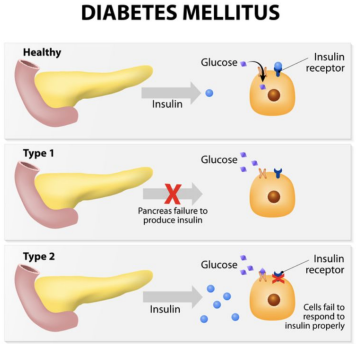
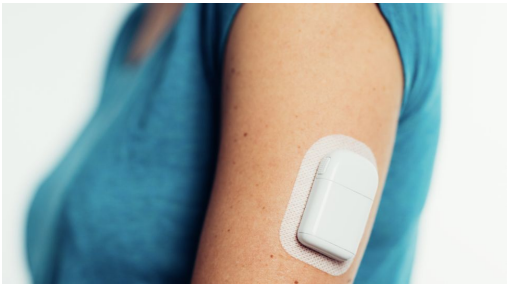
Background

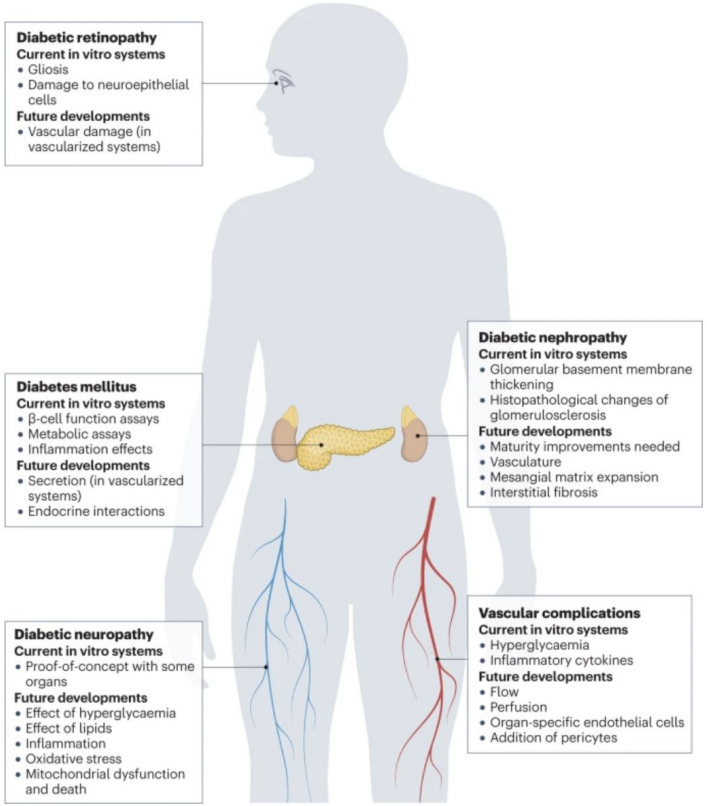
- Over 500 million people in the world suffer from diabetes
  - Including 38 million people in the United States
- Current treatments can ease symptoms, but disease remains
  - Treatments include: Insulin pumps, lifestyle changes, drugs
- Difficult to follow due to expense of drug and the nature of the disease
  - Insulin costs about $60 per vial
  - Constantly regulating blood sugar leads to difficulties in changing diet





Where is Modern Research at?

- Current research is effective at modeling one system at a time
  - Retina, pancreas, and kidneys well researched
  - Nerves and vascular systems less researched
- Pancreas on a chip systems
  - Main focus is on reprogramming stem cells to treat fetal β-cells
  - Generally these systems are made using hydrogels

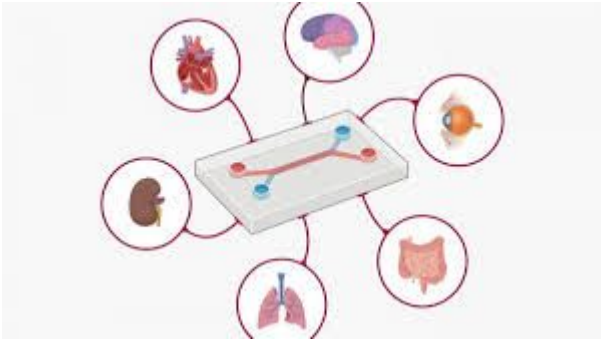


Introduction: Pancreas on a Chip

- Create cheaper testing methods for diabetes medications
  - Not a feature of most pancreas on a chip systems
- Expand current research of islet cell transplantation
  - Potential to reduce dependence on insulin pumps and diabetic medication
- Design Features:
  - Main focus of the design is to study islet cells
  - The key features include microfluidics and cell culturing
- Fabrication Methods:
  - Similar to liver on a chip
  - PDMS molding
  - Subtractive and additive methods

Design

Organ-on-a-chip



Advantages:

- Better replication of pathophysiology of human diseases
- Better understanding for development of drugs for patients

Requirements:

- Multicellular vascular or epithelial interfaces of organs
- Tissue-level organization of parenchymal cells
- Interaction of multiple organs

Disadvantages:

- Material selection
- Cellular fidelity
- Validation and integration with existing drug development platforms
- Scalable production and cost

Key Features of the Pancreas

Dual Roles	Organ of the digestive and endocrine system
Endocrine Pancreas	Secretes hormones like insulin that regulates blood glucose levels
Exocrine Pancreas	Digest protein by secreting enzymes

Requirements for Modeling Pancreas

1. Micro-vasculature
2. Cells
3. Mechanical and Biochemical Signals

Model for formation and differentiation of islet organoids

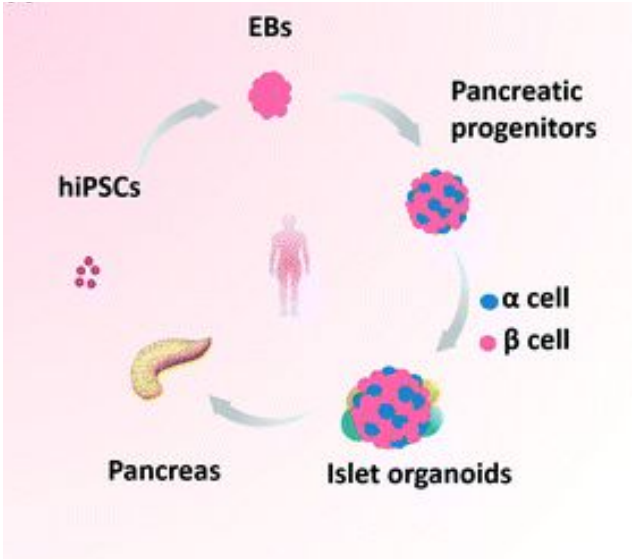
- Engineer human islet organoids from human induced pluripotent stem cells (hiPSCs) using an organ-on-a-chip platform
- In-vivo like human pancreas by mimicking the multicellular architecture and microenvironment
    - Accurate control over mechanical fluid flow, cell-cell interactions, and biochemical signals
- Microsystem contains a multi-layer microfluidic device with wells to culture pancreas cells and perfusion channels.

Design Parameters

Geometric confinement and patterning	Control of Flow	Microfluidics	Incorporating cell samples	Mimics real cell environment

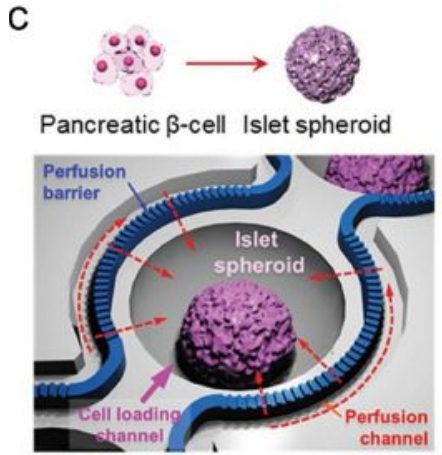
Cells

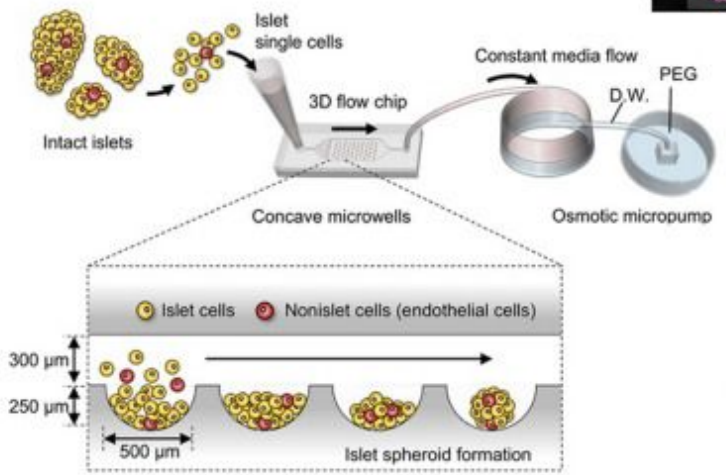
- Differentiation in-vitro
  - Human induced pluripotent stem cells (hiPSCs) differentiate into insulin-producing pancreatic β cells
- Study aims to generate embryoid bodies (EBs) from hiPSCS, guide them to differentiate into progenitors, and then generate islet organoids



Microwells

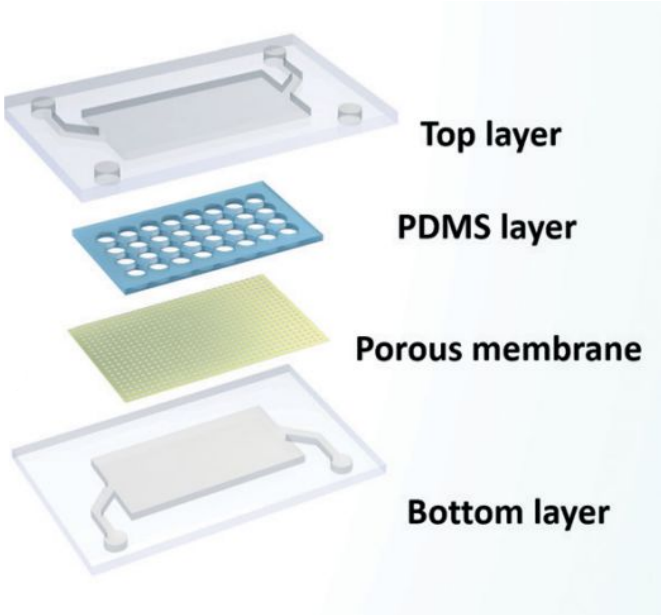
- Hemispherical spheroid culture chamber
- Perfusion channel: mimic blood vessels
- Homogeneously shaped and distributed
- Concave microwells
- Diameter: 500 μm
- Height: 250 μm





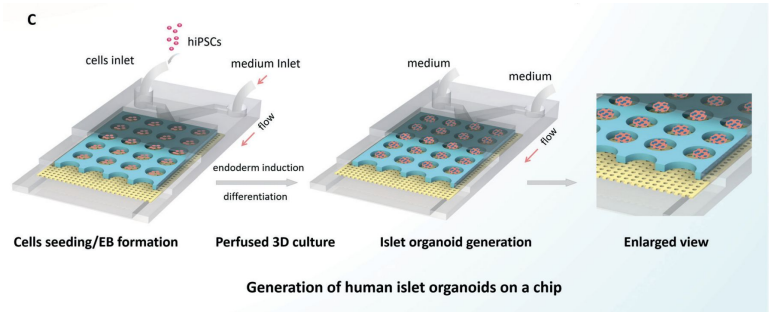
Multilayer Microfluidic Device

- Four layers
  - Top: PDMS, one inlet and outlet for medium infusion
  - Bottom: PDMS, one inlet and outlet for cell infusion
  - Middle PDMS layer has microwells for the 3D culture of EBs and perfusion of media flow
  - Middle porous membrane connects flow in the upper and bottom channels
- Circulatory flow allows sufficient medium exchange and uniform fluid stress



Generation of hiPSC-based islet organoids

1. Dissociated hiPSCs are infused into microfluidic chip via inlets in the bottom layer
    - EBs are differentiated and formed in the device
2. Induction medium with chemicals to guide differentiation is introduced to EBs (upper and lower)
    - EBs become endocrine progenitor (EP)
    - EPs differentiate into islet organoids
3. Culture medium continuously injected into top layer medium channels to provide nutrients long term for islet



Advantages of Device

1) Can generate functional islet organoids derived from hiPSCs

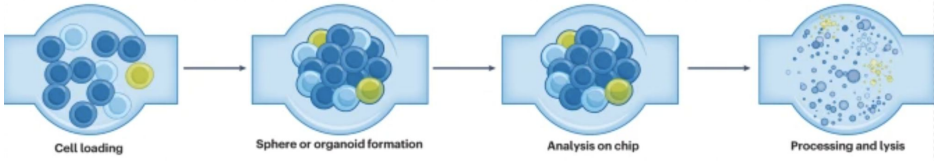
2) Controlled EB formation

3) Perfusion system allows long-term culture
    a) Improved cell viability and islet specific functions such as insulin secretion

Fabrication

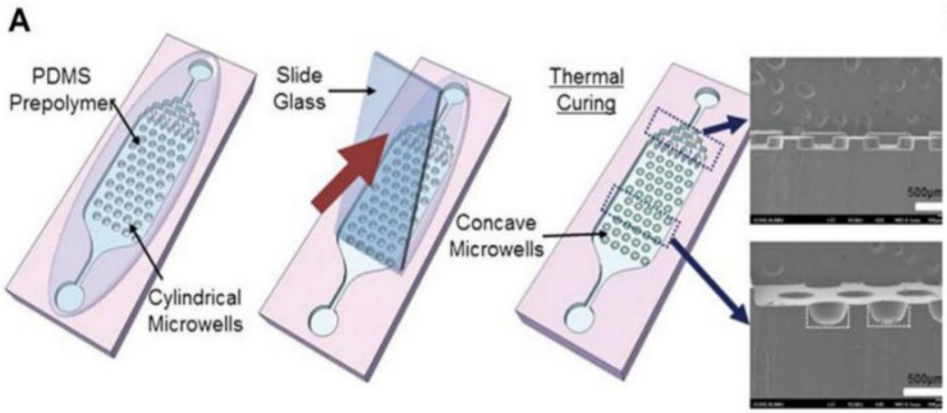
Fabrication Strategy - Inputs

- Key design considerations:
  - Stable recreation of organ function in a baseline (healthy) state
  - Future patient specific storage
  - Allow for interactions that can be studied
- Similarities to Liver-on-a-chip (OOC lecture)
- Develop wells for growth of islet cells in pancreas-like environment
- Allow controlled well interactions
- Ensure proper fluid handling and monitoring



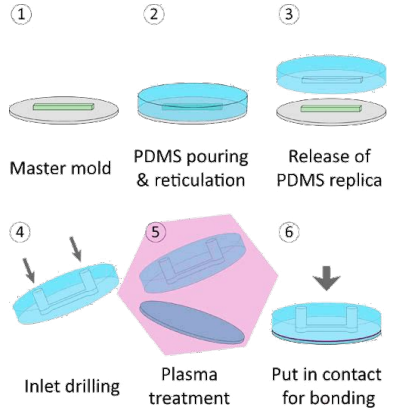
Proposed Design

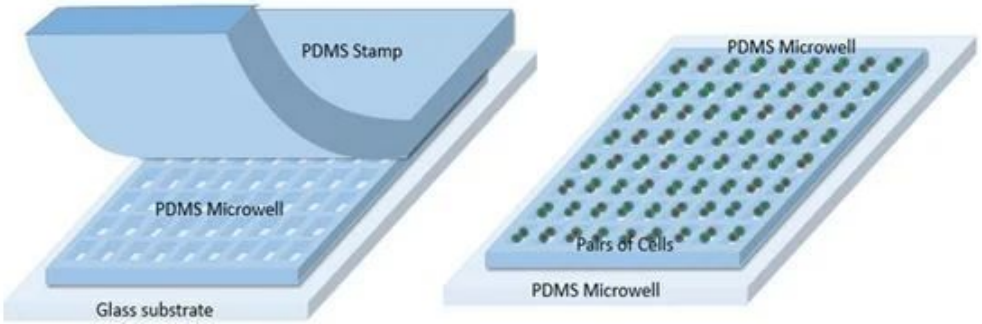
- A microdevice capable of reproducing pancreas function
- Emphasis on sustaining islet cells for study, implantation, and explantation in clinical setting
- Relevant techniques include:
  - PDMS molding
  - Microwell fabrication
    - Subtractive techniques
    - PDMS stamps
  - Microfluidics
  - Advanced polymer scaffolds

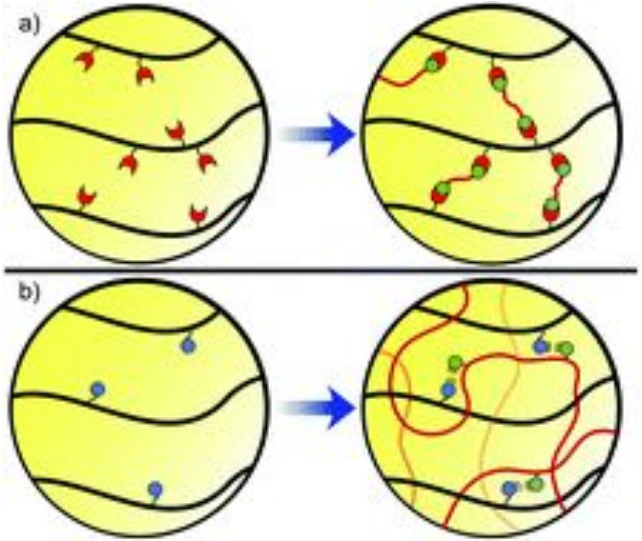


Fabrication Steps

- PDMS Mold base of OOC
  - Insert posts for fluid reservoirs
  - Create channels with mask+lithography
- PDMS stamp microwells
- Insert hydrogel cellular scaffold
- Seed Islet and epithelial cells
- Seal glass slide with plasma oxidation

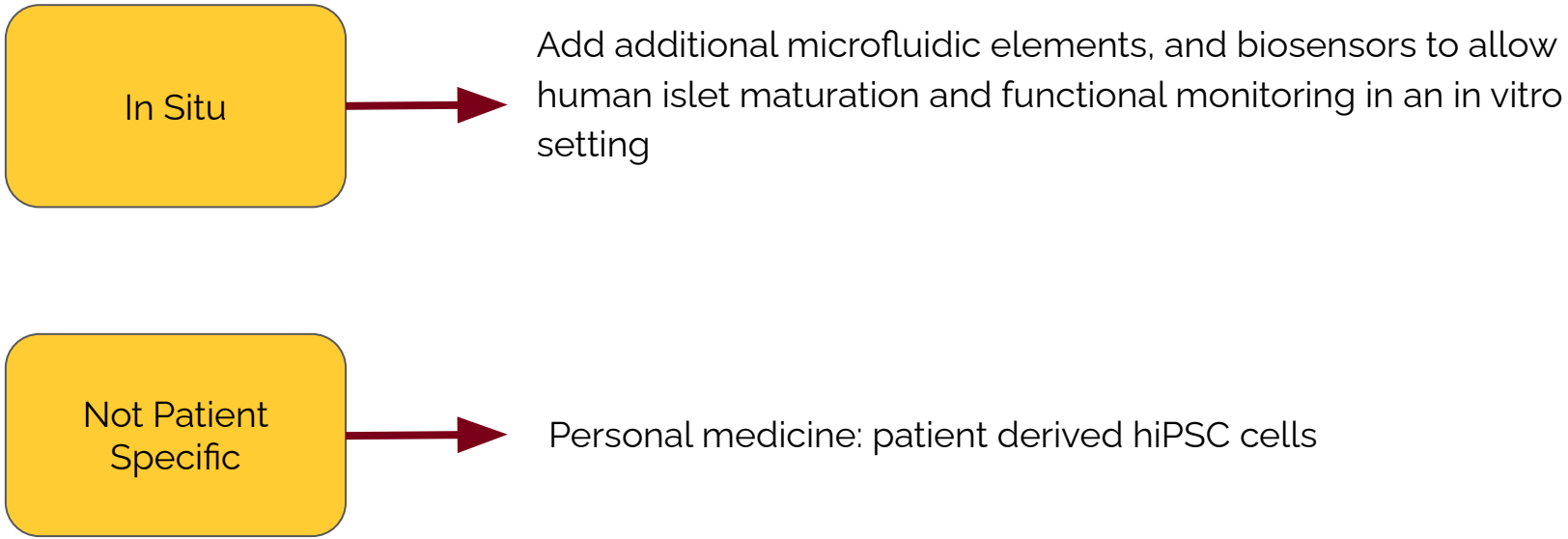






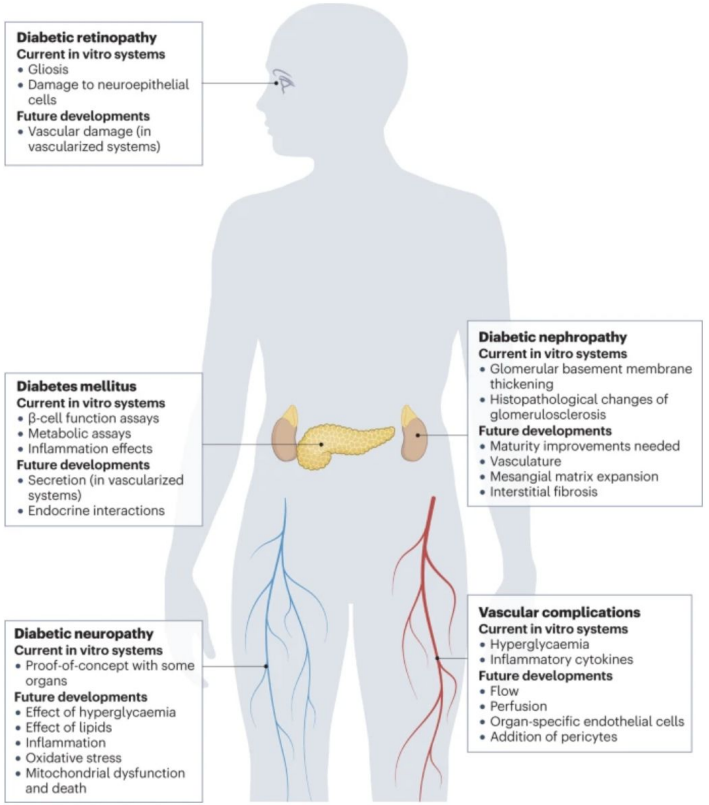
Conclusion

Limitations



Future Directions

- Body on a chip systems
  - Modern methods unable to take a macro look at this issue
  - Better look into whole body reactions of the testings done with our system
  - Further design and fabrication research could allow for the system to analyze islet-cell hormone response



Questions?

Resources

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