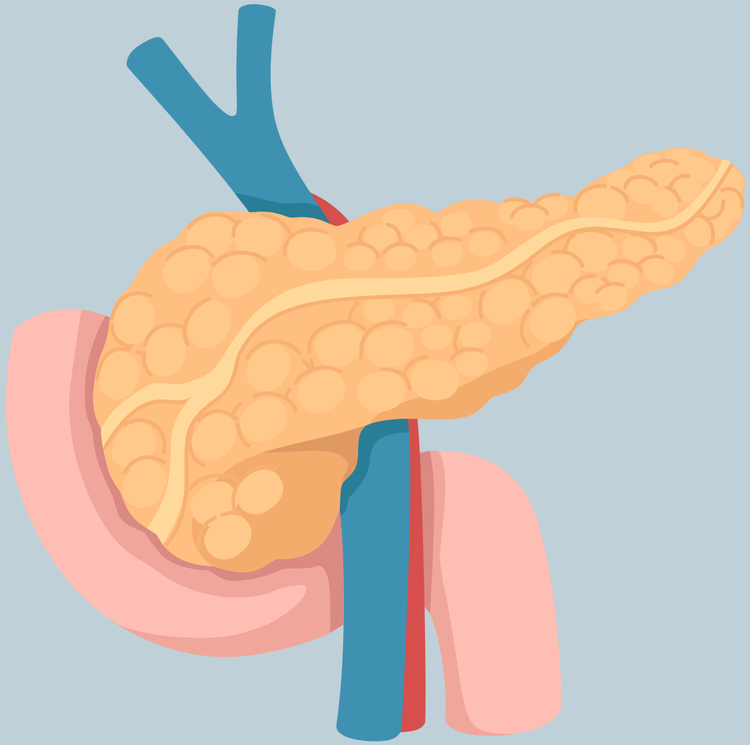
Pancreatic Tissue Engineering



Tissue Engineering 2024/25

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Carolina Canilho - 102499
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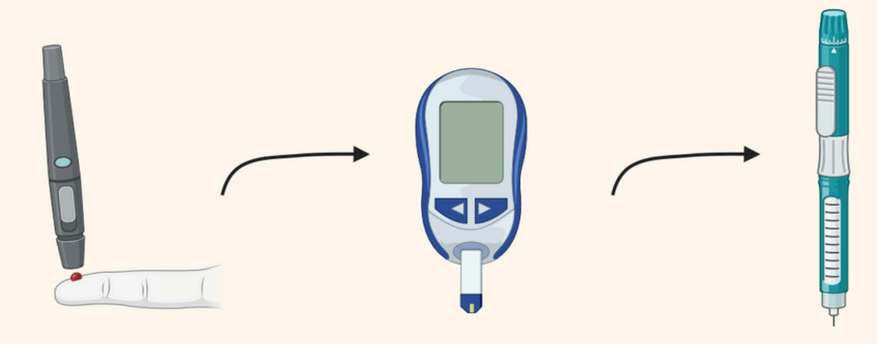
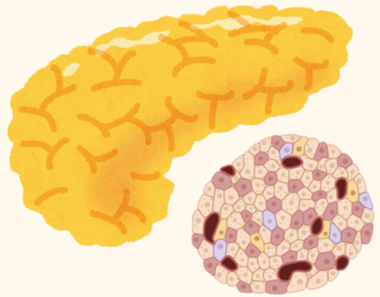
Type 1 Diabetes

Type1 DM is characterized by an autoimmune destruction of pancreas β cells, which are responsible for producing insulin.



risks

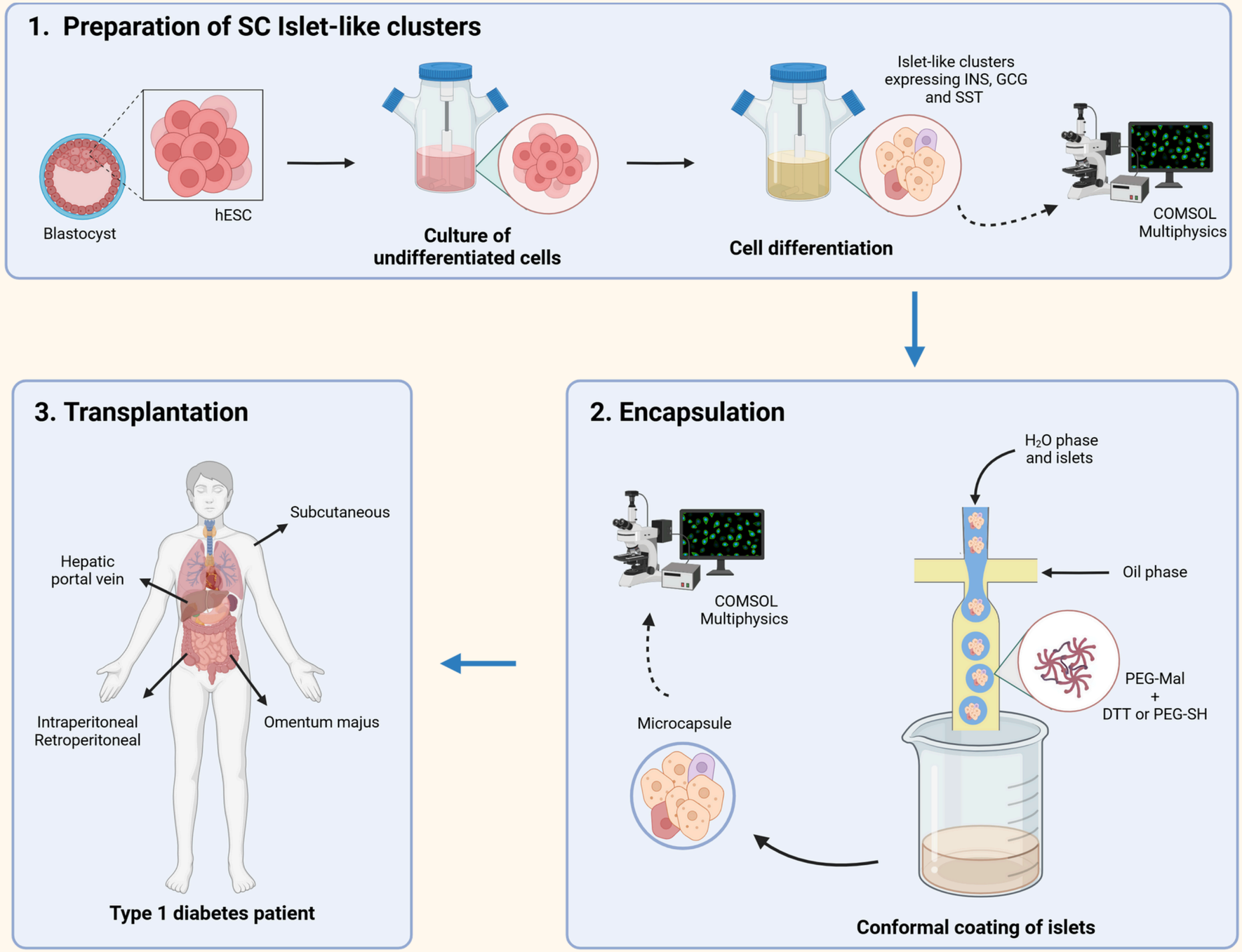


donor shortage

This work aims to address T1DM treatment by differentiating stem cells into β-cells for encapsulation and transplantation

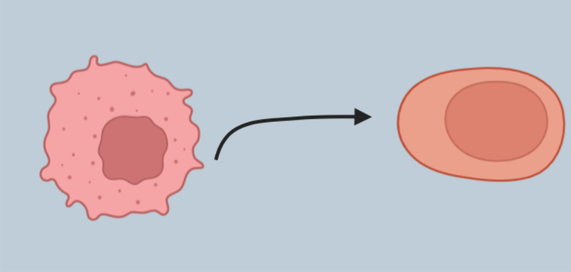
[1]

Workflow


1. Preparation of SC Islet-like clusters
Blastocyst
hESC
Culture of undifferentiated cells
Islet-like clusters expressing INS, GCG and SST
Cell differentiation
COMSOL Multiphysics
2. Encapsulation
H2O phase and islets
Oil phase
PEG-Mal + DTT or PEG-SH
COMSOL Multiphysics
Microcapsule
Conformal coating of islets
3. Transplantation
Subcutaneous
Hepatic portal vein
Intraperitoneal Retroperitoneal
Omentum majus
Type 1 diabetes patient

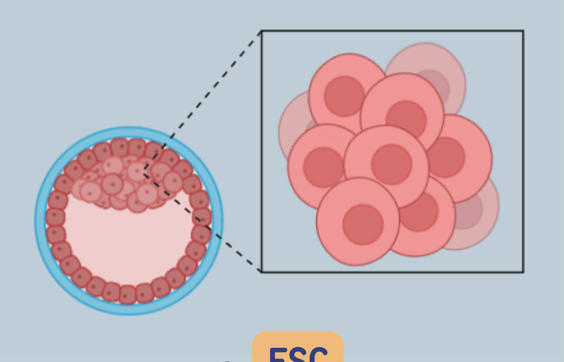
Stem cells

Both hESCs and iPSCs offer an alternative to donor islets, enabling the production of large quantities of β-cells for clinical use.



iPSC

- Can reduce the risk of allograft rejection
- However, T1D patients with autoimmune defects will still require additional immune suppression [2]



ESC

- Ethical concerns
- Established and characterized
- Efficient differentiation [3]

Differentiation Protocol

Pagliuca et al. (2014) [4]

Cell

Resource

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]
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http://dx.doi.org/10.1016/j.cell.2014.09.040

Velazco-Cruz et al. (2019) [5]

Stem Cell Reports

ISSCR

Article

OPEN ACCESS

Acquisition of Dynamic Function in Human Stem Cell-Derived β Cells

Leonardo Velazco-Cruz,[1] Jiwon Song,[1] Kristina G. Maxwell,[1,2] Madeleine M. Goedegebuure,[1] Punn Augsornworawat,[1,2] Nathaniel J. Hogrebe,[1] and Jeffrey R. Millman[1,2,*]
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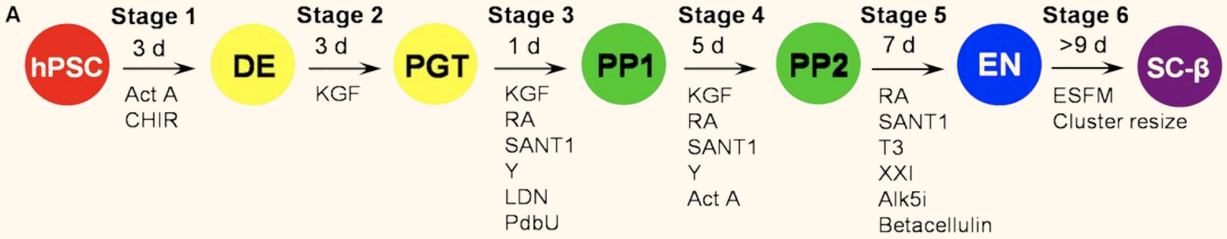
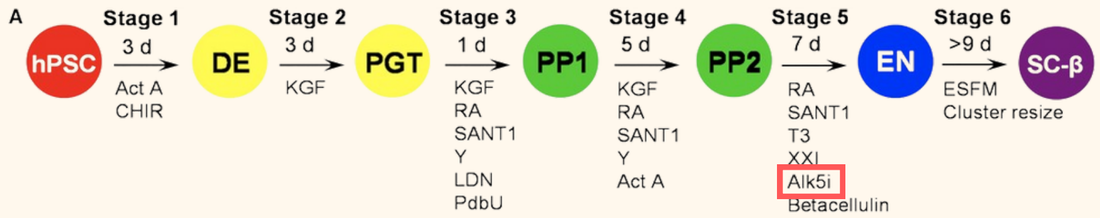
https://doi.org/10.1016/j.stemcr.2018.12.012



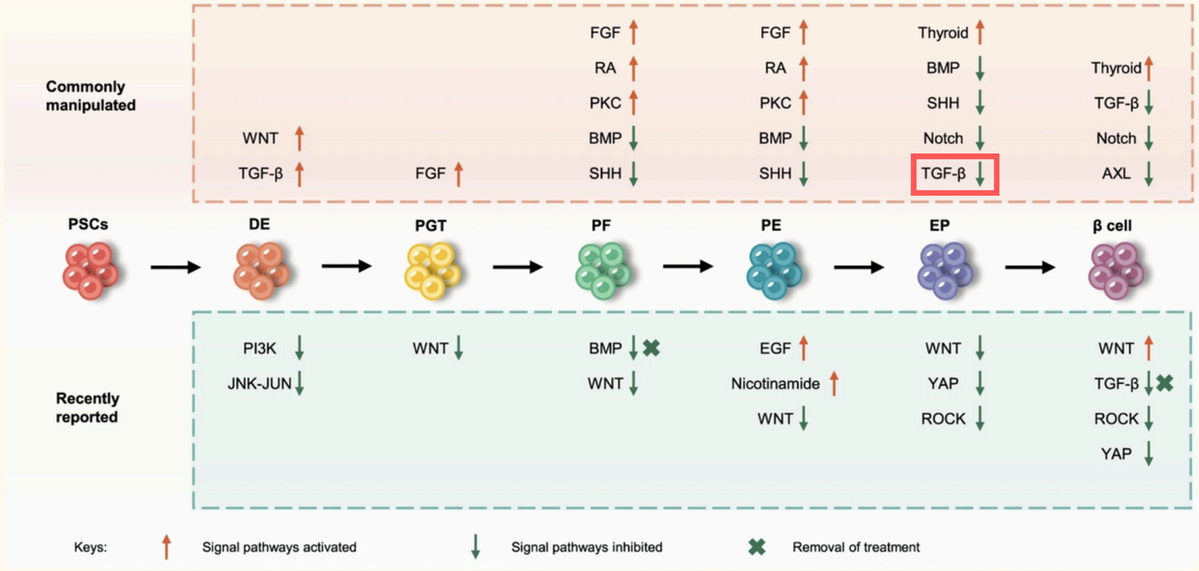
Overview of the differentiation procedure. Source: Velazco-Cruz et al. [5]

- **Six stages** of differentiation
- **Scalable** suspension-based system
- **Serum-free** protocol
- **Small molecules** that modulate several pathways (Wnt, Hedgehog, TGF-β, retinoic acid...)
- **Islet-like clusters** with controlled size
- Enhanced **functional maturation** of SC-β cells and higher measured **insulin** levels

TGF-β Signaling Pathway



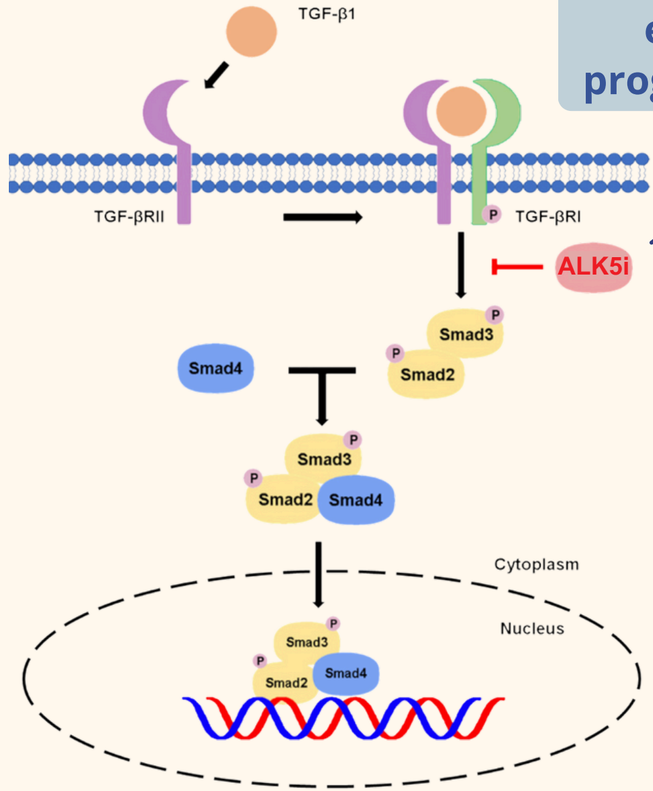
Overview of the differentiation procedure. Source: Velazco-Cruz et al. [5]



Improvements to efficient differentiation of human PSC-derived pancreatic β cells. Source: Jin et al. [3]

Upregulation of **NGN3** triggers the downstream activation of TFs **NEUROD1**, **Pax4**, and **Isl1**. [8]

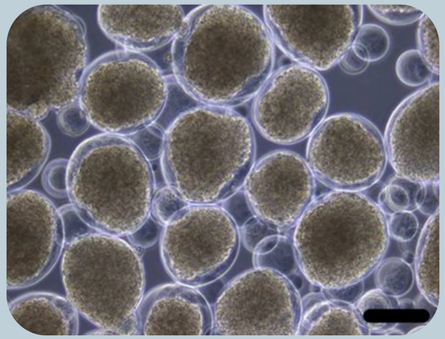
Differentiation of endocrine progenitors [3,7]



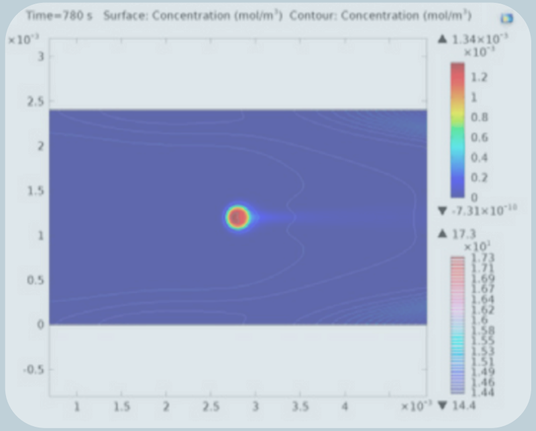
Schematic of TGF-β signaling pathway. Source: Chung et al. [6] (Adapted)

TECHNIQUES

01 ENCAPSULATION



02 COMSOL Multiphysics



01 ENCAPSULATION

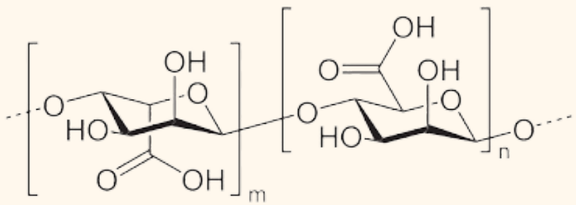
BIOMATERIALS

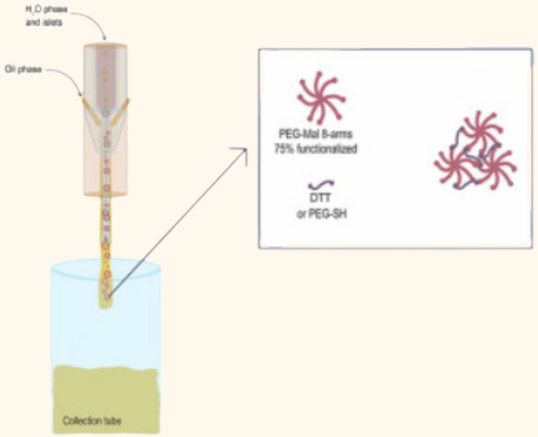
-Alginate:

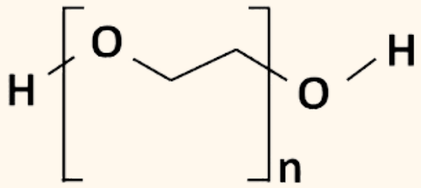
- ✔ Cheap, biocompatible, porous
- ✘ Mechanically unstable, less tunable, immunogenic, non-selective.

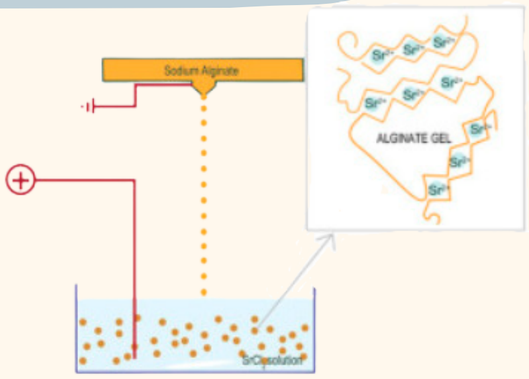
-PEG:

- ✔ Non-immunogenic, tunable properties
- ✘ Cost, insuline diffusion restrictions







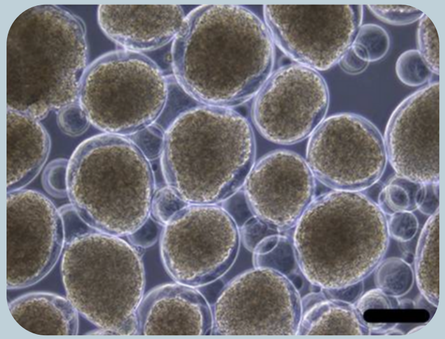


VS

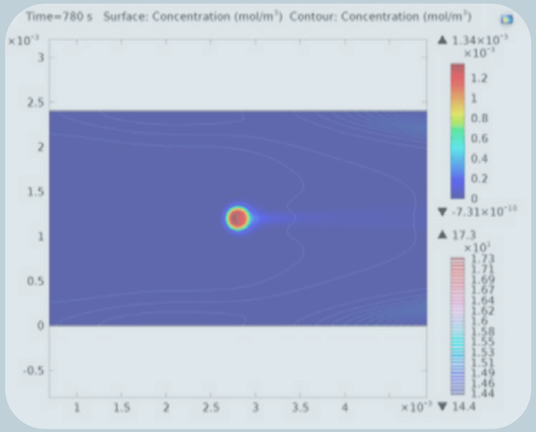
[9, 10]

TECHNIQUES

01 ENCAPSULATION

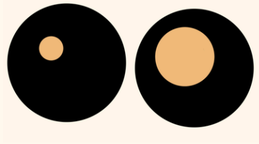


02 COMSOL Multiphysics



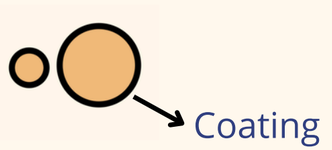
01 ENCAPSULATION

Cell Clusters

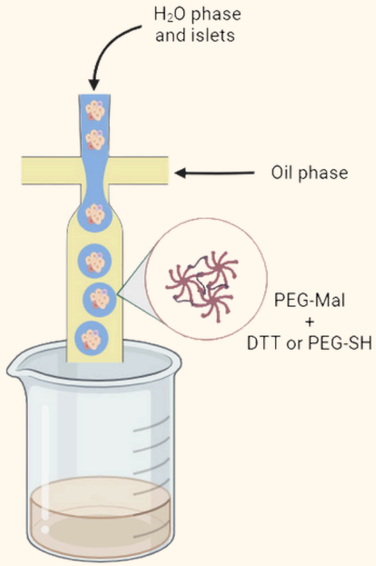


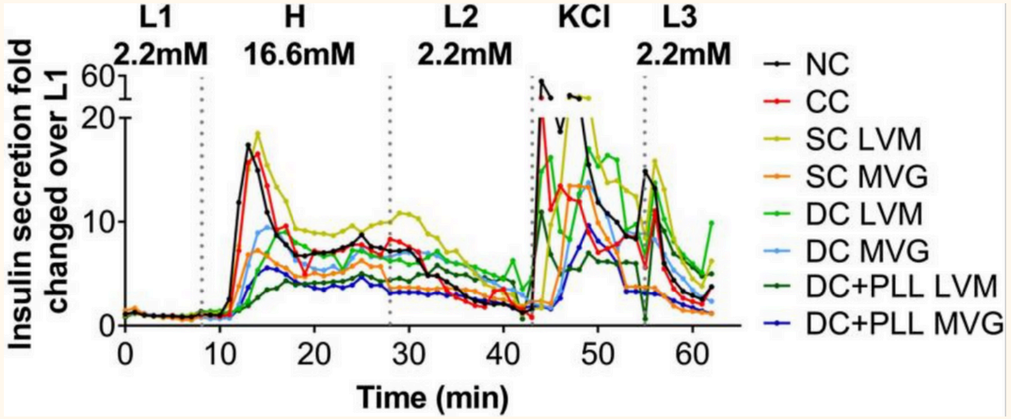
Conventional Microencapsulation

Conformal Coating



Conformal coating (CC) is a specialized form of microencapsulation where a hydrogel layer closely conforms to the shape and size of each individual islet, resulting in a uniform capsule and with minimal thickness.

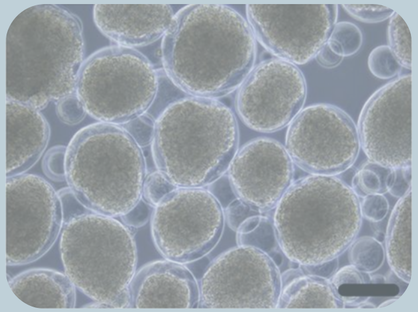




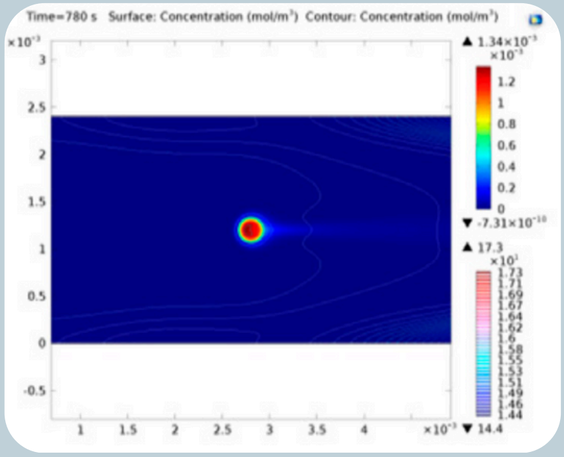
In vitro dynamic perifusion assay of microencapsulated compared with non-coated (NC) human islets. Source: De Toni T et al. [9]

TECHNIQUES

01 ENCAPSULATION

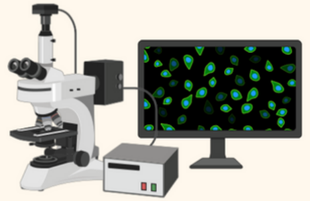


02 COMSOL Multiphysics



02 COMSOL Multiphysics

We are going to measure the insulin secretion of our beta cells before and after encapsulation to assess their functionality.



computational approach in COMSOL Multiphysics, that integrates experimental data and simulations

The islet size

LEICA optical microscope

The thickness of the encapsulation material

ImageJ

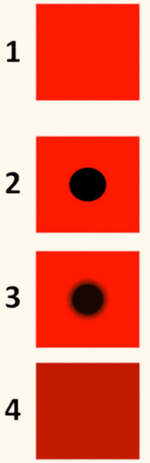
Image Processing & Analysis in Java

Experimental parameters integrated into the computational model to evaluate how encapsulated beta cells respond to glucose stimulation, including their ability to secrete insulin efficiently

diffusion coefficients of insulin and glucose

FRAP

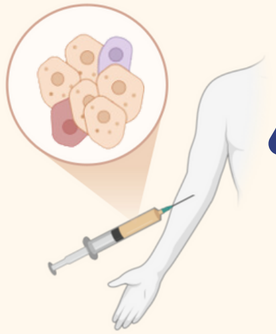
Top View



Provide precise information about the difusion behavior of insulin and glucose

[9]

Challenges and Future Directions



Although smaller encapsulation devices enhance nutrient diffusion, they may also trigger a foreign body response and fibrosis. [11]

To address this issue it can be incorporated a localized anti-inflammatory drug delivery systems to improve biocompatibility.

Acute loss of a significant percentage of the encapsulated islet mass

β cells remain vulnerable to stressors like:

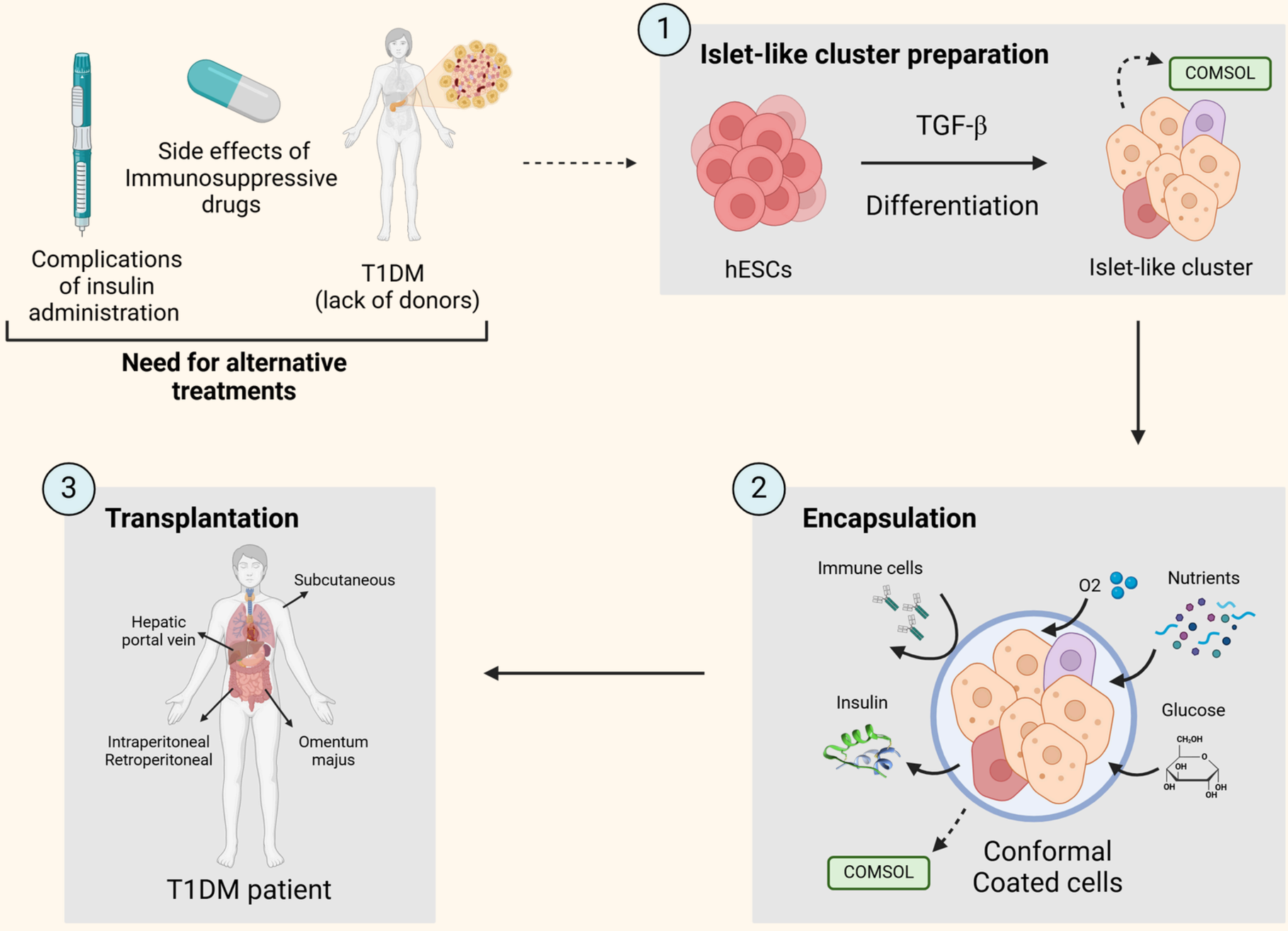
- ER stress
- inflammation
- hypoxia
- hyperglycemia

apoptosis and dysfunction

Future work

- Focus on mitigating acute stressors post-transplantation to reduce β cell loss and dysfunction.
- Genetic engineering offers a potential solution by improving cell viability and resistance to these stressors. [12]

Graphical Abstract



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