



## ISLET CELL ENCAPSULATION IN BIOCOMPATIBLE SCAFFOLDS FOR DIABETES MANAGEMENT

Krishnapriya P. G.<sup>1\*</sup>, Lal Prasanth M. L.<sup>2</sup> and Hiba Fathima<sup>3</sup>

<sup>1</sup>Assistant Professor, Dr Moopen's College of Pharmacy, Wayanad.

<sup>2</sup>Principal, Dr Moopen's College of Pharmacy, Wayanad.

<sup>3</sup>B. Pharm Student, Dr Moopen's College of Pharmacy, Wayanad.



\*Corresponding Author: Krishnapriya P. G.

Assistant Professor, Dr Moopen's College of Pharmacy, Wayanad.

Article Received on 17/09/2024

Article Revised on 07/10/2024

Article Accepted on 27/10/2024

### ABSTRACT

Islet cell encapsulation represents a cutting-edge strategy designed to enhance diabetes treatment, especially for those with type 1 diabetes. This method involves encasing insulin-producing islet cells within biocompatible, semipermeable substances, which protect them from the body's immune response while permitting the flow of nutrients, oxygen, and insulin. Such an approach could enable long-lasting insulin management without the reliance on immunosuppressive medications. Recent improvements in encapsulation methods, including new biomaterials and microencapsulation processes, are promising in boosting the survival, functionality, and integration of islet cells after transplantation, bringing us closer to developing more efficient and less invasive therapies for diabetes.

**KEYWORDS:** Encapsulation, Biocompatible, Microencapsulation, Islet cells.

### 1. INTRODUCTION TO DIABETES MELLITUS

Diabetes mellitus may be a bunch of physiological dysfunctions characterized by hyper-glycemia coming about specifically from affront resistance, lacking affront discharge, or over the top glucagon emission.<sup>[1]</sup> It is the foremost common endocrine clutter and by the year 2010, it is evaluated that more than 200 million individuals around the world will have DM and 300 million will in this way have the illness by 2025. As the illness advances tissue or vascular harm results driving to serious diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. In this way, diabetes covers a wide extend of heterogeneous maladies.<sup>[2]</sup>

#### 1.1 Types of diabetes

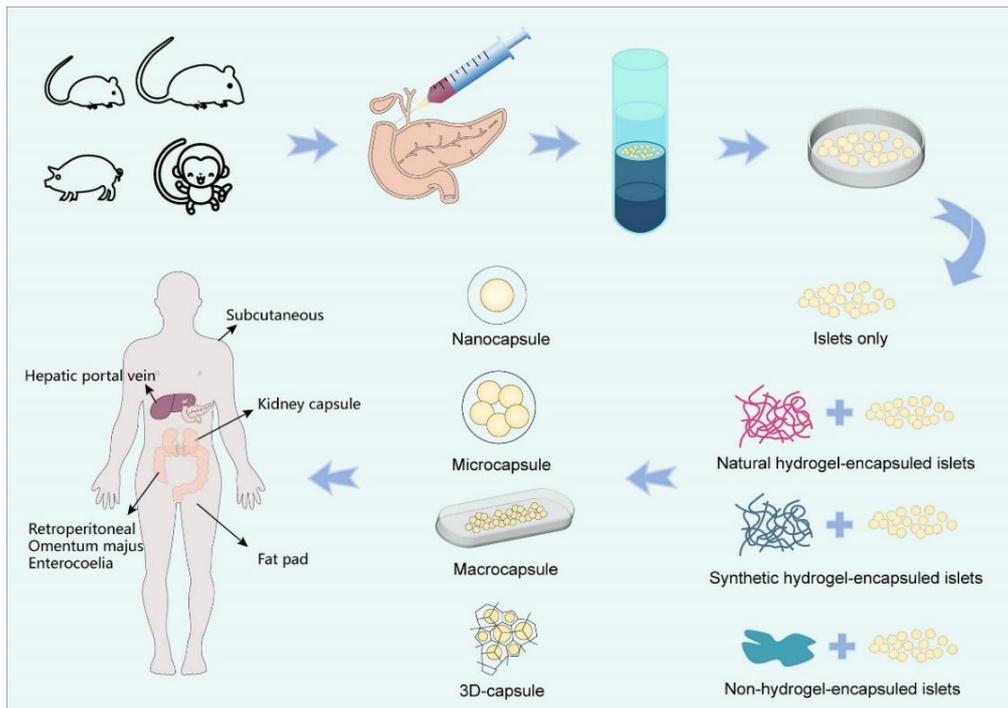
Type 1 diabetes is an immune system condition where the body assaults insulin-producing cells within the pancreas. This sort regularly creates in childhood or early adulthood and requires every day affront injections.<sup>[3]</sup> Type 2 diabetes, the foremost common frame, happens when the body gets to be safe to affront or doesn't deliver sufficient of it.<sup>[4]</sup> It is regularly related with way of life variables like slim down and physical movement.<sup>[4]</sup> Gestational diabetes happens amid pregnancy and as a rule settle after childbirth.<sup>[5]</sup>

#### 1.2 Clinical presentation

Common indications of diabetes incorporate visit urination, over the top thirst, starvation, weakness, and obscured vision. In any case, side effects can be gentle or missing, especially in Type 2 diabetes, making early determination troublesome.<sup>[6]</sup> Diabetes is analyzed through blood tests that degree blood sugar levels, such as fasting blood glucose tests or the A1C test, which gives a normal of blood sugar levels over the past few months.<sup>[7]</sup>

#### 2. Islet cell encapsulation

Islet cell epitome is a developing exploratory procedure pointed at progressing the treatment of diabetes, especially Type 1 diabetes.<sup>[8]</sup> The epitome handle includes encasing these islet cells in a biocompatible fabric that secures them from safe framework assault whereas permitting them to discharge affront in reaction to blood sugar levels. By protecting the cells, epitome holds the guarantee of diminishing or dispensing with the require for long lasting affront treatment or immunosuppressive drugs, which are ordinarily required after islet transplantation.<sup>[9]</sup>



**Figure 1.1: Steps involved in the encapsulation process.**

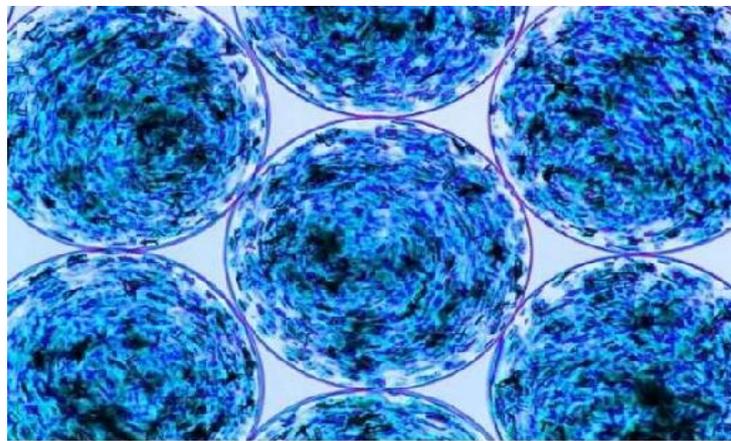
### 2.1 Isolation of islet cells

The pancreas is to begin with gotten from a perished or living giver beneath sterile conditions. It is transported in cold conservation arrangement to preserve cell practicality some time recently assist handling.<sup>[10]</sup> The pancreas is at that point dismembered to evacuate undesirable tissues, such as fat and connective tissue, guaranteeing as it where the practical parcel of the organ is utilized.<sup>[11]</sup> To discharge islet cells from the pancreas, the tissue is subjected to enzymatic assimilation.<sup>[10]</sup> Chemicals like collagenase are imbued into the pancreatic channels to break down the extracellular network. This can be regularly taken after by mechanical absorption, ordinarily utilizing shaking or tumult, to assist extricate the islets from the encompassing tissue.<sup>[12]</sup> The wellbeing of these cells is basic, as it where practical islet cells can be utilized for transplantation or advance inquire about.<sup>[10]</sup>

### 2.2 Microencapsulation

Microencapsulation of islet cells is a progressed biotechnological procedure outlined to secure insulin-producing islets from the resistant framework when transplanted into diabetic patients, especially those with Type 1 diabetes. This approach includes encasing islet cells in a semi-permeable film, which permits basic supplements and oxygen to pass through whereas anticipating resistant cells and antibodies from assaulting the typified islets.<sup>[13]</sup>

The biomaterial used for encapsulation are usually obtained from natural sources due to their compatible nature with the environment of implantation site. Their biodegradable nature poses the advantage of retrieval and renewal process.<sup>[12]</sup>



**Figure 1.2 Microcapsules containing islet cells.**

### 2.2.1 Materials utilized for microencapsulation

The materials utilized in microencapsulation are significant for guaranteeing biocompatibility and usefulness. Commonly utilized materials incorporate alginate, an actually happening polysaccharide that shapes gel-like capsules around the cells.<sup>[14]</sup> Alginate is broadly favored due to its biocompatibility, ease of utilize, and capacity to create a defensive obstruction.<sup>[13]</sup> Other materials like polyethylene glycol (PEG) and poly (ethylene glycol)-based hydrogels have too been investigated to improve the strength and defensive highlights of the microcapsules.<sup>[14]</sup>

### 2.2.2 Embodiment prepare

The epitome prepare starts with the confinement of practical islet cells from a giver pancreas. Once isolated, the cells are suspended within the chosen typifying fabric, such as an alginate arrangement.<sup>[15]</sup> The arrangement is at that point subjected to a crosslinking handle, regularly utilizing calcium particles, which actuates the arrangement of little, uniform capsules around the islet cells.<sup>[12]</sup>

### 2.3 Macroencapsulation

Macroencapsulation is an inventive method utilized to secure transplanted cells, such as islet cells for diabetes treatment, inside bigger, defensive gadgets or capsules.<sup>[18]</sup> Not at all like microencapsulation, which employments little, person capsules for each cell or little cluster of cells, macroencapsulation includes inserting a bigger mass of cells in a single gadget or chamber.<sup>[19]</sup> This strategy points to supply a more organized, controlled environment for cell survival and work, whereas moreover advertising assurance from the resistant framework.<sup>[18]</sup>

Sheet-based macroencapsulation gadgets comprise of level, lean films that house a layer of cells between two porous sheets. These sheets are made from biocompatible materials like alginate or polymer layers that permit the dissemination of oxygen, supplements, and affront, but piece bigger resistant cells from entering.<sup>[16]</sup> These gadgets are ordinarily embedded subcutaneously (underneath the skin). Their lean plan makes a difference guarantee proficient supplement and oxygen trade, which is vital for cell survival.<sup>[17]</sup>

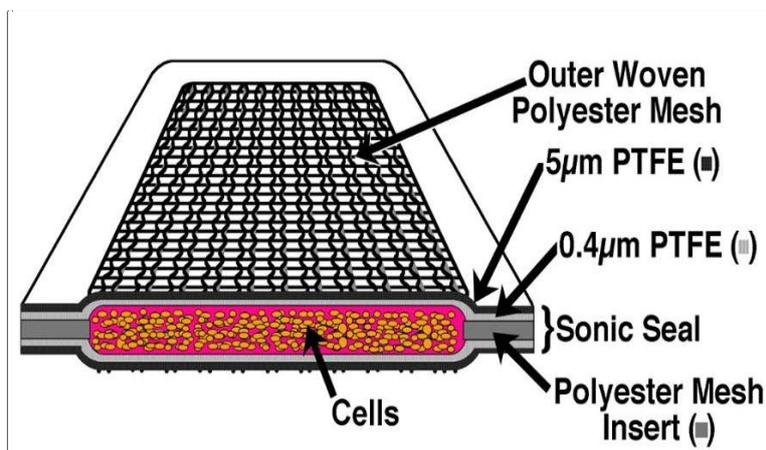


Figure 1.3: Silicon based sheet device.

### 3. Challenges to encapsulation method

The immune system's response to the encapsulation device itself is one of the primary obstacles to islet cell encapsulation. The body can still identify the device as foreign and mount an immunological reaction even though the encapsulating materials are intended to shield the islet cells from direct immune attack. Fibrosis, or the creation of scar tissue, is frequently the result around the encapsulating device. The function and viability of the encapsulated islet cells can be severely reduced by fibrosis, which can hinder the flow of oxygen, nutrients, and insulin across the encapsulation barrier.<sup>[22]</sup>

Providing encapsulated islet cells with an adequate supply of oxygen and nutrients is still a significant difficulty. Low oxygen levels in the enclosed cells can result from encapsulation devices restricting oxygen transport, especially in larger macroencapsulation systems. Hypoxia can result in cell death and lessen the islet cells' capacity to control blood sugar. Although the

dispersion of smaller, microencapsulated systems can be enhanced, the thinner protective covering of these systems may make them more vulnerable to immune assaults.<sup>[21]</sup>

Over time, encapsulated islet cells may become less viable, especially if they are exposed to unfavorable circumstances like starvation or inadequate oxygenation. It can be difficult to preserve the islet cells' long-term survival and functionality, even in cases when the encapsulating device is initially effective. These limitations cause many encapsulated cells to not survive past the first several weeks or months.<sup>[20]</sup>

### 4. Strategies to improve oxygen supply

Embodiment materials with tall oxygen penetrability, such as perfluorocarbons or silicone-based polymers, can improve the dissemination of oxygen to the typified cells.<sup>[24]</sup> These materials permit superior oxygen trade whereas still ensuring the cells from resistant assault.<sup>[25]</sup>

Implanting oxygen-releasing compounds (e.g., calcium peroxide or magnesium peroxide) inside the epitome lattice can give a supported discharge of oxygen. These compounds generate oxygen in situ, making a difference

to preserve higher oxygen levels around the typified cells, especially within the early stages after implantation.<sup>[26]</sup>

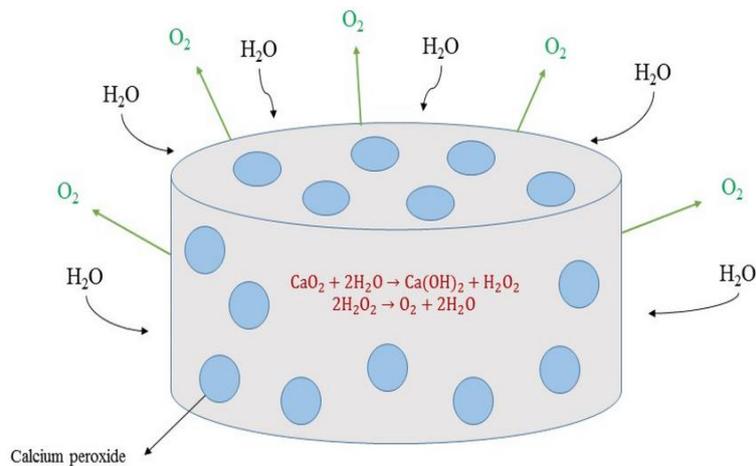


Figure 1.4: Oxygen releasing mechanism of calcium peroxide.

## 5. Immunoprotective properties

### 5.1 Biocompatible embodiment materials

#### Alginate

Commonly utilized due to its biocompatibility, but it should be profoundly decontaminated to anticipate safe responses.<sup>[27]</sup>

#### Polyethylene Glycol (PEG)

PEG can frame hydrogels that are non-immunogenic and can be custom-made for particular porousness.<sup>[28]</sup>

### Hydrogels

Other hydrogels, such as hyaluronic corrosive and collagen, can too be utilized due to their biocompatibility.<sup>[29]</sup>

### 5.2 Surface Adjustment and Coatings

#### PEGylation

PEGylation, the method of joining polyethylene glycol (PEG) chains to molecules or surfaces, has developed as a significant technique within the field of islet cell embodiment. Within the setting of islet cell transplantation for treating Type 1 diabetes, PEGylation offers a promising methodology to upgrade the biocompatibility and resistant assurance of typified islet cells.<sup>[30]</sup>

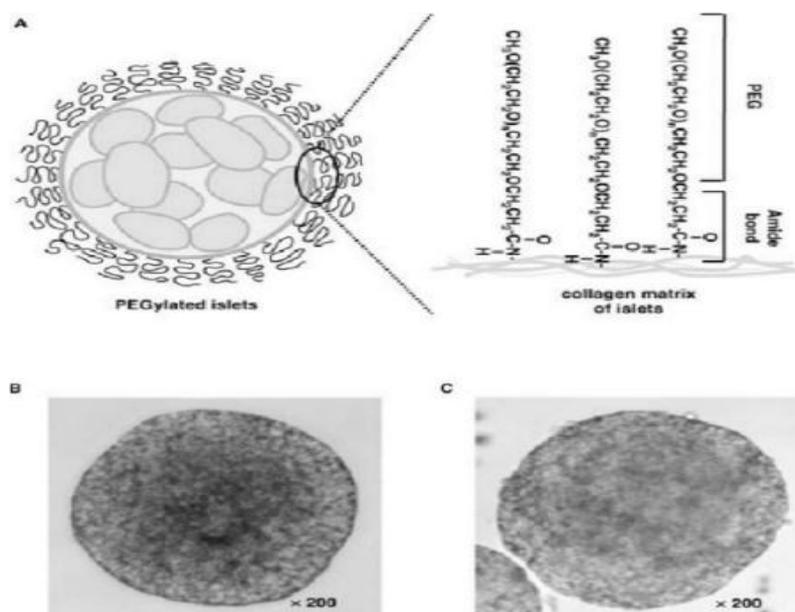


Figure 1.5: Polyethylene glycol chain coating.

### Anti-inflammatory coatings

Anti-inflammatory coatings for islet cells are an imaginative methodology pointed at improving the victory and life span of islet cell transplantation by relieving neighborhood resistant reactions.<sup>[31]</sup> These coatings are planned to discharge anti-inflammatory operators that smother irritation and tweak the resistant system's action around the typified islets. By joining compounds such as dexamethasone, interleukin-10 will avoid the enactment of resistant cells that would something else target and annihilate the transplanted islets.<sup>[32]</sup>

## 6. Clinical trials

### 6.2 Completed clinical trials

#### Theracyte encapsulation device

A macroencapsulation technique called the Theracyte encapsulation device is intended to prevent immunological rejection in transplanted cells, such as islet cells.<sup>[33]</sup> The technology in question is specifically designed to enhance cell-based therapy for Type 1 diabetes by facilitating the transplantation of islet cells that produce insulin without requiring permanent immunosuppression. It is a potential tool for the treatment of diabetes because of its design, which provides immunoprotection as well as the capacity to supply vital nutrients and oxygen to the encapsulated cells.<sup>[34]</sup>

Usually, a semi-permeable membrane made of a biocompatible polymeric material makes up the Theracyte device.<sup>[33]</sup> This membrane prevents larger immune cells and antibodies from getting to the encapsulated cells while allowing smaller molecules like oxygen, glucose, and insulin to pass through.<sup>[34]</sup> The flat, pouch-like form of the device maximizes surface area for diffusion, allowing the encapsulated cells to sustain viability and functionality over prolonged periods of time.<sup>[33]</sup>

#### Sernova's cell pouch

An innovative implantable medical device called the Sernova Cell Pouch is intended to cure diabetes by facilitating the transfer of therapeutic cells, specifically islet cells. Sernova Corp. produced this cell pouch, which is thought to be a viable long-term option for islet cell transplantation that functions.<sup>[35]</sup>

Made of a flexible polymer substance, the Sernova Cell Pouch is a tiny, biocompatible device intended for subcutaneous (under the skin) implantation. The numerous chambers and pockets in the pouch give the transplanted islet cells a vascularized environment.<sup>[36]</sup> The body's own tissue and blood arteries grow around and into these chambers once they are implanted.<sup>[35]</sup>

## 7. Future prospects

With improvements in immunological balance, stem cell innovation, and biomaterials anticipated to incredibly move forward islet cell encapsulation's viability as a

Type 1 diabetes treatment, the field's future appears greatly shinning. In arrange to superior ensure islets from the safe framework and keep up their long-term practicality, analysts are making next-generation biomaterials, which may incorporate brilliantly advances that respond to changes in their environment.<sup>[38]</sup> To advance protect typified islets and upgrade comes about, methods for nearby resistant direction and quality altering are too being examined. Within the future, islet cell embodiment combined with computerized wellbeing instruments and manufactured pancreas innovations may totally change diabetes care by giving more exact and responsive glucose control.<sup>[37]</sup>

## 8. CONCLUSION

Islet cell epitome represents a noteworthy progression within the treatment of Sort 1 diabetes, with the potential to revolutionize the way this long-term sickness is dealt with. This strategy is a vital step toward setting up long-term affront autonomy without requiring persistent immunosuppression. It points to protect transplanted islet cells from the resistant system while empowering them to make affront.<sup>[39]</sup>

Within the future, islet cell epitome will be able to overcome its show confinements as it were on the off chance that biomaterials science, stem cell investigates, and immunology proceed to combine.<sup>[38]</sup> Patients may advantage from a more responsive and customized approach to overseeing their diabetes on the off chance that computerized wellbeing innovation and manufactured pancreas frameworks are coordinates.<sup>[39]</sup>

## REFERENCE

1. Alam U, Asghar O, Azmi S, Malik RA. General aspects of diabetes mellitus. Handbook of clinical neurology, 2014; 1, 126: 211-22.
2. Bastaki S. Diabetes mellitus and its treatment. International journal of Diabetes and Metabolism, 2005; 13(3): 111-34.
3. Katsarou A, Gudbjörnsdóttir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, Jacobsen LM, Schatz DA, Lernmark Å. Type 1 diabetes mellitus. Nature reviews Disease primers, 2017; 30, 3(1): 1-7.
4. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, Simonson DC. Type 2 diabetes mellitus. Nature reviews Disease primers, 2015; 23, 1(1): 1-22.
5. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature reviews Disease primers, 2019; 11, 5(1): 47.
6. Ramachandran A. Know the signs and symptoms of diabetes. Indian Journal of Medical Research, 2014; 1, 140(5): 579-81.
7. Nathan DM. Diabetes: advances in diagnosis and treatment. Jama, 2015; 8, 314(10): 1052-62.

8. Krishnan R, Alexander M, Robles L, Foster 3rd CE, Lakey JR. Islet and stem cell encapsulation for clinical transplantation. The review of diabetic studies: RDS, 2014; 11(1): 84.
9. Hu S, De Vos P. Polymeric approaches to reduce tissue responses against devices applied for islet-cell encapsulation. *Frontiers in bioengineering and biotechnology*, 2019; 4, 7: 134.
10. Corbin KL, West HL, Brodsky S, Whitticar NB, Koch WJ, Nunemaker CS. A practical guide to rodent islet isolation and assessment revisited. *Biological Procedures Online*, 2021; 23: 1-21.
11. Almacá J, Caicedo A. Blood flow in the pancreatic islet: not so isolated anymore. *Diabetes*, 2020; 69(7): 1336.
12. Wigger L, Barovic M, Brunner AD, Marzetta F, Schöniger E, Mehl F, Kipke N, Friedland D, Burdet F, Kessler C, Lesche M. Multi-omics profiling of living human pancreatic islet donors reveals heterogeneous beta cell trajectories towards type 2 diabetes. *Nature Metabolism*, 2021; 3(7): 1017-31.
13. Basta G, Montanucci P, Calafiore R. Microencapsulation of cells and molecular therapy of type 1 diabetes mellitus: The actual state and future perspectives between promise and progress. *Journal of Diabetes Investigation*, 2021; 12(3): 301-9.
14. Krishtul S, Moshe MS, Kovrigina I, Baruch L, Machluf M. ECM-based bioactive microencapsulation significantly improves islet function and graft performance. *Acta Biomaterialia*, 2023; 1, 171: 249-60.
15. Huan Z, Li J, Luo Z, Yu Y, Li L. Hydrogel-encapsulated pancreatic islet cells as a promising strategy for diabetic cell therapy. *Research*, 2024; 4, 7: 0403.
16. Toniolo F, Bristow H, Babics M, Loiola LM, Liu J, Said AA, Xu L, Aydin E, Allen TG, Meneghetti M, Nunes SP. Efficient and reliable encapsulation for perovskite/silicon tandem solar modules. *Nanoscale*, 2023; 15(42): 16984-91.
17. Yuan Y, Yuan W, Wu Y, Wu X, Zhang X, Jiang S, Zhao B, Chen Y, Yang C, Ding L, Tang Z. High-Performance all-printed flexible micro-supercapacitors with hierarchical encapsulation. *Energy & Environmental Materials*, 2024; 7(4): e12657.
18. Grogg J, Vernet R, Charrier E, Urwyler M, Von Rohr O, Saingier V, Courtout F, Lathuiliere A, Gaudenzio N, Engel A, Mach N. Engineering a versatile and retrievable cell macroencapsulation device for the delivery of therapeutic proteins. *Iscience*, 2023; 18: 26(8).
19. Heller C, Rosenberger C, Sarangova V, Welzel PB, Ludwig B. 228.9: Microarrangement of islets to prevent hypoxia within a macroencapsulation device. *Transplantation*, 2023; 1, 107(10S2): 62.
20. Siwakoti P, Rennie C, Huang Y, Li JJ, Tuch BE, McClements L, Xu X. Challenges with cell-based therapies for type 1 diabetes mellitus. *Stem Cell Reviews and Reports*, 2023; 19(3): 601-24.
21. Liu SS, Shim S, Kudo Y, Stabler CL, O'Ceirbhail ED, Karp JM, Yang K. Encapsulated islet transplantation. *Nature Reviews Bioengineering*, 2024; 24: 1-20.
22. Kabakchieva P, Assyov Y, Gerasoudis S, Vasilev G, Peshevska-Sekulovska M, Sekulovski M, Lazova S, Miteva DG, Gulinac M, Tomov L, Velikova T. Islet transplantation-immunological challenges and current perspectives. *World Journal of Transplantation*, 2023; 6, 13(4): 107.
23. Qin T, Smink AM, de Vos P. Enhancing longevity of immunoisolated pancreatic islet grafts by modifying both the intracapsular and extracapsular environment. *Acta Biomaterialia*, 2023; 29.
24. Hutapea YA, Nishihara M, Gautama ZA, Mufundirwa A, Lyth SM, Sugiyama T, Nagayama M, Sasaki K, Hayashi A. Reduction of oxygen transport resistance in PEFC cathode through blending a high oxygen permeable polymer. *Journal of Power Sources*, 2023; 1, 556: 232500.
25. Han N, Shen Z, Zhao X, Chen R, Thakur VK. Perovskite oxides for oxygen transport: Chemistry and material horizons. *Science of The Total Environment*, 2022; 1, 806: 151213.
26. Xu Q, Huang QS, Wei W, Sun J, Dai X, Ni BJ. Improving the treatment of waste activated sludge using calcium peroxide. *Water research*, 2020; 15, 187: 116440.
27. Bennacef C, Desobry-Banon S, Probst L, Desobry S. Advances on alginate use for spherification to encapsulate biomolecules. *Food Hydrocolloids*, 2021; 1, 118: 106782.
28. Dai J, Dong X, Wang Q, Lou X, Xia F, Wang S. PEG-Polymer Encapsulated Aggregation-Induced Emission Nanoparticles for Tumor Theranostics. *Advanced Healthcare Materials*, 2021; 10(24): 2101036.
29. Ghavimi MA, Bani Shahabadi A, Jarolmasjed S, Memar MY, Maleki Dizaj S, Sharifi S. Nanofibrous asymmetric collagen/curcumin membrane containing aspirin-loaded PLGA nanoparticles for guided bone regeneration. *Scientific reports*, 2020; 23, 10(1): 18200.
30. Pelosi C, Tinè MR, Wurm FR. Main-chain water-soluble polyphosphoesters: Multi-functional polymers as degradable PEG-alternatives for biomedical applications. *European polymer journal*, 2020; 5, 141: 110079.
31. Tang J, Chen X, Shi H, Zhang M, Zhou Z, Zhang C, Ke T, Kong D, Li C. Prebiotic inulin nanocoating for pancreatic islet surface engineering. *Biomaterials Science*, 2023; 11(4): 1470-85.
32. Kim MJ, Park HS, Kim JW, Lee EY, Rhee M, You YH, Khang G, Park CG, Yoon KH. Suppression of fibrotic reactions of chitosan-alginate microcapsules containing porcine islets by dexamethasone surface coating. *Endocrinology and Metabolism*, 2021; 24, 36(1): 146-56.

33. Loudovaris T. Encapsulation devices to enhance graft survival: The latest in the development of micro and macro encapsulation devices to improve clinical, xeno, and stem cell transplantation outcomes. In *Pancreas and Beta Cell Replacement*, 2022; 1: (125-152). Academic Press.
34. Liu SS, Shim S, Kudo Y, Stabler CL, O’Cearbhaill ED, Karp JM, Yang K. Encapsulated islet transplantation. *Nature Reviews Bioengineering*, 2024; 24: 1-20.
35. Bachul P, Generette GS, Perez-Gutierrez A, Borek P, Wang LJ, Golab K, Basto L, Perea L, Tibudan M, Juengel B, Kumar J. 307.5: Modified approach allowed for improved islet allotransplantation into pre-vascularized sernova cell pouch device-preliminary results of the phase i/ii clinical trial at University of Chicago. *Transplantation*, 2021; 1, 105(12S1): S25.
36. Bachul PJ, Generette GS, Pyda JS, Borek P, Perez-Gutierrez A, Golab K, Basto L, Perea L, Tibudan M, Juengel B, Kumar J. 1146-P: Persistent Graft Function after Islet Allotransplantation into Prevascularized Sernova Cell Pouch Device: Preliminary Results from the University of Chicago. *Diabetes*, 2021; 1, 70(1).
37. Wang Q, Huang YX, Liu L, Zhao XH, Sun Y, Mao X, Li SW. Pancreatic islet transplantation: current advances and challenges. *Frontiers in Immunology*, 2024; 3, 15: 1391504.
38. Opara A, Canning P, Alwan A, Opara EC. Challenges and perspectives for future considerations in the bioengineering of a bioartificial pancreas. *Annals of Biomedical Engineering*, 2024; 52(7): 1795-803.
39. Ho BX, Teo AK, Ng NH. Innovations in bio-engineering and cell-based approaches to address immunological challenges in islet transplantation. *Frontiers in Immunology*, 2024; 8, 15: 1375177.