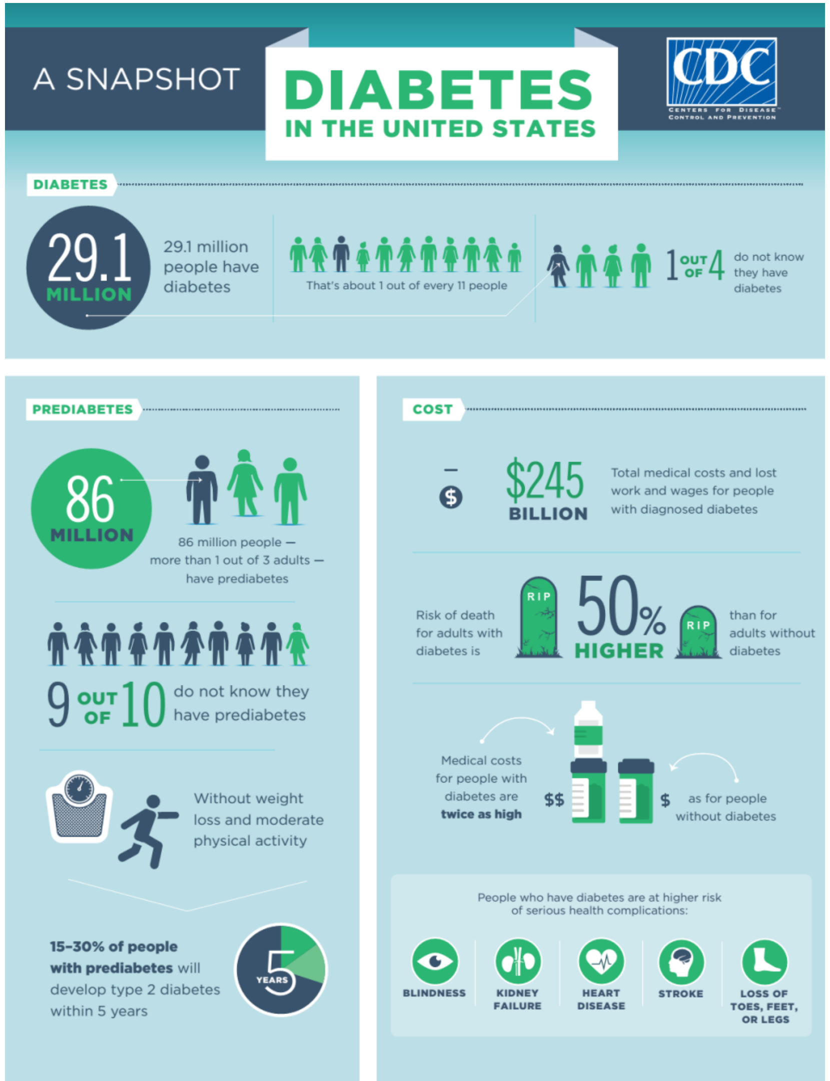
14 July 2022, CRS 2022 Annual Meeting and Expo

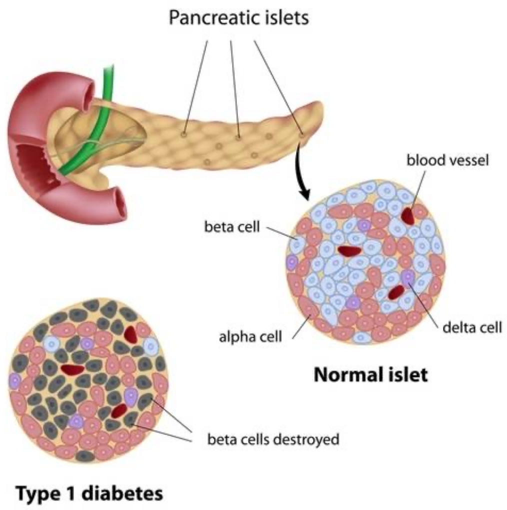
On-demand Surface-Triggered In Situ Gelation (STIG) for Coating of Therapeutic Cells and Biomedical Devices

Jee-Heon Jeong, Ph.D.
Associate Professor
Laboratory of Drug Delivery and Cell Therapy (LDDCT)
Department of Precision Medicine, School of Medicine
Sungkyunkwan University

Diabetes



Type I diabetes-Autoimmune disease



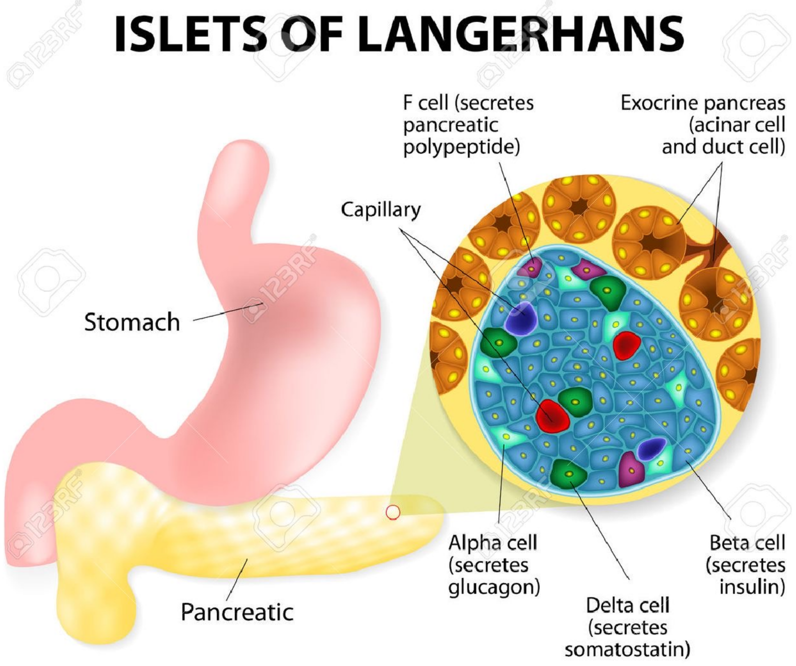
Insulin injection

Side effects

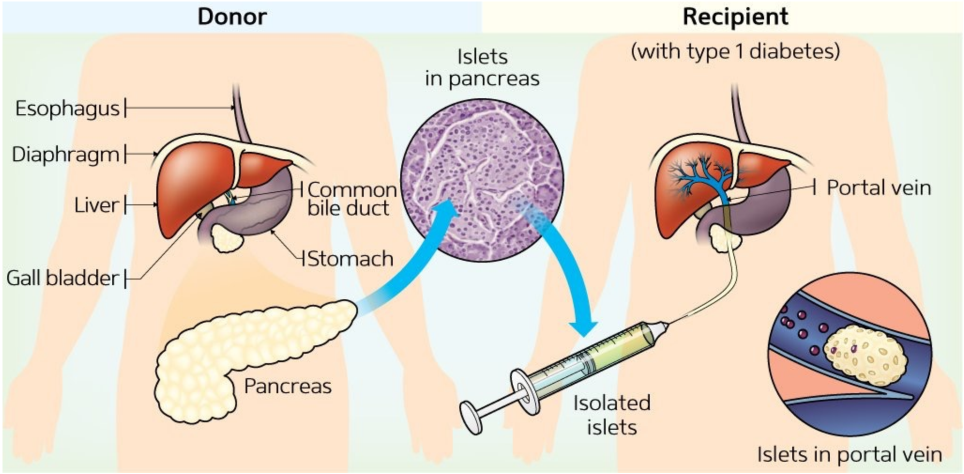
- Injection site - Itching, mild pain, redness, or swelling at the injection site
- Systemically - Hypoglycemia, weight gain, insulin edema.
- Inconvenience

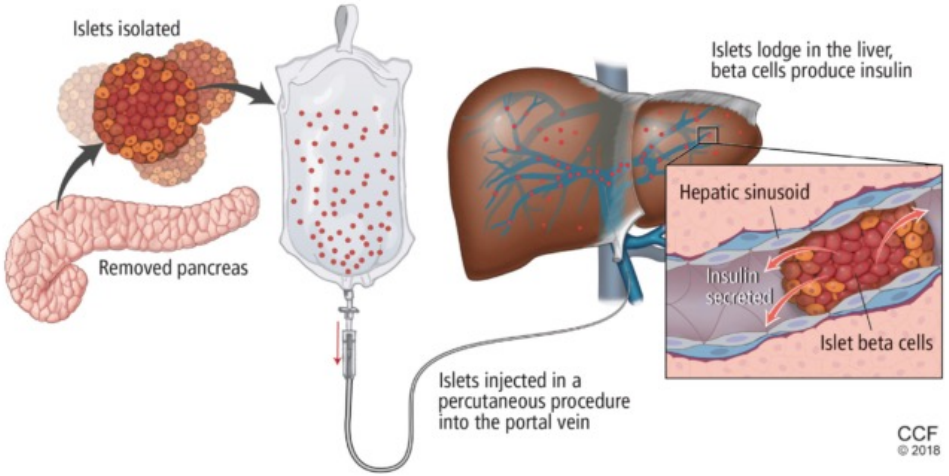
http://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html

Pancreatic islet transplantation



Intraportal islet transplantation

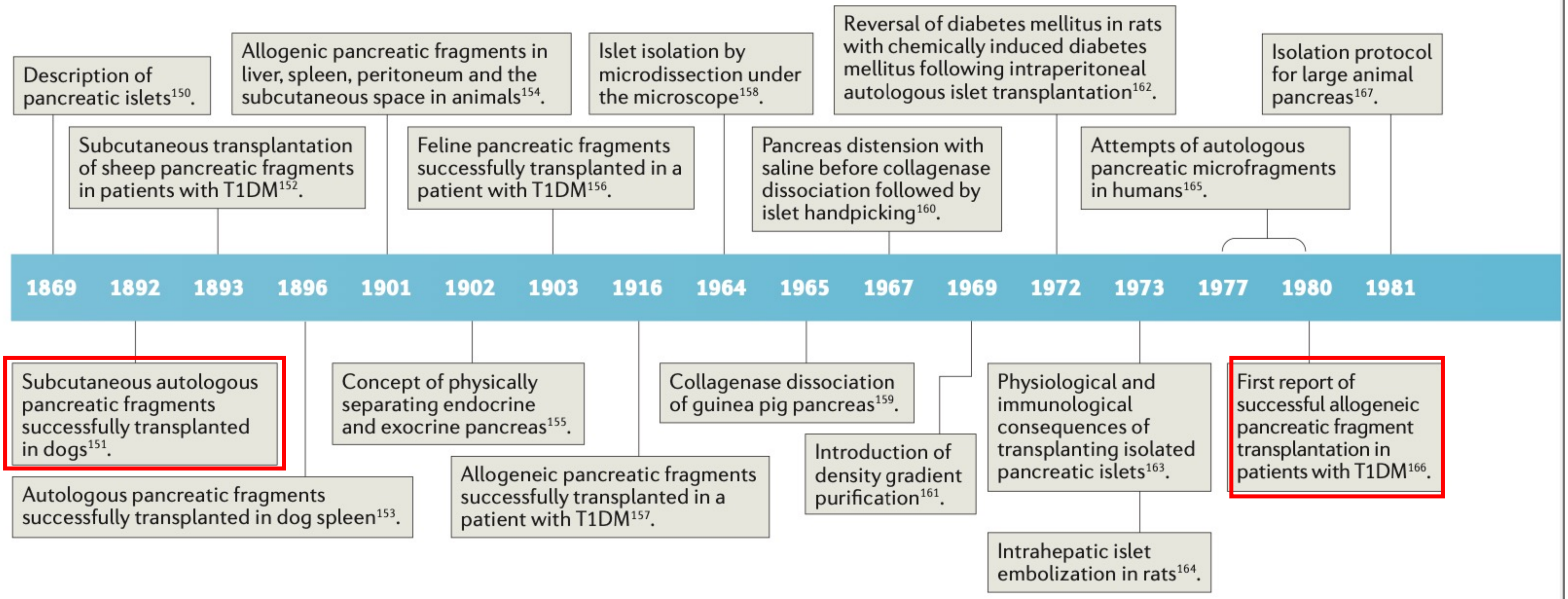




- Alpha cells producing glucagon (15–20% of total islet cells)
- Beta cells producing insulin and amylin (65–80%)
- Delta cells producing somatostatin (3–10%)
- PP cells producing pancreatic polypeptide (3–5%)
- Epsilon cells producing ghrelin (<1%)

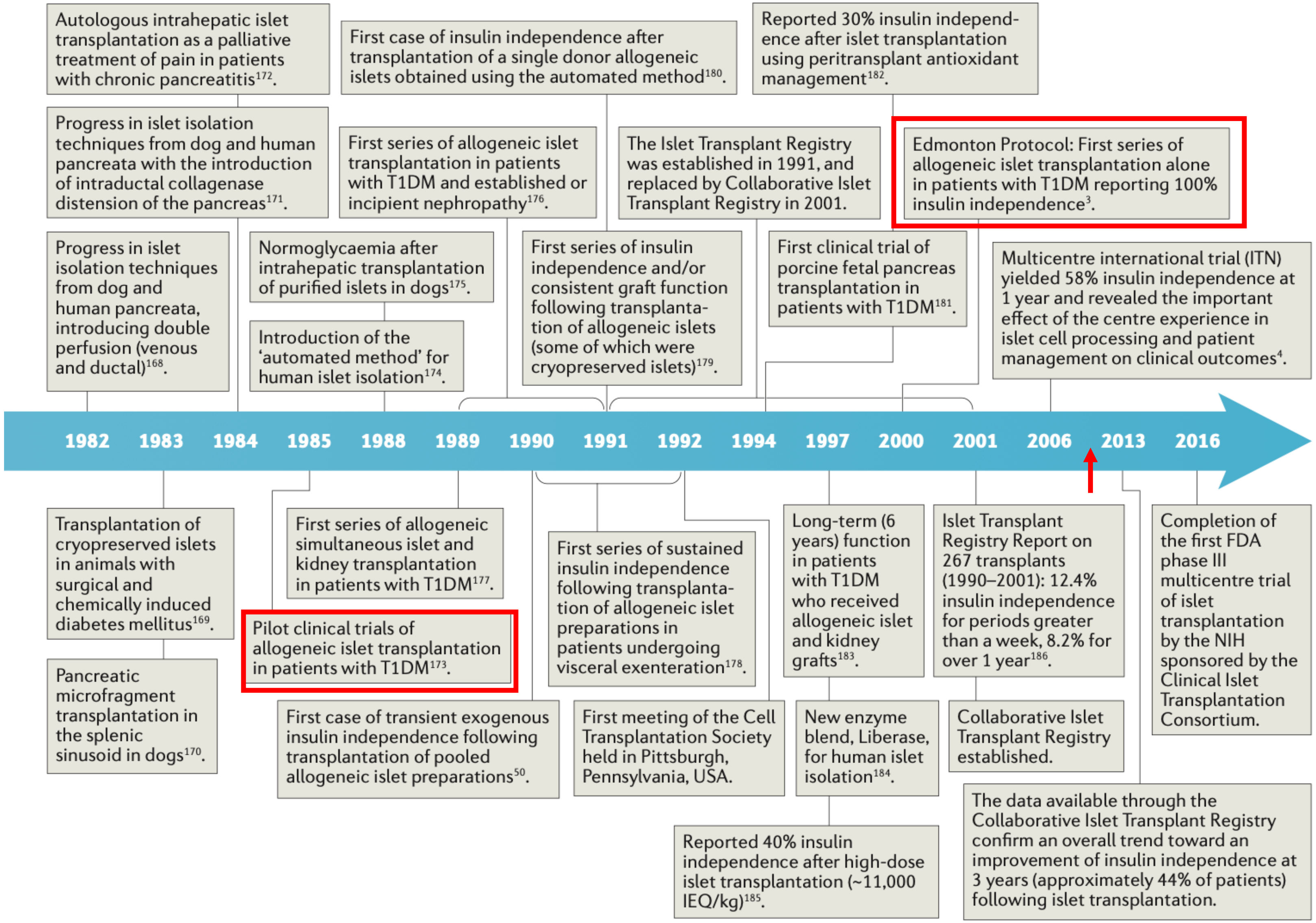
Ref) J. R. T. Lakey et al., Transpl. Int. (2003) 16:6 13-632

History of pancreatic islet transplantation



Ref) *Nat Rev Endocrinol* **13,** 268–277 (2017)

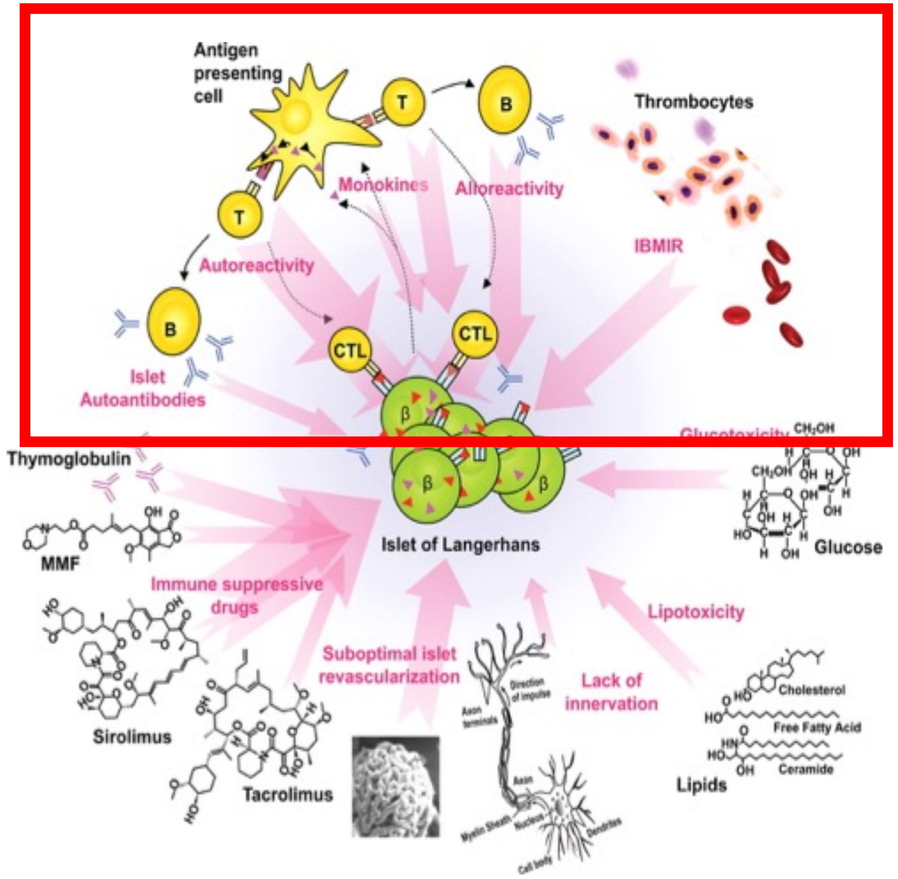
History of pancreatic islet transplantation

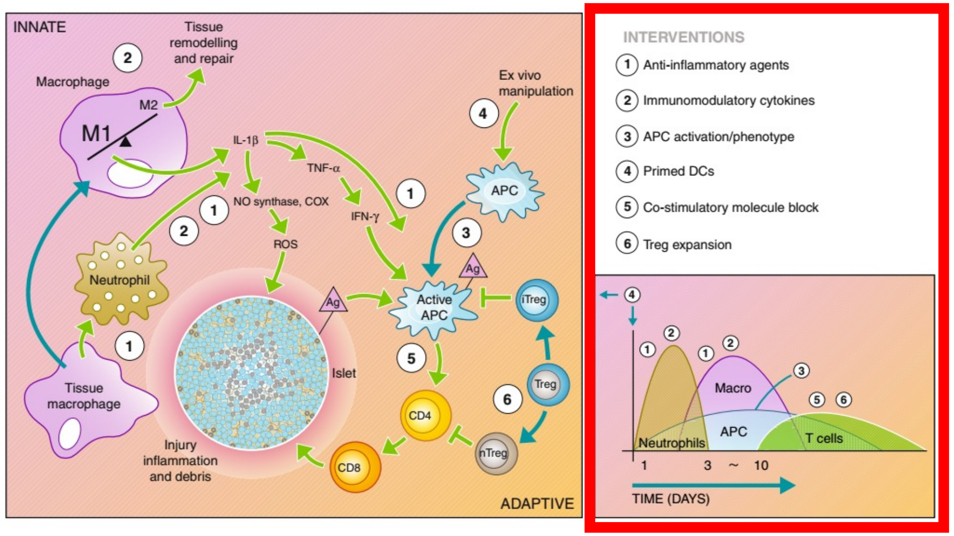


Ref) *Nat Rev Endocrinol* **13,** 268–277 (2017)

Hurdles of Islet transplantation

Inflammation & Immune reaction





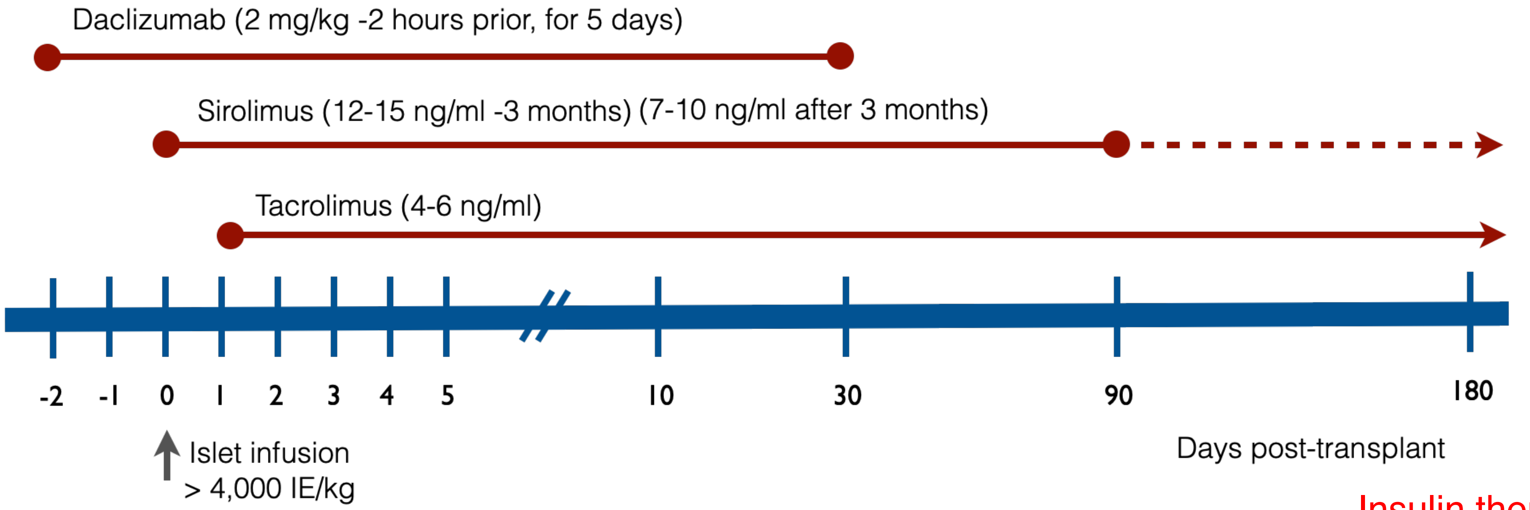
R. F. Gibly et al., *Diabetologia (2011), 54:2494-2505*, Harlan D M et al. *Diabetes 2009;58:2175-2184*

Immunosuppressive drugs

Immunomodulators: Immunosuppressive drugs				
Intracelluar (initiation)	Antimetabolites			Purine synthesis inhibitor: Azathioprin, **Mycophenolic acid** Pyrimidine synthesis inhibitors: **Leflunomide**, Teriflunomide Antifolate: Methotrexate
	Macrolides/other IL-2 inhibitors			FKBP/Cyclophilin/Calcineurin: **Tacrolimus**, **Cyclosporin**, Pimercrolimus
	TNF inhibitor			Abetimus, Lenalidomide
Intracellular (reception)	IL-1 receptor antagonists			Anakinra
	mTOR			**Sirolimus**, Everolimus, Ridaforolimus, Temsirolimus, Umirolimus, Zotarolimus
Extracellular	**Antibodies**	Monoclonal	Serum target (noncellular)	Compliment component 5 (Eculizumab), TNFs (Infiximab, Adalimumab, Certolizumab pegol, Afelimomab, Golimumab), Interleukin 5 (Mepolizumab), Immunoglobulin E (Omalizumab), BAYX (Nerelimomab), Interferon (Faralimomab), IL-6 (Elsilimomab) IL-12 and IL-23 (Lebrikizumab, Ustekinumab)
			Cellular target	**CD3** (Muromonab-CD3, Otelixizumab, Visilizumab), CD4 (Clenoliximab, Keliximab, Zanolimumab), CD11a (Efalizumab), CD18 (Erlizumab), CD20 (Afutuzumab, Rituximab, Ocrelizumab, Pascolizumab), CD23 (Gomiliximab, Lumiliximab), CD40 (Teneliximab, Toralizumab), CD62L/L-selectin (Aselizumab), CD80 (Galiximab), CD147/Basigin (Gavilimomab), **CD154** (Ruplizumab) Blys (Belimumab), **CTLA-4** (Lipilimumab, Tremelimumab), CAT (Bertilimumab, Lerdelimumab, Metelimumab), Intergrin (Natalizumab), Interleukin-6 receptor (Tacilizumab), LFA-1 (Odulimomoab), **IL-2 receptor/CD25** (Basiliximab, **Daclizumab,** Inolimomab), T-lymphocyte (Zolimomab aritox)
			Unsorted	Atorolimumab, Cadelizumab, Fontolizumab, Maslimomab, Morolimumab, Pexelizumab, Resizumab, Rovelizumab, Sipizumab, Talizumab, Telimomab aritox, Vapaliximab, Vepalimomab
		Polyclonoal	Anti-thymocyte globulin, Anti-lymphocyte globulin	
	-cept (Fusion)	CTLA-4 (Abatacept, Belatacept), TNF inhibitor (Etanercept, Pegsunercept), Aflibercept, Alefacept, rilonacept)		

Ref) Modified from wikipedia

Edmonton Protocol for Immunosuppression



Update on Islet Transplantation

Michael McCall and A.M. James Shapiro

Clinical Islet Transplant Program and Department of Surgery, University of Alberta, Edmonton, Alberta T6G 2B7, Canada

Correspondence: amjs@islet.ca

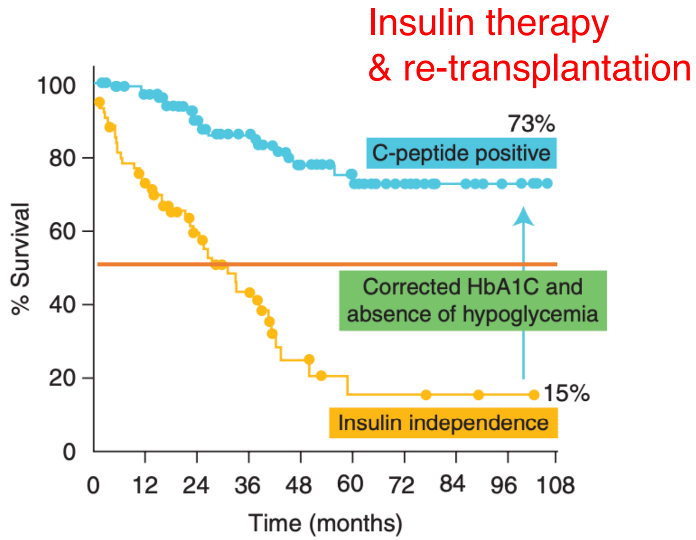


Figure 3. Nine-year insulin independence and C-peptide islet graft function rates with the original Edmonton Protocol immunosuppression. (Data from the University of Alberta.)

Ref) Cold Spring Harb Perspect Med, 2012 Jul;2(7):a007823.

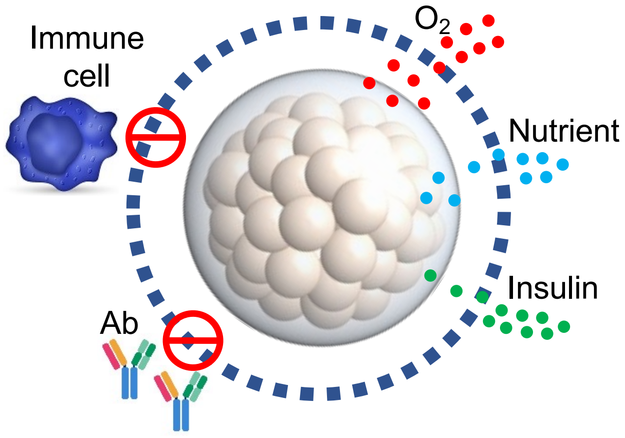
Approaches to improve survival of transplanted islets

Systemic immunosuppression

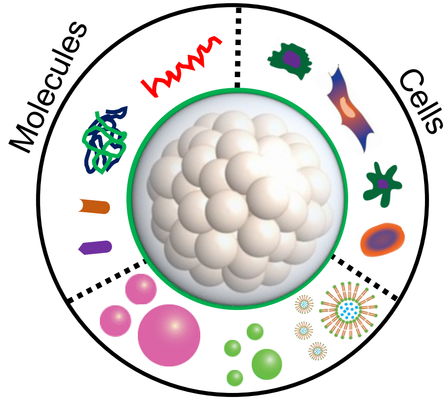
- Tacrolimus (FK506)
- Sirolimus/rapamycin
- Cyclosporine
- Tofacitinib
- Daclizumab (binding to CD25)
- Anti-thymocyte globulin (ATG)

Edmonton Protocol (2000) NEJM

Encapsulation



Surface modification

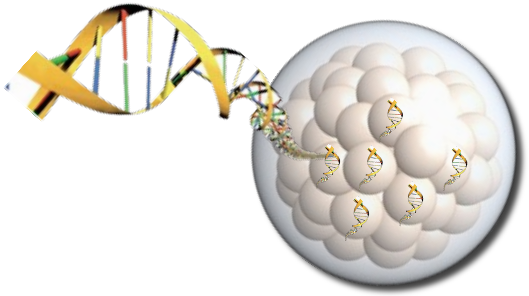


Particles

Cell empowerment

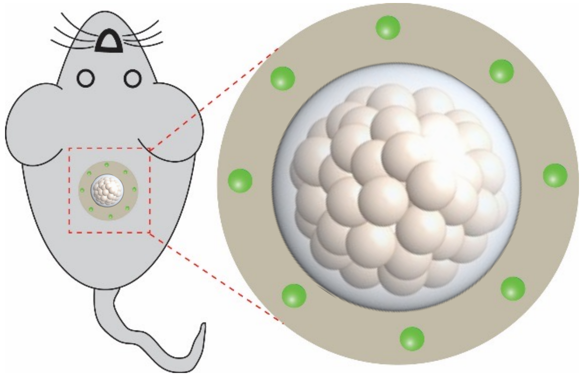
$BetaO_2$ device

Gene therapy



Gene transfection

Local immunosuppression

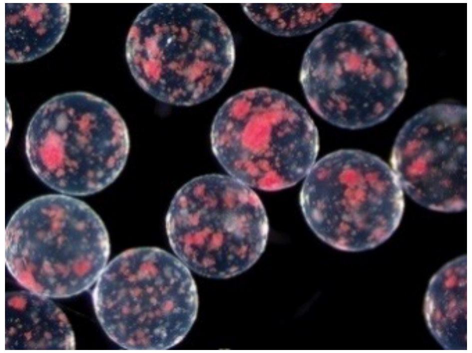


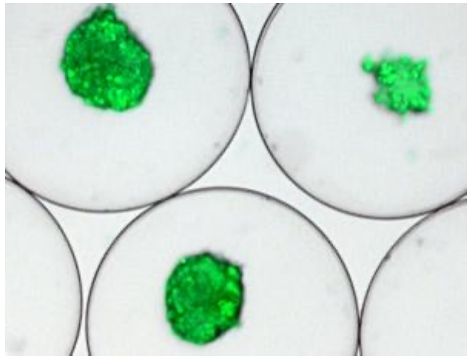
Cell encapsulation

ARTICLES
https://doi.org/10.1038/s41551-018-0275-1
nature biomedical engineering

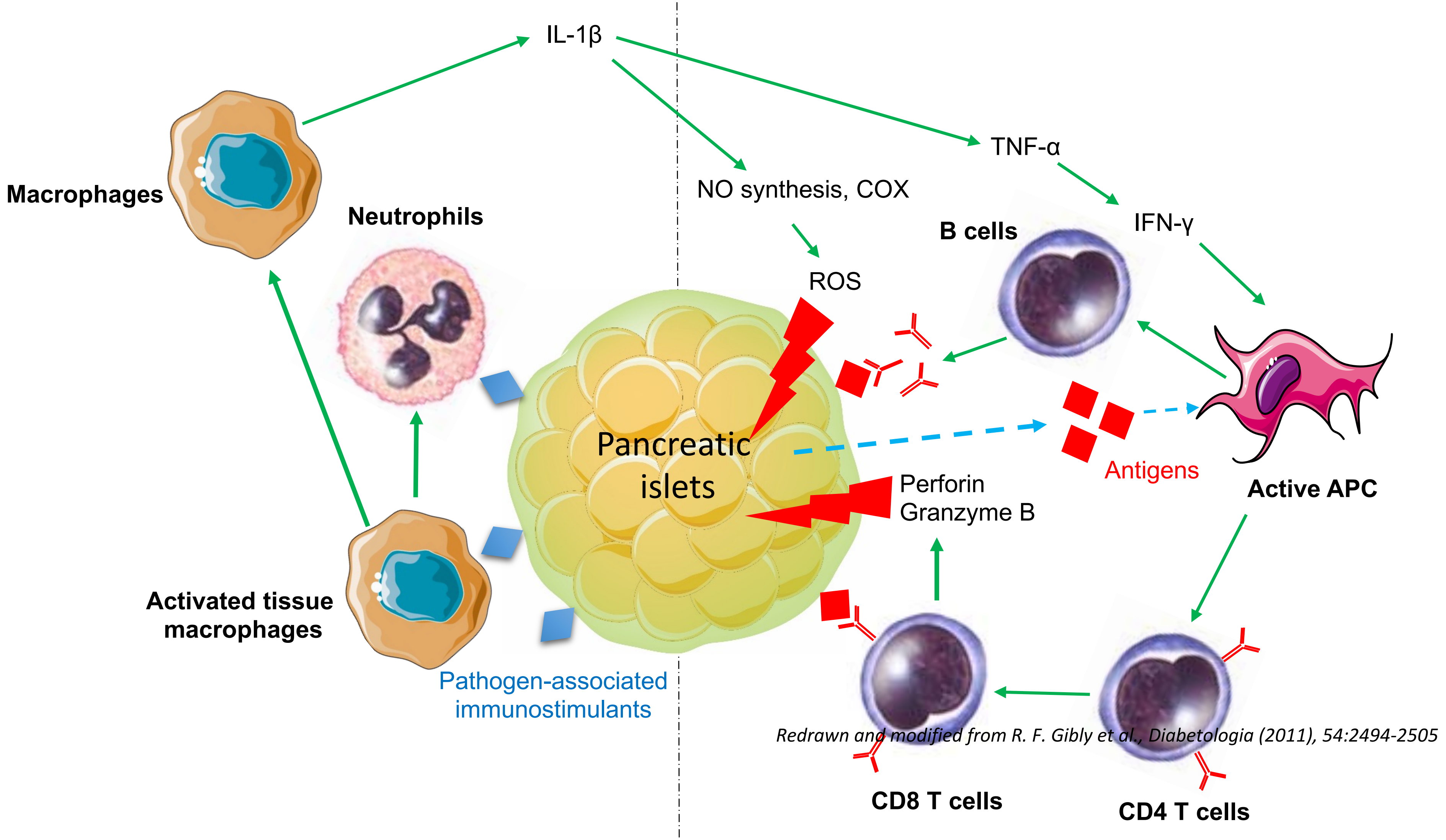
Alginate encapsulation as long-term immune protection of allogeneic pancreatic islet cells transplanted into the omental bursa of macaques

Matthew A. Bochenek[1,2,3,4,5,21], Omid Veiseh[3,4,5,15,16,21], Arturo J. Vegas[3,4,5,17], James J. McGarrigle[1,18], Meirigeng Qi[1], Enza Marchese[1], Mustafa Omami[1], Joshua C. Doloff[3,4,5], Joshua Mendoza-Elias[1,2], Mohammad Nourmohammadzadeh[1,2,19], Arshad Khan[1], Chun-Chieh Yeh[1], Yuan Xing[1,2,20], Douglas Isa[1,18], Sofia Ghani[1,18], Jie Li[3,4,5,15,16], Casey Landry[3,4,5], Andrew R. Bader[3,4,5], Karsten Olejnik[3,4,5,15,16], Michael Chen[3,4,5], Jennifer Hollister-Lock[6], Yong Wang[1,2,20], Dale L. Greiner[7], Gordon C. Weir[6], Berit Løkensgard Strand[8], Anne Mari A. Rokstad[9,10], Igor Lacik[11], Robert Langer[3,4,5,12,13,14], Daniel G. Anderson[3,4,5,12,13,14]* and Jose Oberholzer[1,2,20]*





Immune responses in pancreatic islet transplantation

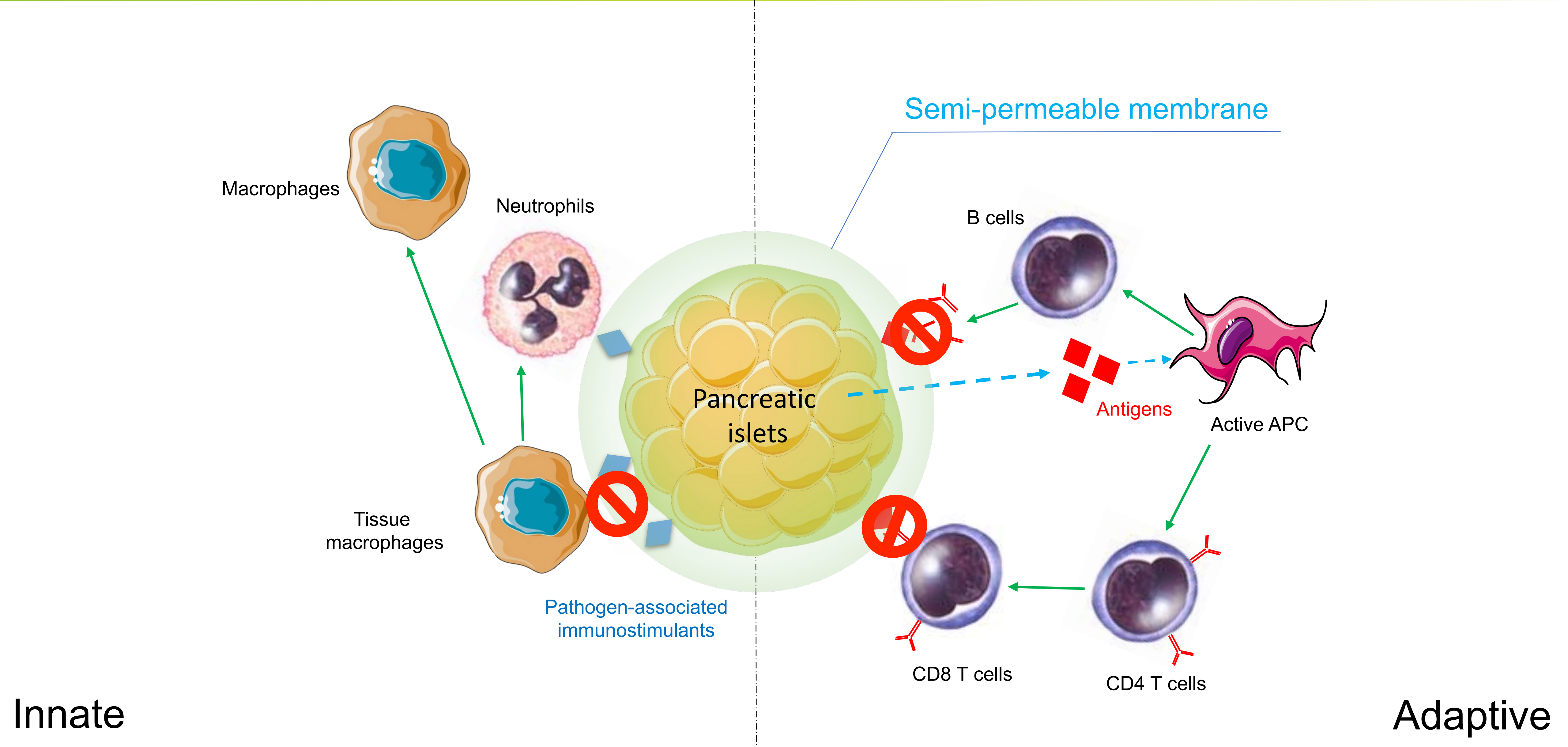


Innate

Adaptive

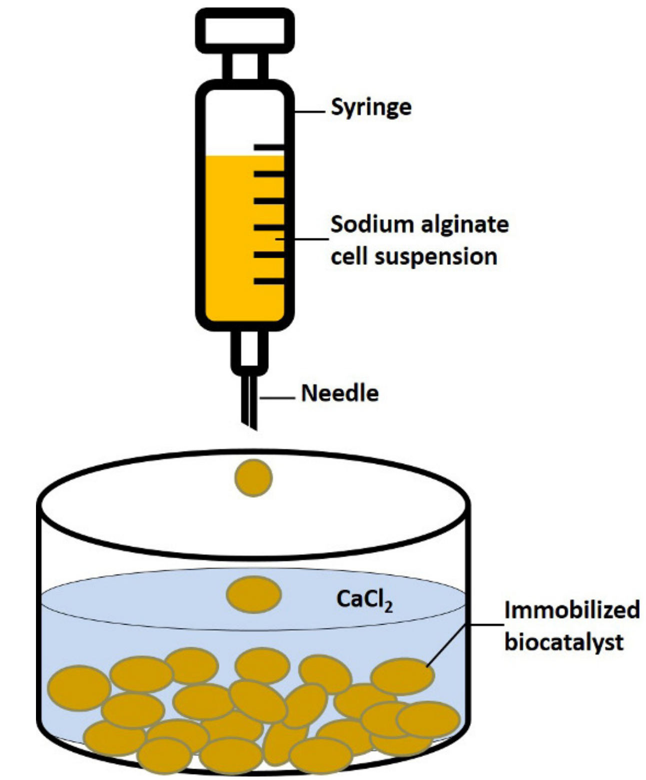
Redrawn and modified from R. F. Gibly et al., Diabetologia (2011), 54:2494-2505

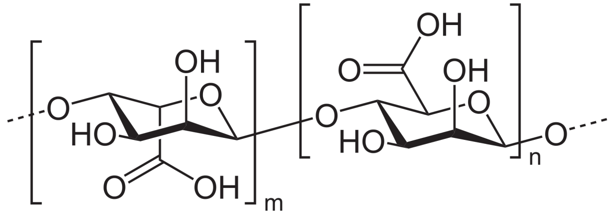
Immunoprotection by alginate encapsulation



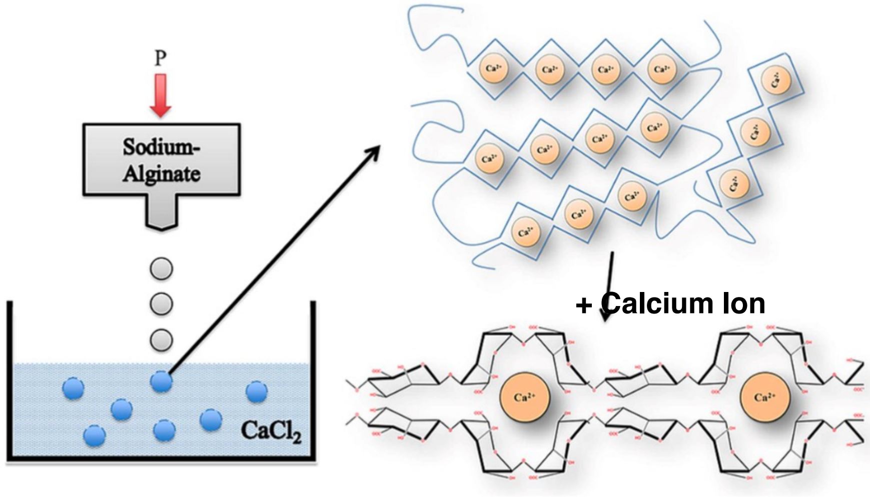
Redrawn and modified from R. F. Gibly et al., Diabetologia (2011), 54:2494-2505

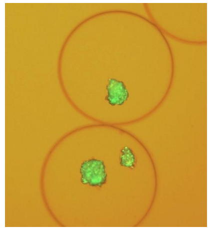
Alginate encapsulation



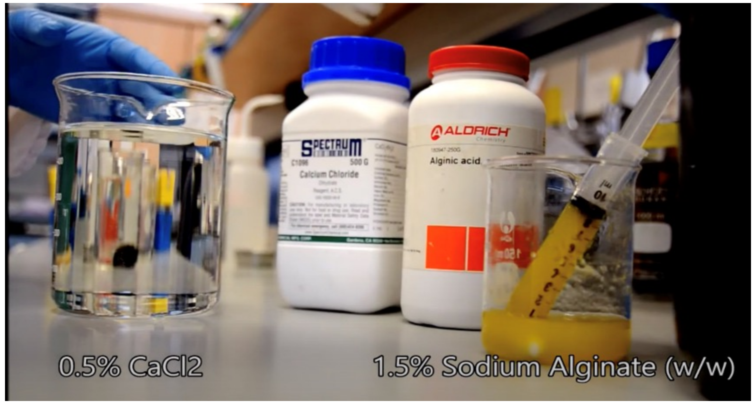


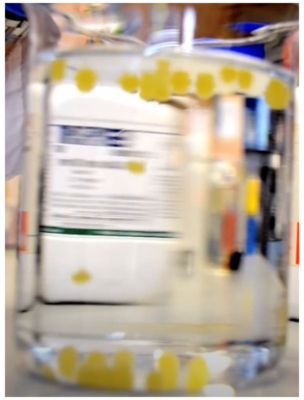
Alginic acid, also called algin, is a naturally occurring, edible polysaccharide found in brown algae.





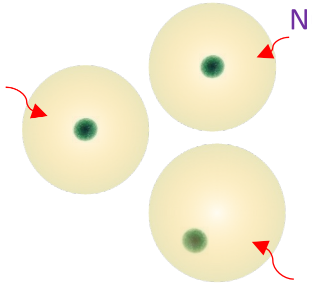
Alginate encapsulated porcine islets





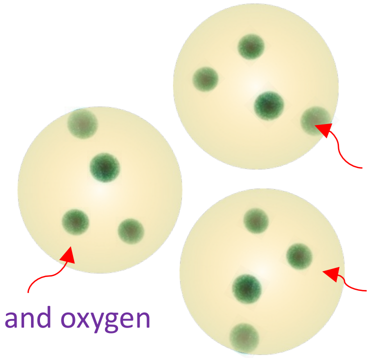
Limitations of droplet-based encapsulation technology

Large capsules

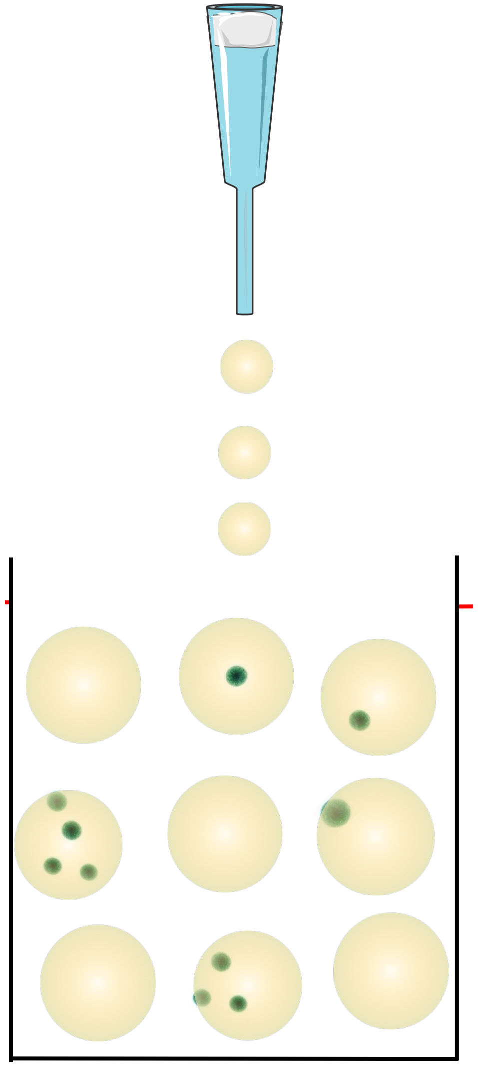


- *Thickness of alginate layer > 150 µm results in insufficient diffusion of nutrients and oxygen.*
- *Larger capsules increase the transplantation volume → limit the transplantation site*

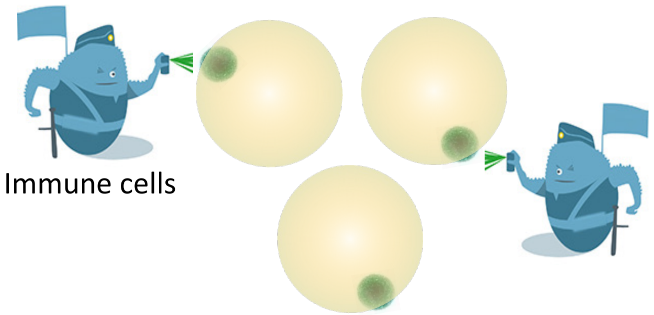
Multi-cell encapsulation



- *Cells experience different levels of nutrients and oxygen, causing biased outcome.*

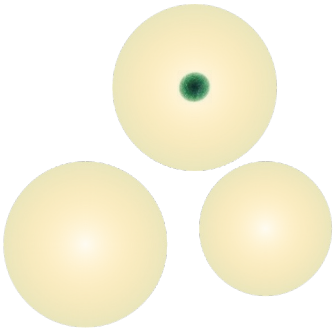


Incomplete encapsulation



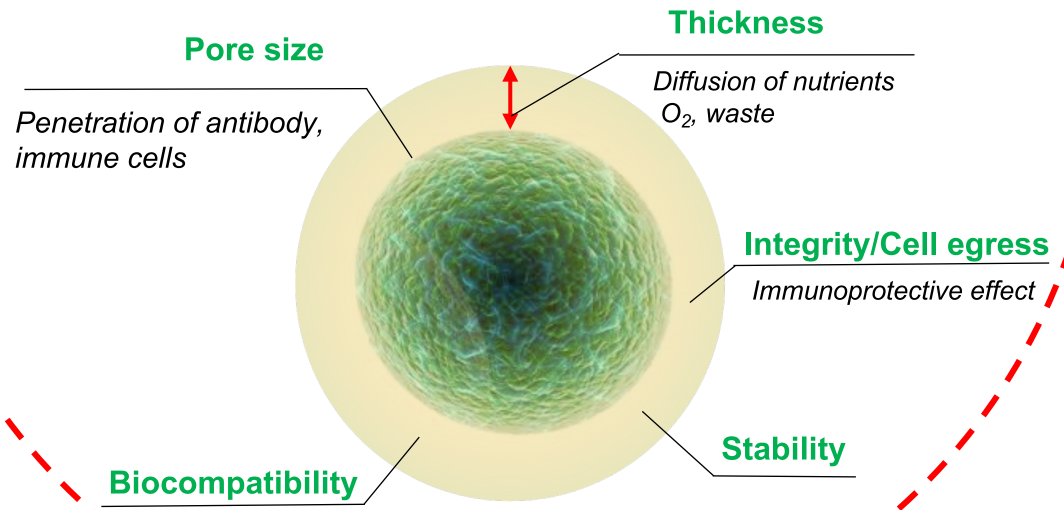
- *More than 20% of capsules containing protruding cells leads to immediate graft failure.*

High percentage of empty capsules

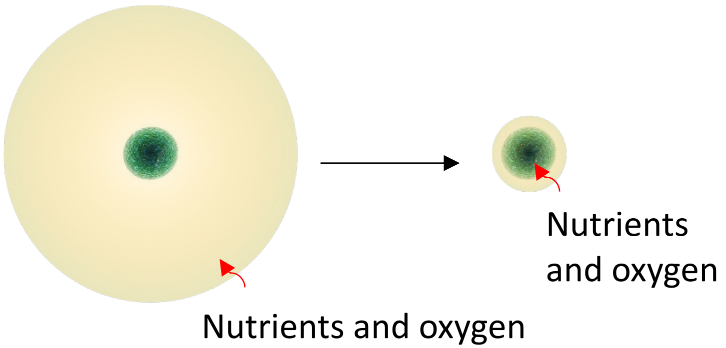


- *High percentage of empty capsules leads to the increase of transplantation volume → limit the transplantation site to only abdominal cavity.*

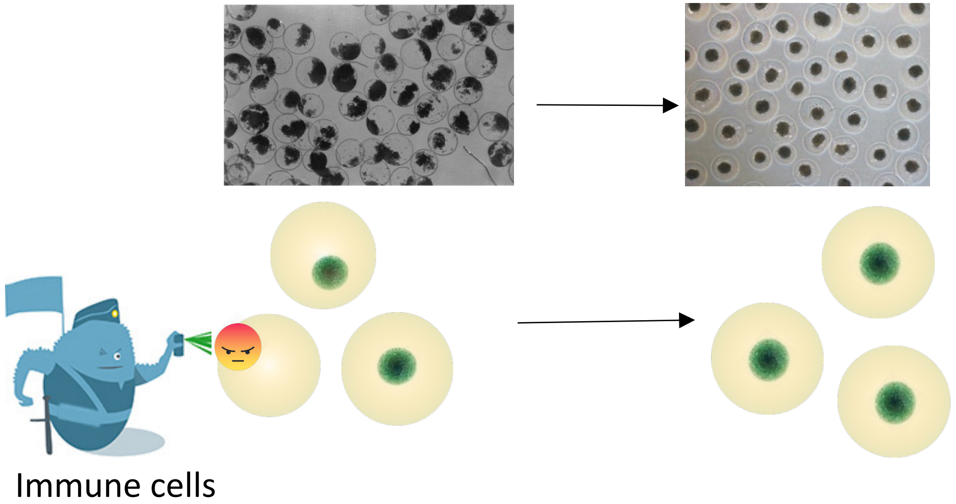
Critical factors in cell encapsulation



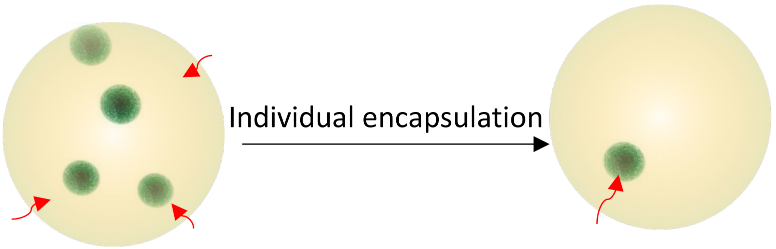
Thin layer cell encapsulation



Complete cell encapsulation

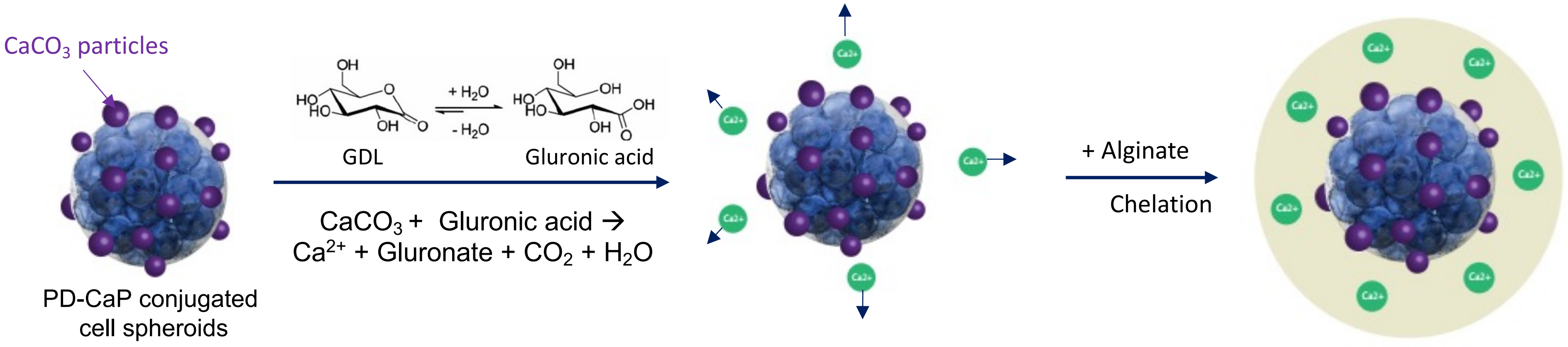


Individual cell encapsulation

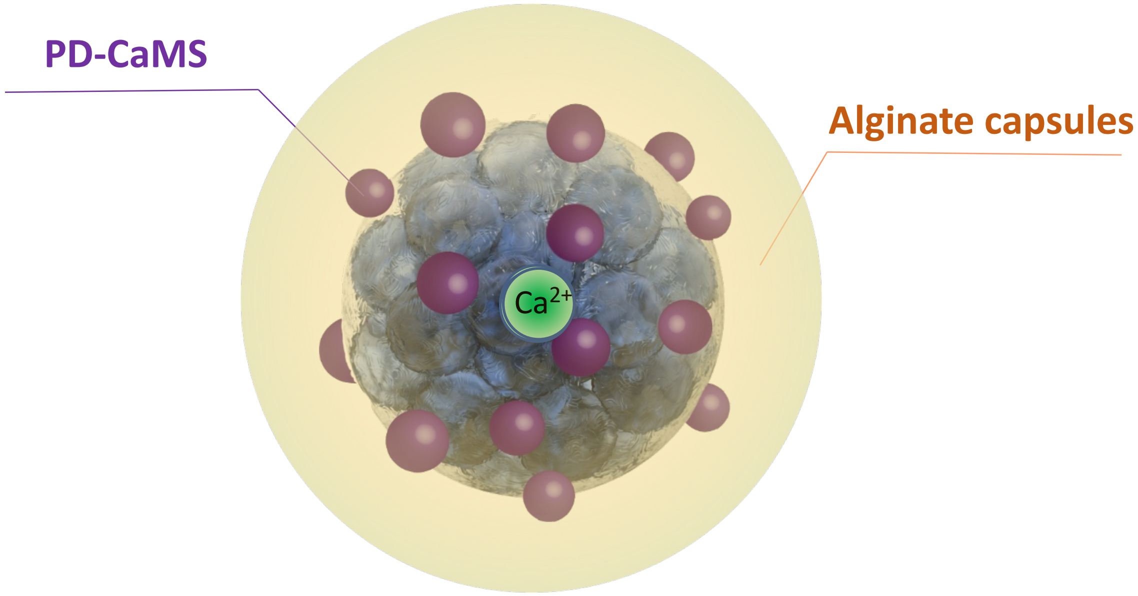


Surface triggering in situ gelation (STIG) for cell encapsulation

Mechanism of STIG



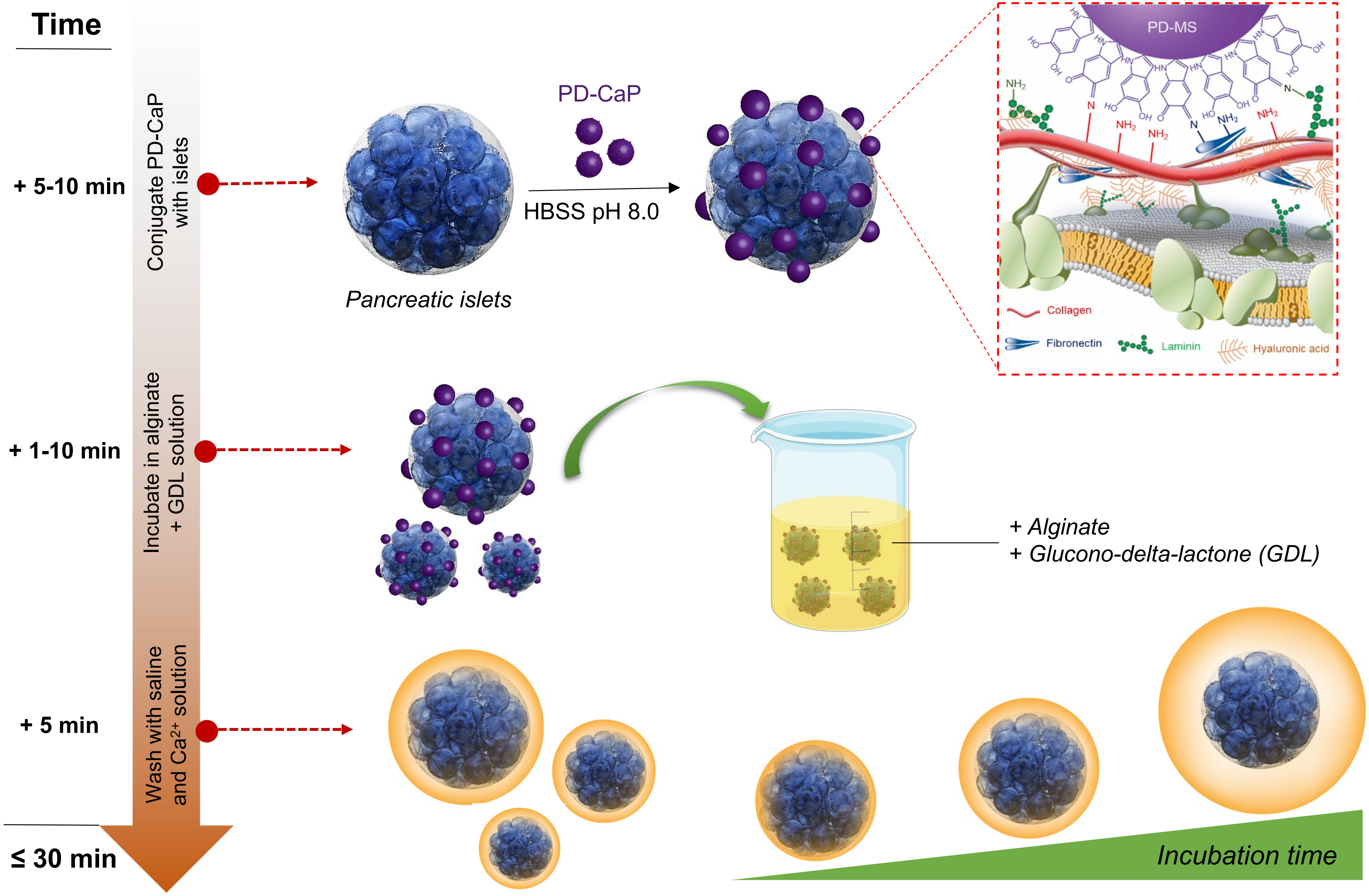
Precisely-controlled thickness of alginate capsule by STIG



- Controllable capsule thickness

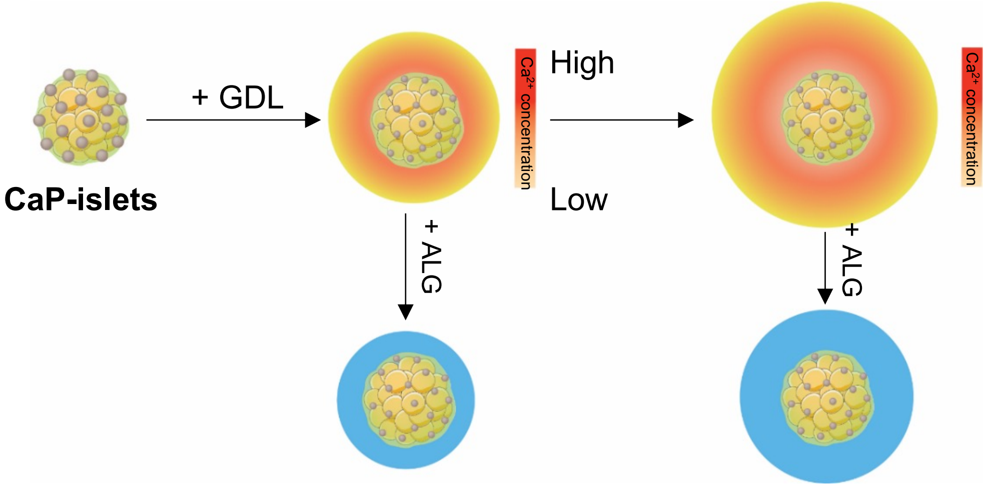
  (1-hundreds of micrometer)
- Complete cell encapsulation
- Individual cell encapsulation
- No empty capsules
- No equipment requirement

STIG for encapsulation of pancreatic islets

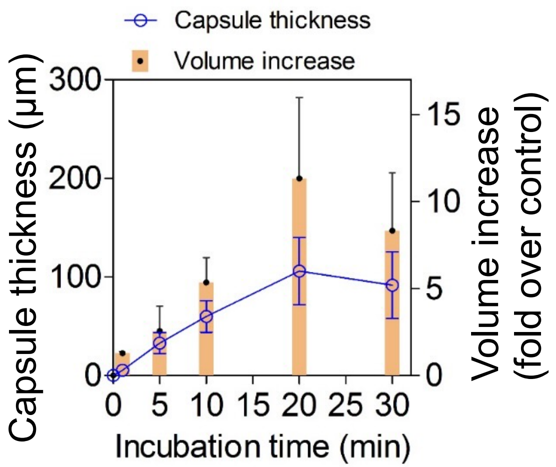


Progressive propagation of alginate capsules by STIG

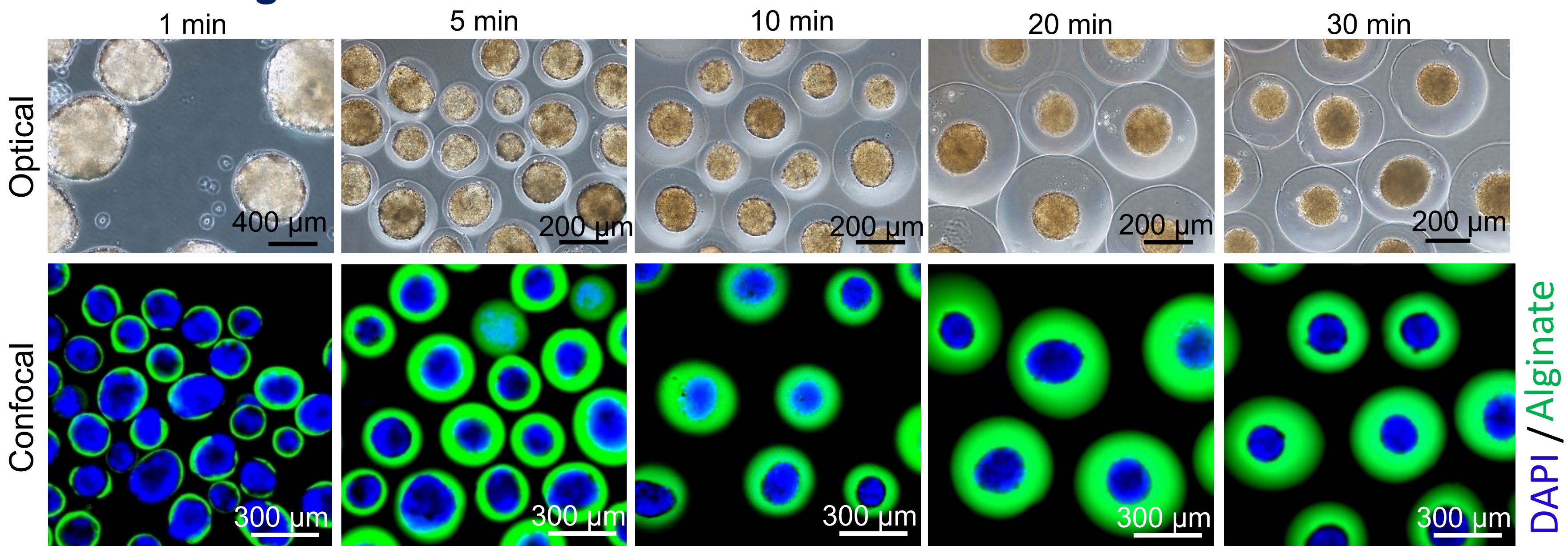
Proposed mechanism



Tunable thickness by STIG



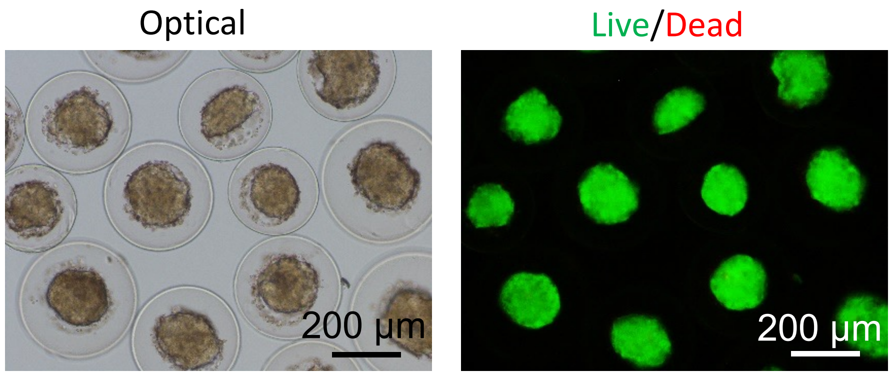
Optical & confocal images



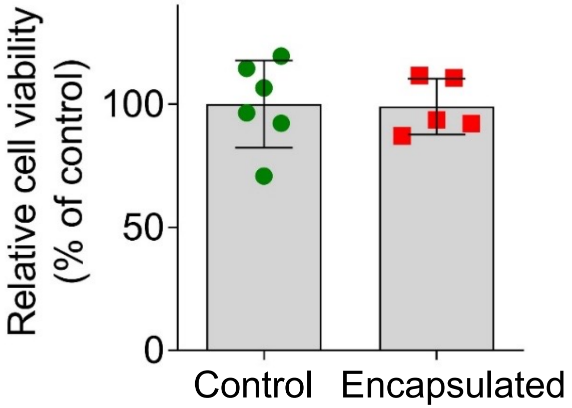
Impacts of encapsulation on islet viability and functionality

Viability

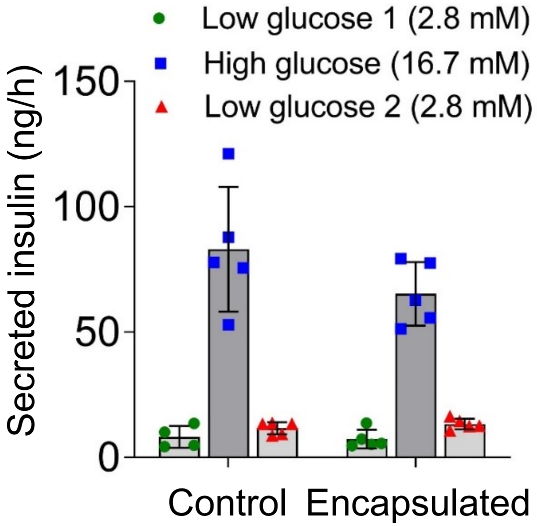
Live/dead staining



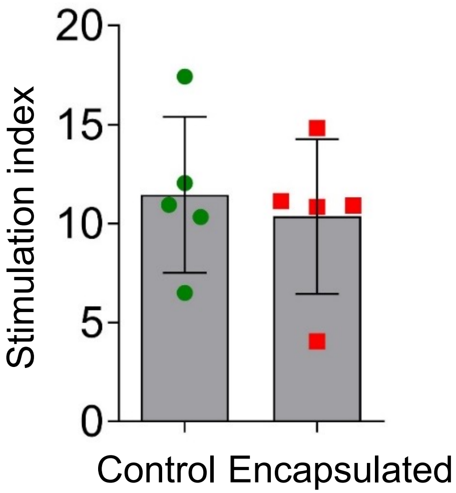
CCK-8 assay



Glucose-stimulated insulin secretion

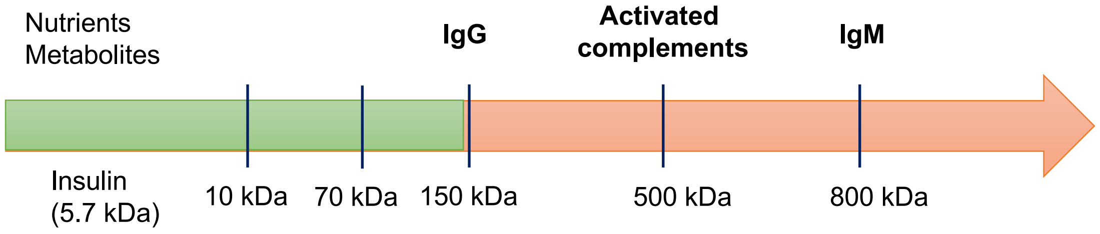


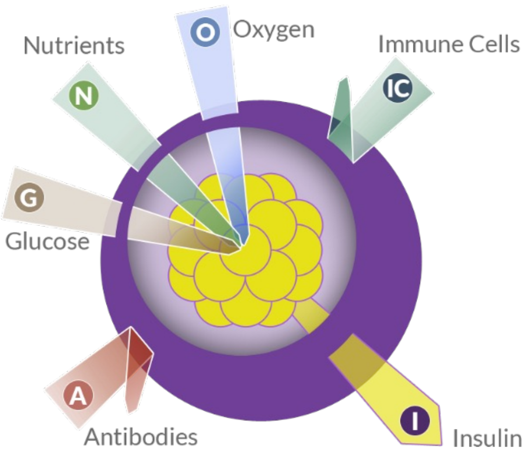
Stimulation index



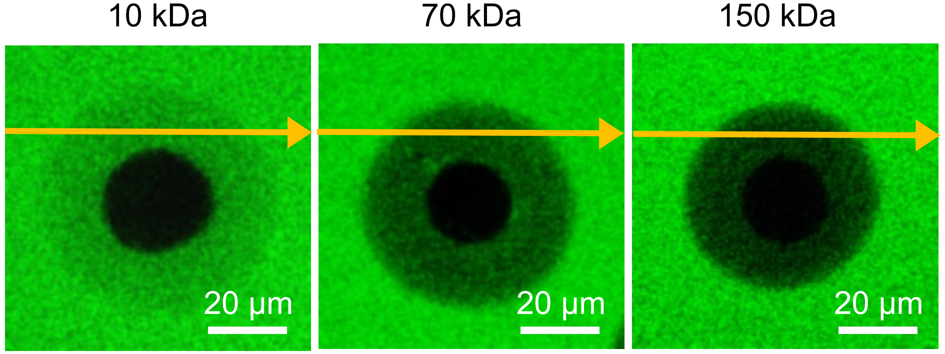
Selective permeability of alginate capsules

Immunoisolation by selective permeability

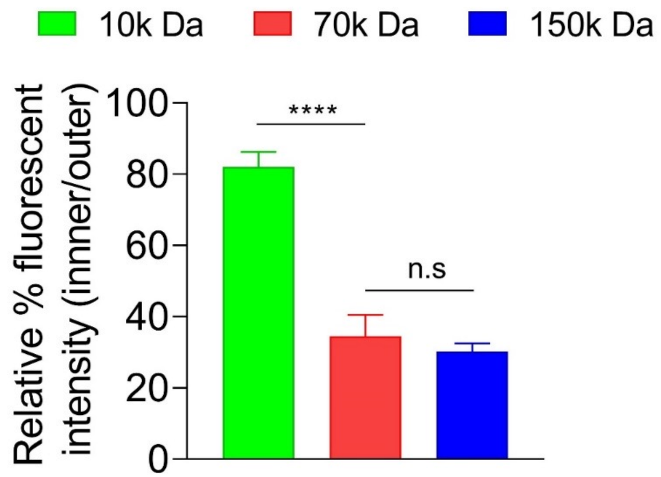




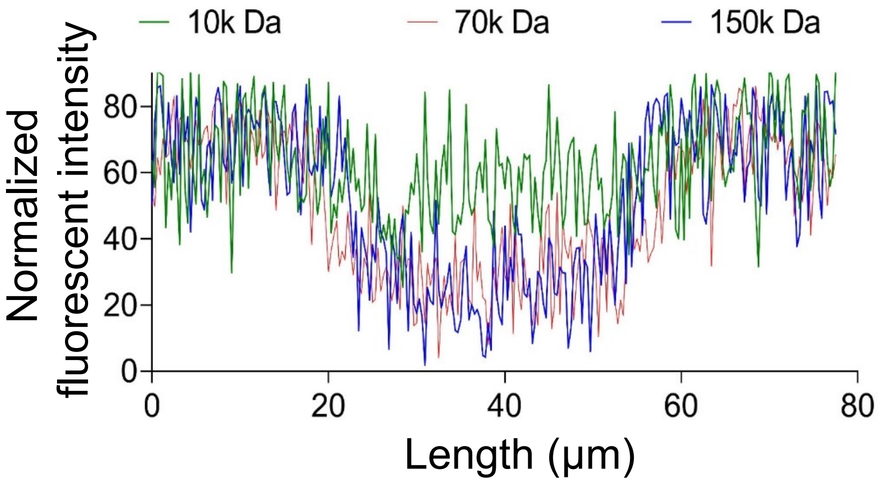
Confocal images



Relative diffusion rate



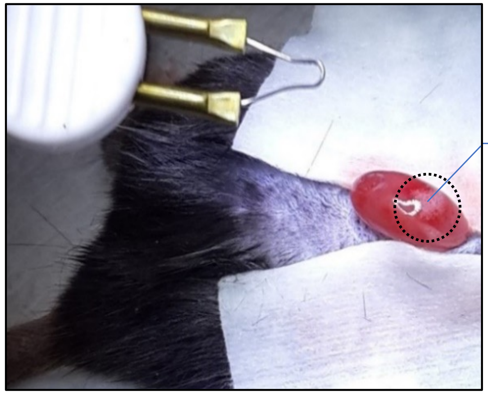
Fluorescence intensity profiles



In vivo islet transplantation

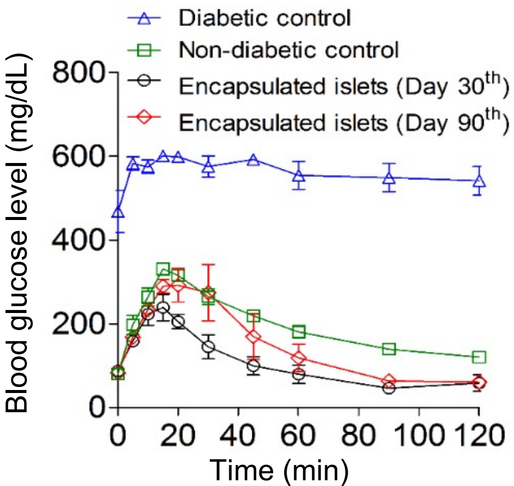
Method

- ❖ **Donor**: Male SD rats
- ❖ **Recipient**: Male C57BL/6 mice
- ❖ **Transplantation site**: Kidney capsule
- ❖ **Mass of islets**: 400 IEQ

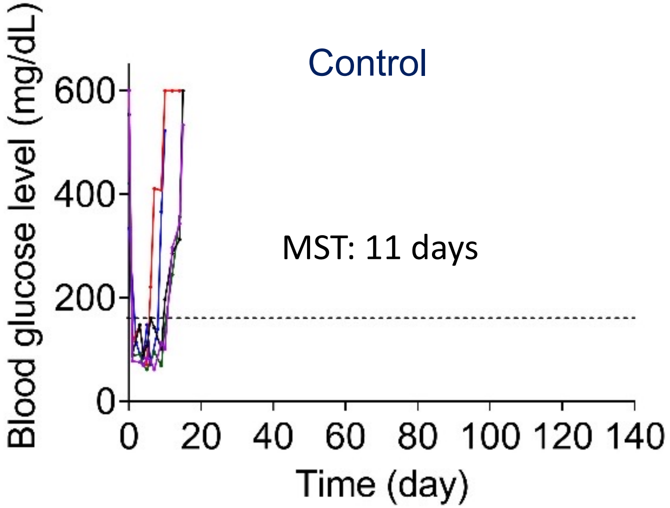


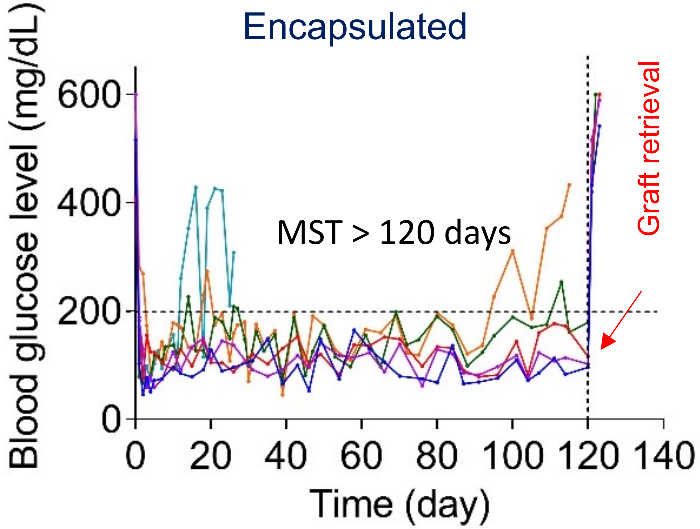
Transplanted islets

Intraperitoneal glucose tolerance test



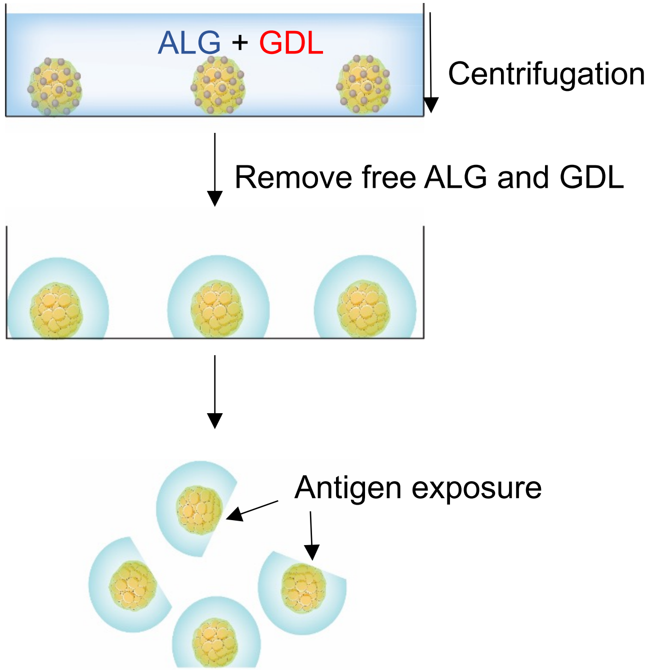
Non-fasting blood glucose levels



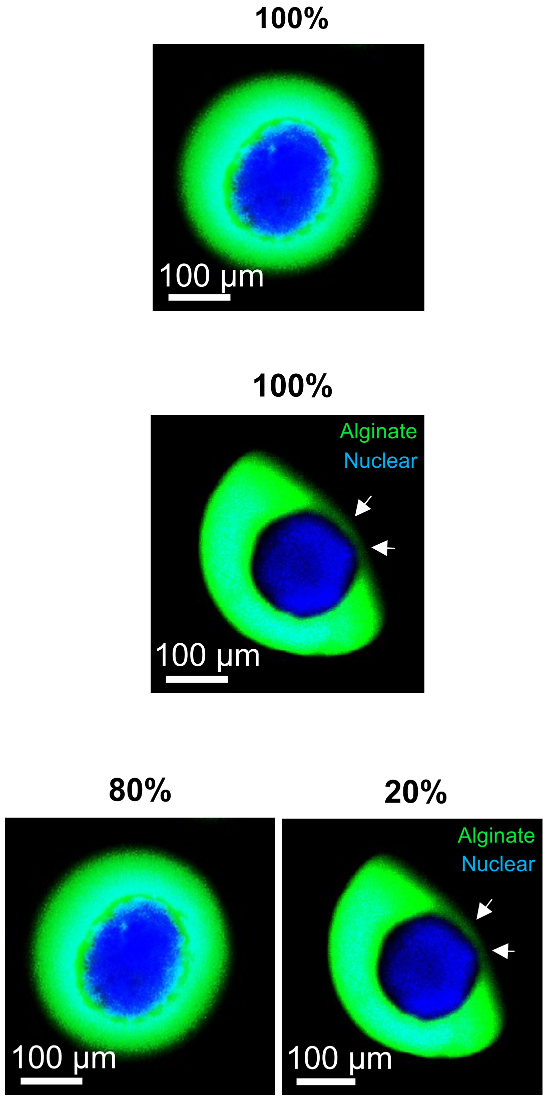


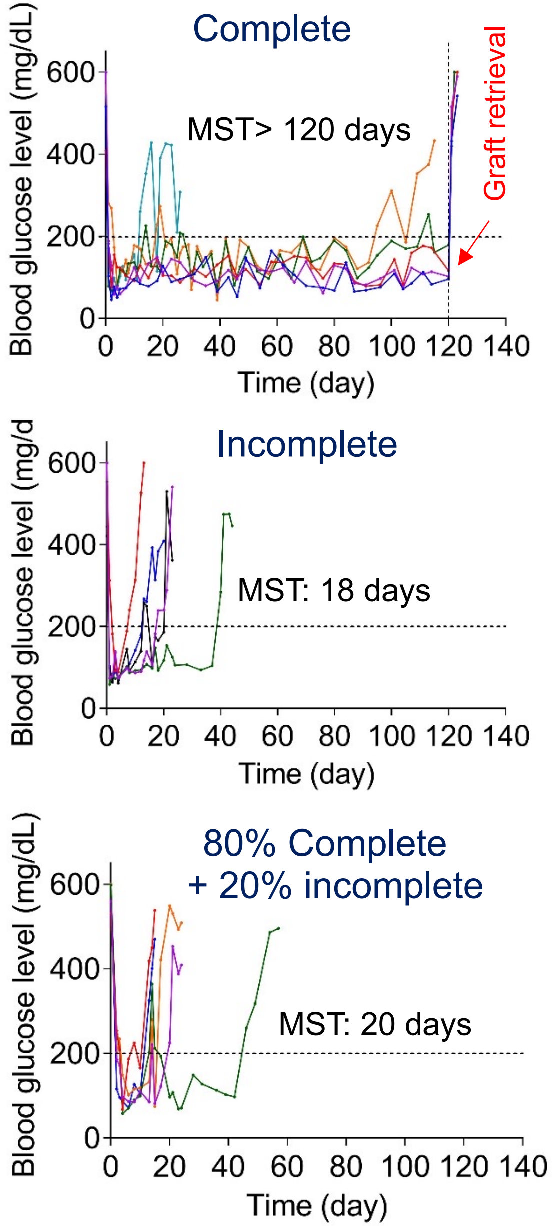
Role of complete encapsulation on islet survival

Preparation of incomplete capsules

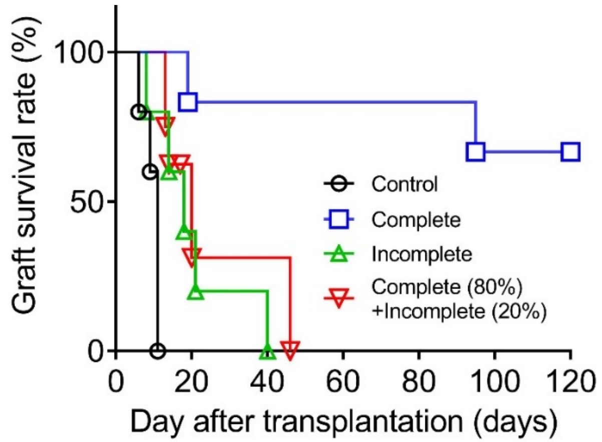


Confocal images



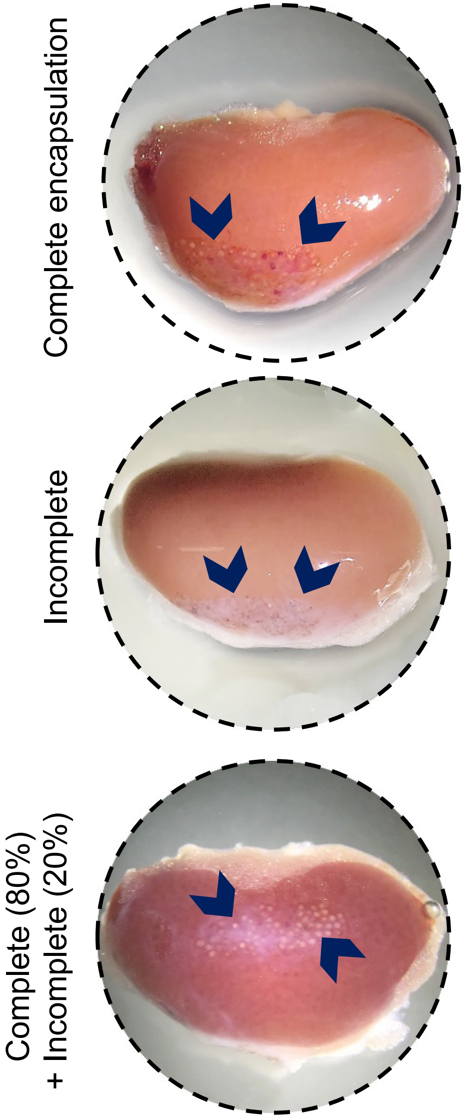


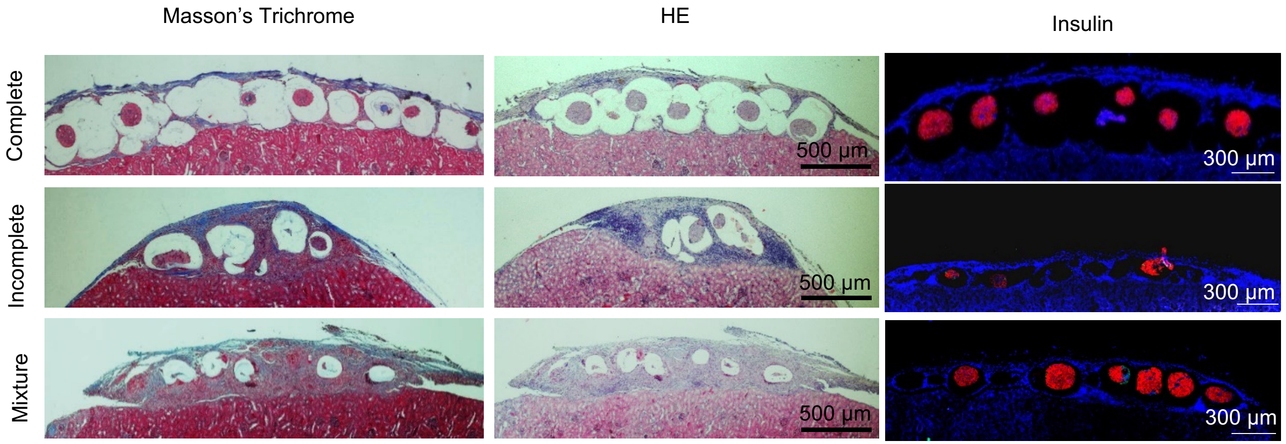
Graft survival rate

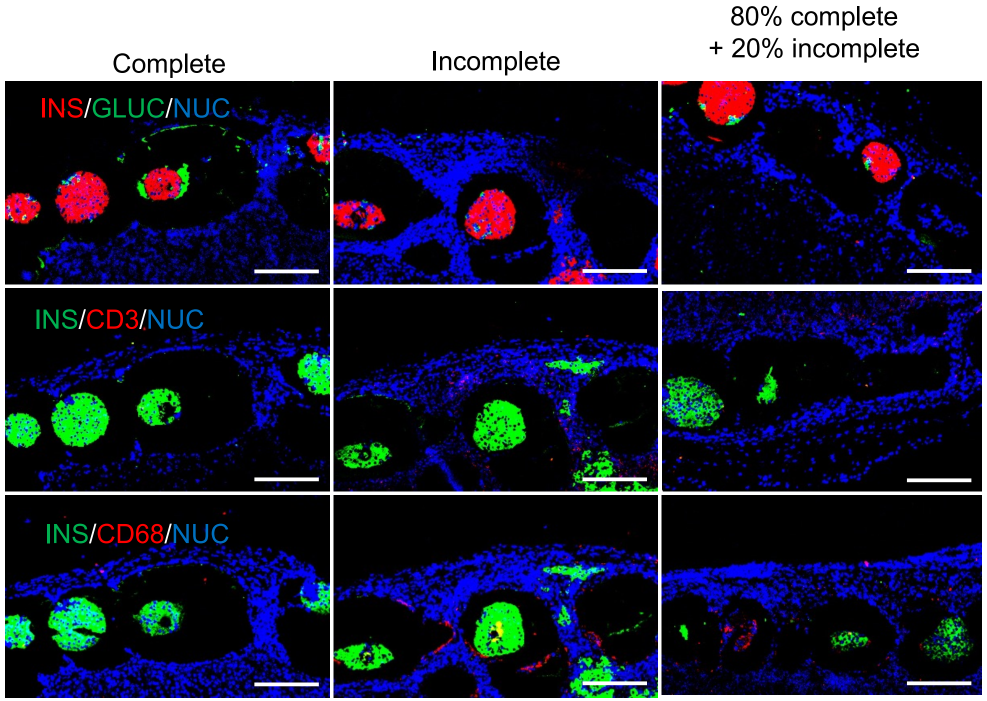


Evaluation of encapsulated islets after transplantation

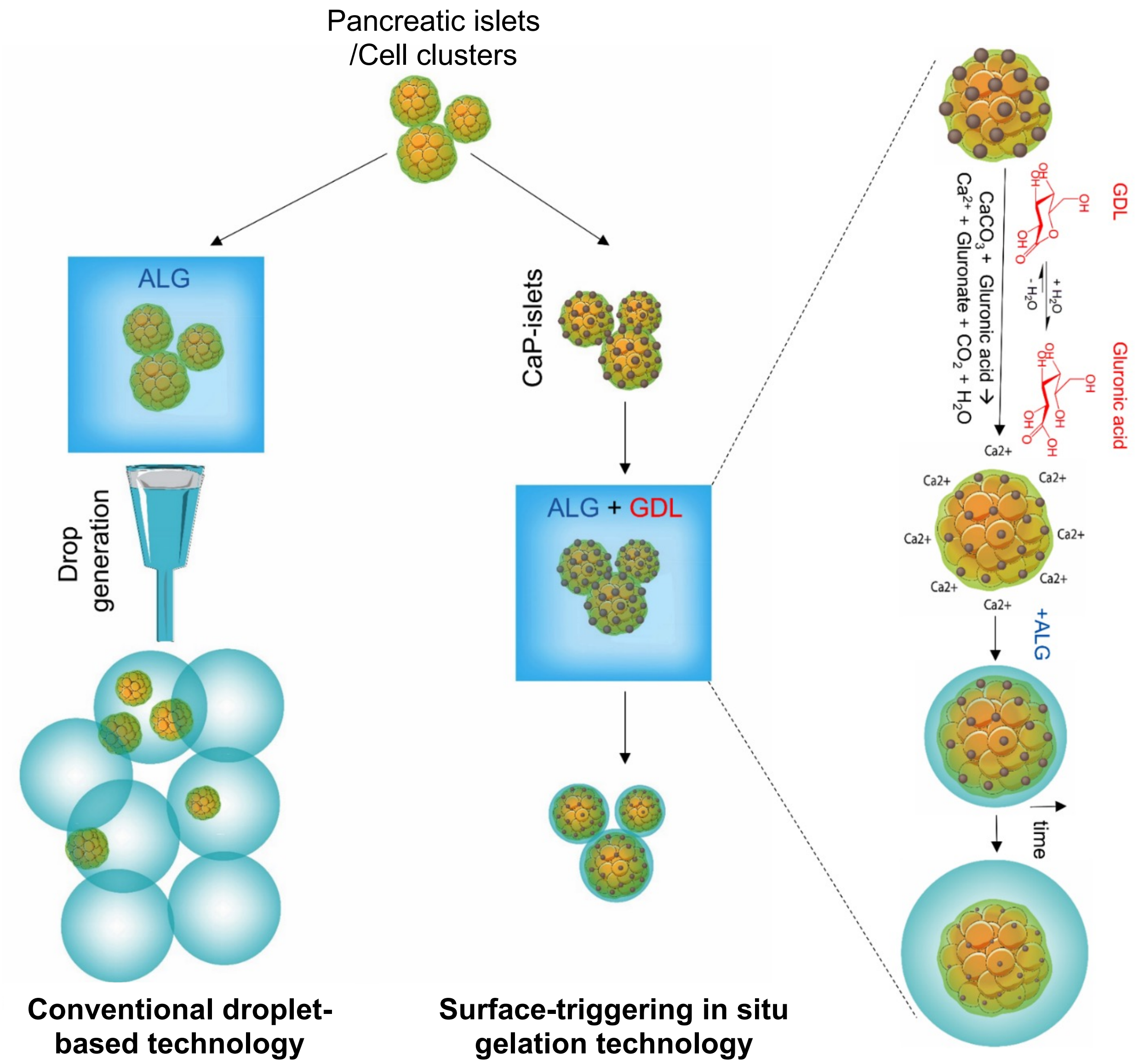
Graft retrieval







Surface triggering in situ gelation (STIG) for cell encapsulation

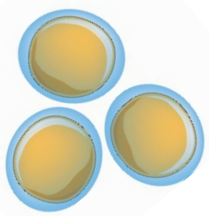


Advantages

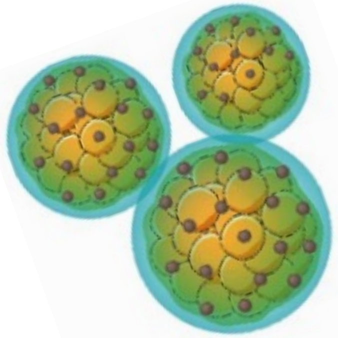
- Easy manufacturing into a kit form (only includes basic materials: calcium carbonate particles, alginate + GDL mixture, HBSS solution, Ca^{2+} and Ba^{2+} solution).
- FDA-approved materials.
- Can be performed in all labs and transplantation center without the need for specific devices.
- Can be applied for multiscale objects (from single cells to cell clusters to biomedical devices).

Conformal coating of multi-scale cells and biomedical devices

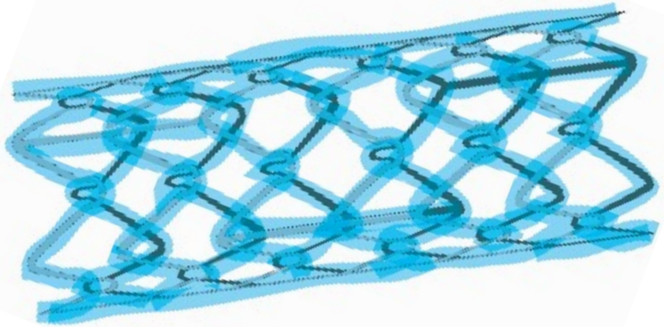
Single cells



Cell clusters/Organoids



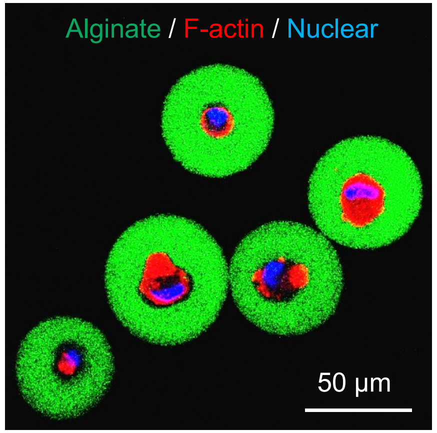
Biomedical devices

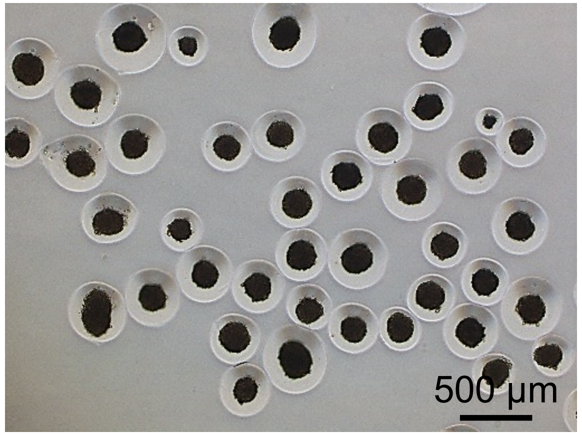


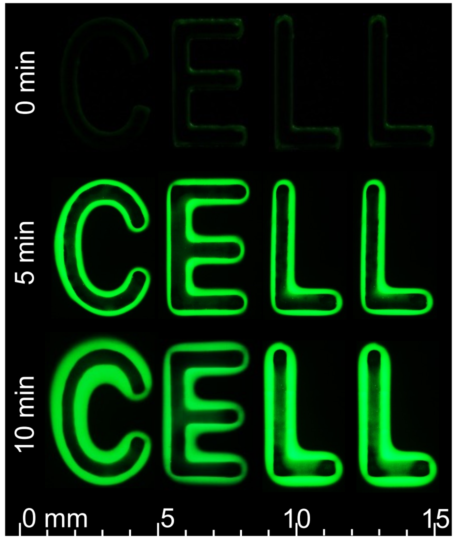
Individual encapsulation of stem cells

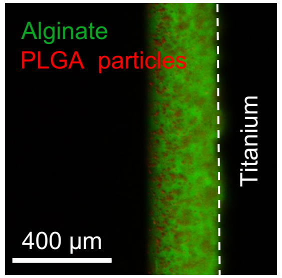
Individual encapsulation of pancreatic islets

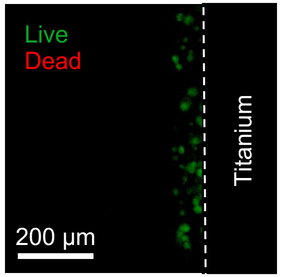
Universal conformal hydrogel coating





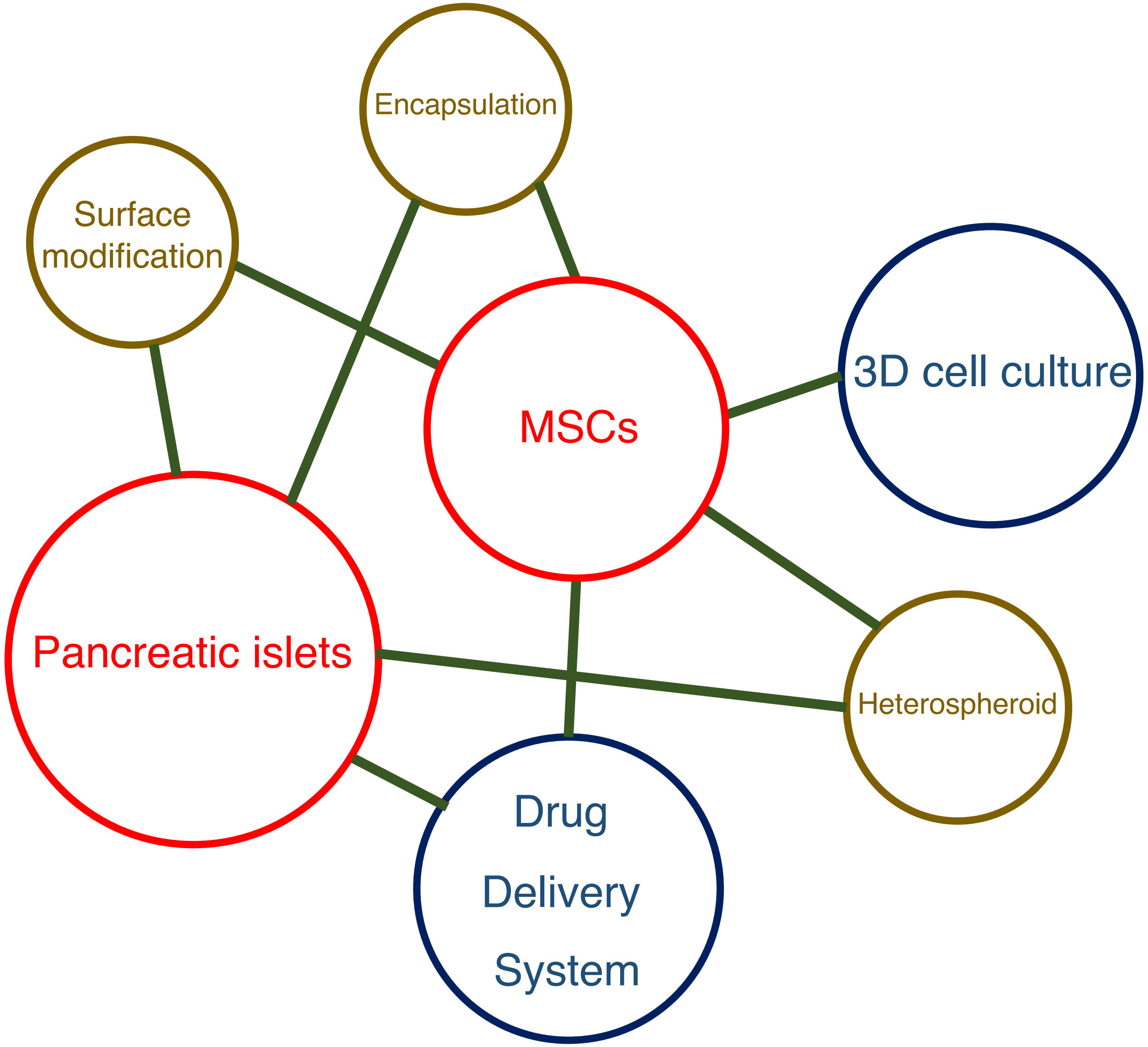






T.T. Pham et al. Advanced Functional Materials, 2021

Lab interconnected keyworks



Acknowledgements

Prof. Jee-Heon Jeong, Ph.D

Pathak Shiva, Ph D.

Pham Thanh Tung, Ph D.

Regmi Shobha, Ph D.

Tiep Tien Nguyen, Ph D.

Dong-Ho Ha, MS.

Tran Le Phuong, Ms.

Sunghoon Lee, Ms.

Prakash Shrestha, Ph D. Student

Jun Hyung Park, Ph D. Student

Manju Shrestha, Ph D. Student

Grants

NRF 한국연구재단

KFRM 범부처재생의료기술개발사업단 Korean Fund for Regenerative Medicine

ATIS 농촌진흥사업 종합관리시스템 Agriculture science Technology Information System

FOUR BrainKorea21

KANG STEM BIOTECH

Collaboration

Yeungnam University

Prof. Jong-Oh Kim, Ph.D.

Prof. Pil-Hoon Park, Ph.D.

Prof. Jae-Ryong Kim,MD. Ph.D.

Prof. Il-kug Kim, MD. Ph.D.

Prof. Hyukjae Choi. Ph.D.

Prof. Joo Won Nam. Ph.D.

Pusan National University

Prof. Jin-Wook Yoo, Ph.D.

Prof. Hyungsik Kim, D.V.M., Ph.D.

Keimyung University

Prof. Simmyung Yook, Ph.D.

The Catholic University of Korea

Prof. Jun-Beom Park, D.D.S., Ph.D.