Semi-Artificial Pancreas for the Treatment of Type 1 Diabetes: Perspectives, Challenges and Solutions

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Introduction:

- **Type 1 Diabetes Mellitus (T1DM)** is an autoimmune condition where infiltration of **T-cells** into pancreatic tissue initiates **β- cell destruction**, preventing the patient from maintaining **normoglycemia** through **insulin secretion**
- Whilst **Type 2 Diabetes** is **more common**, UK residents have a **1 in 30 chance** of developing T1DM over their lifetime.
- Contemporary solutions to address the blood glucose control in T1DM have included **pancreas transplant** and **insulin injections.**
- **Pancreas transplants** provide a **large amount** of pancreatic tissue immediately, but suffer from the need for **immune-suppressant drugs**,

  T-cell mediated degradation and **tissue necrosis** if **revascularisation** does not occur **promptly**
- **Limitations** of **insulin injection** include **patient compliance**, **financial burden** and **physiological effects** of continuous injection (Though recently **wearable Insulin pumps** have started to address some of these issues)
- **Immunoisolation devices** attempt to use a **semi-permeable membrane** to allow **free flow** of **oxygen**, **glucose** and **insulin** in and out of the device whilst providing a **physical barrier** to **immune cells** and accompanying **chemical factors**

Microencapsulation and Immunoisolation:

- **Immunoisolation** comprises **intravascular, extravascular** and **microencapsulated** systems**.** Microencapsulation is popular because **small construct size** and **cell number per system,** increases **treatment flexibility,** reduces **hypoxia-mediated toxicity** and increases **surface area to volume ration** whilst **preserving immunoisolation.**
- The **ideal microencapsulation material** for bioartificial pancreas would have **optimised porosity** for **selective permeability**, **tuneable degradation** characteristics, **biocompatibility** with islet cells (and surrounding host tissue) and the ability to **incorporate proliferation/ phenotype** promoting **chemical factors**
- **As a class, hydrogels possess many of these characteristics with PEG and alginate hydrogels already used in microencapsulation systems**

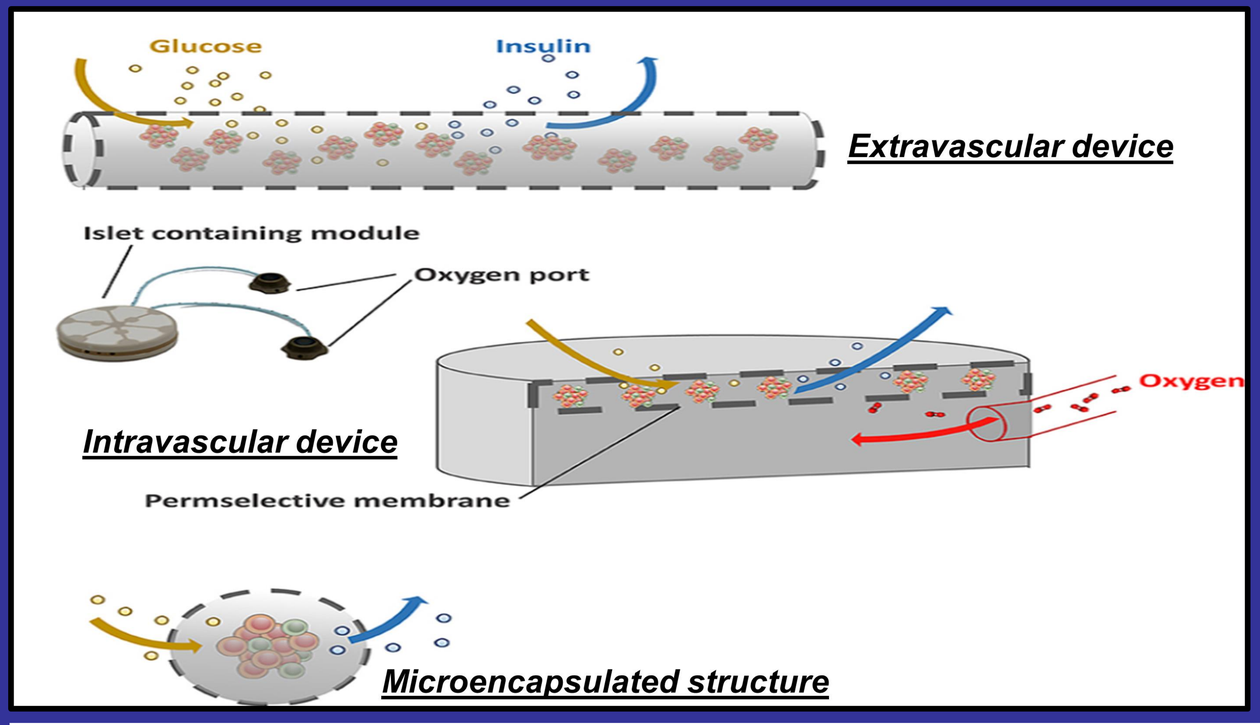


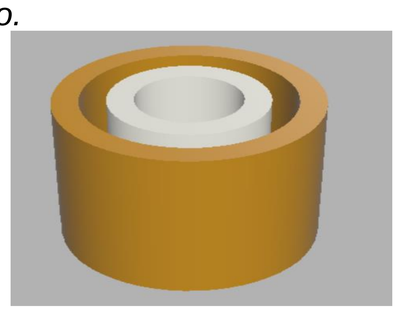
Figure 1: Classes of Immunoisolation devices, (Modified from Hu and Devos, 2019)

Bioprinting using pancreatic islet cells:

Bioprinting has been achieved using pancreatic islet cells:

- Although hydrogels have many of the required characteristics required for successful encapsulation and bioprinting, they suffer from poor mechanical properties
- Marchioli *et al*. (2015) described the handleability of their bioplotted islet-containing woodpile construct as adequate, noting that their hydrogel had mechanical properties akin to that of soft tissue
- Liu. (2019) partially remedied this issue by generating coaxial layers of hydrogel and more mechanical resistant polymer.
- It appears multimaterial printing may be useful for situations where the compromise between membrane permeability comes at the cost of islet survival *in vivo.*

a



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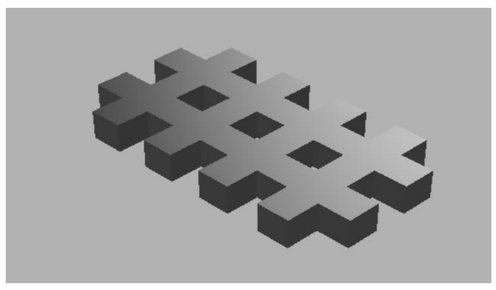

Figure 2. a: Coaxially arranged construct geometry (modified from Liu, 2019), b. Construct modified from Marchioli's *et al.*, 2015) bioplotted woodpile system

Islet cell tissue engineering

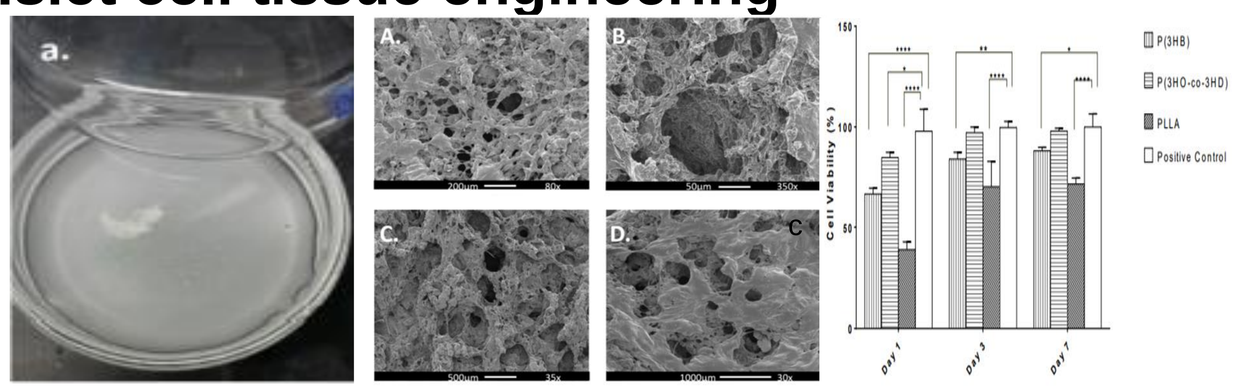

Figure 3. a: Macrostructure of a porous PHA film b: SEM images of a microporous structure of porous PHA films c: Relative viability of BRIN-BD11 cells grown on polymers including two types PHAs, P(3HB) and P(3HO-co-3HD)

- The viability and insulin release of BRIN-BD11 (rat islet cell line) was confirmed when grown on PHA films and was better viability was observed compared to PLLA films.
- We now aim to generate an **implantable 3D-printed system** that combines the excellent mechanical properties and biocompatibility of **Polyhydroxyalkanoates**, with modifiable-porosity encapsulation materials such as alginate (Figure below)

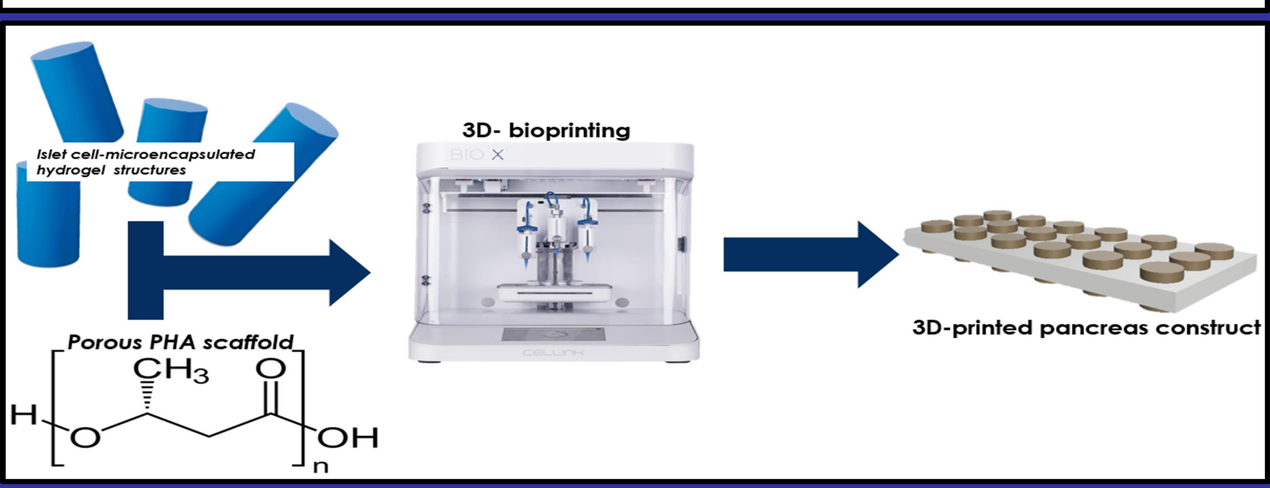

Figure 4: Method of producing a multimaterial islet-hosting construct

References:

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- Hu, S. and De Vos, P., 2019. Polymeric approaches to reduce tissue responses against devices applied for islet-cell encapsulation. *Frontiers in Bioengineering and Biotechnology*, *7*, p.134.

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