The Islet Confidential: Recent Trends and Perspectives in Pancreatic Islet Transplantation

Baburajan Radha1*, Gnanaraj Muniraj2, Nandhakumar Rengasamy3, Deva Arumugam3, Raghu Paramasivam3 Prabhakaran Krishnan4 and Ravikumar Rasu1

1. Hitech Diagnostic laboratory-MVK Hospital, Tanjavur-02, Tamilnadu, India.
2. Research Scholar, Department of Plant Morphology and Algology, School of Biological Sciences, Madurai Kamaraj University, Madurai-21, Tamil Nadu, India.
3. Research Scholar, PG and Research Department of Zoology, Periyar EVR College, Trichy-23, Tamilnadu, India.
4. Assistant Professor, PG and Research Department of Zoology, Periyar EVR College, Trichy-23, Tamilnadu, India.

*Corresponding author: Email: babumkubct@gmail.com.

Keywords: Pancreatic islets, Transplantation, Immunoactivation, Encapsulation, Crosslinking and Ageing.

ABSTRACT: Diabetes ranks among the top 5 killer diseases of the current world population. Transplantation of pancreatic islets is a common surgical procedure used to combat the late stage diabetic complications. A successful and long lasting islet transplant is an enigma as the complex immunoactivation mechanisms against the transplants, the subsequent graft rejection and the proper maturation and functioning of the islets in the host microenvironment, are the subjects of research for many years. This review details certain recent studies performed upon primate, porcine, murine and rabbit models, in relation to islet transplantation, with a critical standpoint.

1. INTRODUCTION:
Diabetes is a complex disease with various sub-classifications, characterized primarily by insulin dependency and multiple organ damage. Diabetic etiology is very extensive involving family genetics, life style, food habits, environment and microbial infections.
In humans, glucose metabolism is primarily controlled by insulin secretion by the endocrinal pancreatic β cells. In spite of their physiological significance, the β cells are one of the most endangered and least equipped cells, as they are much vulnerable to the attacks by free radicals, metabolic and endoplasmic reticular stress and inflammatory cytokines [1-4].
Pancreatic islet transplantation is one of the treatment strategies for diabetes. The Edmonton protocol for islet transplantation [5] pioneered numerous subsequent studies on islet transplantation. Following this study begun the long list of reports focusing upon trends such as usage of inert crosslinking materials, molecules for islet survival and graft rejection mechanisms, in order to achieve transplantations optimal. Some of these trends are detailed below.

2. IMMUNOACTIVATION:
The activation of immune system and the subsequent coup by tissue specific cytotoxic T lymphocytes, T_h1 cells, antibodies and the safety measures following any immunosuppression are serious problems to be considered. Various studies are reported regarding the immunoactivation, and suppression mechanisms involved in the onset of diabetes, graft rejection and stability.
Studies report the association of certain polymorphisms of the genes IL-17E, ATF-6, HNF4A, PRDM14 [6] and mannose binding lectin (MBL) gene [7] to be associated with the development of diabetes in transplantation. Certain non-MHC regions on chromosomes 1, 4, 6 and 9 also are reported in porcine model of immunologically mediated corneal graft rejection [8].
Cornelis R. van der Torren et al.[9] in their interesting study, report the generation of β cell lines EndoC-βH1 and ECi50 to study both the innate and adaptive immune processes involved in the β cell destruction In-Situ, both in diabetes and transplantation. Lentiviral induction of HLA A*02:01 upon EndoC-βH1 cells was achieved. Transduction with exogenous Cytomegalovirus (CMV) peptide epitope also was performed. The cell lines were cultured with T<sub>H1</sub> cells and incubated with inflammatory cytokines. Hence, this study meticulously simulated the cellular and molecular conditions a β cell could encounter.

As a result, the HLA class 1 and class 2 expressions were profiled and the EndoC-βH1 cells were typed to be HLA A*33:03 and HLA A*68:01 and the ECi50 cells to be HLA A* 02:02 and HLA A*68:01. Significant increase of β cell death was observed in both cell lines. Incubation with PPI (Pre-pro-insulin)-specific cytotoxic T lymphocyte (CTL) increased the cytolysis.

Cells transduced with CMV epitope were killed by CMV-specific CTLs. Cells with HLA A*02:02, if upregulated by IFNγ were killed by alloreactive T cells. Higher HLA expression also resulted in lysis of cells by alloreactive antibodies, especially upon cells with HLAs upregulated by IFNγ. Cells expressing low HLAs were, in turn, killed by activated natural killer (NK) cells. The cells expressed complimentary inhibitory receptors, such as CD59 and CD46 and escaped the killing by complements. This work elucidated various immunoactivation mechanisms associated with β cell death. Xiaohai Zhang et al. [10] report the role of HLA class 1 antibodies in immunoactivation by binding with antibodies and the cascade of leukocyte recruitment.

Similar to these works is the study by Ines G. Harper et al.[11] which suggest a major role of donor lymphocytes in alloimmunity against the heart transplants in murine model. They have generated a bm12- C57BL/6 mice model with additional MHC class 1 and class 2 molecules. bm12-specific passenger CD4T cells initiated the production of antibodies. No complement C4d deposition was observed in T cell deficient (Tcrbd<sup>-/-</sup>) mice (Figure.1).

![Picture of heart allografts and Tcrbd<sup>-/-</sup> mice](image)

**FIGURE 1:** (A) Syngeneic, (B) bm12.K<sup>d</sup>.IE heart allografts, and (C) Tcrbd<sup>-/-</sup> mice. (Adopted from Ines G. Harper et al.)

Nan Wang et al., [12], in their extensive study with bone marrow derived haematopoietic stem cells (BM-HSCs) in murine model detail various factors which could lead to immunoactivation and subsequent diabetes.

In their study, they report higher number of conventional T cells (T<sub>con</sub> cells ) and lower T<sub>reg</sub> cells in pancreatic lymph nodes (PLNs) of older recipients. The proliferation rates of T<sub>con</sub> cells of PLNs, blood and mesenteric lymph nodes (MLNs) in younger recipients were observed to be lower. Significant reduction of Thymic T<sub>con</sub> cells also was observed in younger recipients. This study suggests that older recipients could develop diabetes more rapidly. Hyperthyroidism also is reported, in rabbits, to induce immunoactivation which could, in turn, lead to infiltration of immune cells [13].

Indoleamine 2,3-dioxygenase (IDO)[14] has been reported to be involved in the suppression of immunoactivated cells. Inhibition of Cyclin dependent kinase-9 (CDK-9) by PHA767491 also could protect the graft from alloreactive CD4T cells [15].

Nadine Nagy et al.,[16], in their study with DORmO and NOD murine models reports that deposition of hyaluronan (HA) could be implicated in the immunoactivation as it lead to the development of autoimmune diabetes. Inhibition of HA synthesis by 4-methylumbelliferone (4-MU) prevented various complications of diabetes. Similar view was reflected in the work by
Marika Bogdani et al. [17] in their work with diabetic tissue donors in the Network for pancreatic organ donors with diabetes (nPOD) program. The same group [18]) reports the detection of glycosaminoglycan hyaluronan and heparin sulphate in pancreatic β cells. They achieved it using an hyaluronan binding protein (HABP) specific probe.

3. MICROBIAL INFECTION:
Suresh Paudel et al.,[19], in their meta-analyses of reports of subjects received solid organ transplantation (SOT) during the period of 1991 to 2014 indicate that there is a high prevalence of Clostridium difficile infections (CDI) among the transplant recipients. The prevalence of CDI infection among the pancreas recipients is determined to be 3.2% [95% CI, (0.5%-7.9%)].This analyses necessitates proper interventions to combat CDI.
Sung hang kim et al., [20], in their study with kidney transplants suggest that early diagnosis for CMV specific T cells could effectively predict post transplantation CMV infections.
In their study with North american child solid organ transplant (SOT) recipients, Paul K. Sue et al.,[21], reports that hepatitis E virus (HEV) is the major infection which could lead to graft rejection of SOT. Marcio F. Chedid et al. [22] reports the significance of hepatitis C virus (HCV) infections in the elicitation of hepatocellular carcinoma in liver transplants. This study recommends post transplantation strategies such as transarterial embolization and ethanol injection to combat this dilemma. In addition to HEV, HCV infections also are implicated in graft rejection in liver transplantation [23].

4. ENCAPSULATION:
Various encapsulation approaches are devised to insulate the grafts and stem cells from immune cells and enable the proper adaptation and functioning of the transplants in the host microenvironment.
Alan D. Agulnick et al. [24] report the use of VC-01,a macroencapsulation device for the In- vivo transfer and differentiation of human embryonic stem cells (hESCs).These cells effectively differentiated into islet-like cells (ICs) as observed by PDX1+ and NKX6.1+ cells (Figure.2).

Andrew R. Pepper et al.[25] reports the use of Sernova Corp's Cell Pouch (CP), subcutaneous cell pouch. The islets were capsulated in CP and transplanted in diabetic mice. CP- encapsulated BALB/c mice responded well to glucose challenge and exhibited enhanced positivity for both insulin and glucagon (Figure.3).
Woon Teck Yap et al. [26] suggest the use of modified collagen scaffolds for islet transplantation. Another similar work [27] suggests the use of collagen-chitosan hydrogel for islet transplantation. Friederike Ehrhart et al. [28] report the use of multilayered alginate coatings for the encapsulation. The islets were reported to be biocompatible with optimal insulin secretion. Naturally occurring compounds such as fibrin [29], Amylin [30] and laminin also were reported [31] to be used as effective scaffolds for islet encapsulation. The usages of scaffolds for various tissue types are reported [32]. Interestingly, scaffold-free stem cell constructs also are recommended for osteoinduction [33].

The significance of surrounding matrice environments were considerably reported [17, 34] in their relation with islet function and survival. Ulrika Johansson et al. [35] recommend the usage of spider silk matrices for effective transplantation and long term survival of β cells. In their study, three forms (Fiber, foam and film) of silk were used. The cell binding motif RGD was clonally inserted to the silk matrices. The β cells were transplanted into the anterior chamber of the eye to enable in vivo imaging of islets. As result, the cells kept in foam form exhibited significant revascularization (Figure 4).

**FIGURE 3:** A: Macroscopic view of the CP implanted in left lower abdominal quadrant of mice. B: Fluorescent staining of a serial section depicting an islet graft within the CP staining positive for insulin (red), blood vessels (green) and nuclei. (Adopted from Andrew R. Pepper et al.)

**FIGURE 4:** Mouse pancreatic islets adhere to silk matrices (A) Photographs of the various formats; fiber (left), foam (middle) and film (right) and micrographs together with adhered islet (lower panel, asterisks). Scale bars = 50μm. (B) Micrographs of islets after 2 weeks in control wells (left), on WT foam (middle) and on RGD foam (right). Scale bars = 50 μm. (C). Morphology by H/E (left panel) and insulin (green, right panel) staining of eye sections showing representative (n = 3) control islet (upper graphs) and islet from RGD foam (lower graphs). Vasculature was seen in islets from both culture conditions (white arrowhead) although vessels with erythrocytes were more common in islets from RGD foam. Areas of visual cell death were sometimes present in control islet (white lined circle). Scale bars = 50 μm. (Adopted from Ulrika Johansson et al.).
Di Wu et al. [36] reports the MIN-6 β cells embedded in engineered 3D-decellularized extra cellular matrix (ECM) scaffold could effectively simulate tissue microenvironment. Pancreas were harvested from C57BL/6J mice. Decellularization was achieved by removing perfusate using peristaltic pump, washing by distilled water and subsequent storage by -80°C. Later the cells were washed by PBS and Triton X. Vasculature was measured by Angiography. The scaffold was placed subcutaneously. Eosin–Hematoxilin (HE) and immunofluorescence staining was performed on the scaffold. Finally, the MIN-6 β cells were infused into the scaffold. The recellularization of the engrafted cells was confirmed by SEM imaging. Expression of the Insulin gene of the grafted cells was sufficiently higher (Figure 5). Intriguingly, one of the test groups of the scaffolded grafts indicated higher blood glucose levels. It was reasoned in this study, that it could be the result of a lack of nutrition supply.
5. CROSSLINKING:

Crosslinking is another process utilized to prevent any elicitation of immune reactions against the graft. An acellular tissue environment could provide a compatible and safe environment for tissue growth and repair [37, 38].

One of such crosslinking agents commonly used was Glutaraldehyde (GA) [39]. But GA is limited by its immunogenicity. In contrast, Saeromi Jeong et al. [40] suggest the better cross-linking property of GA.

Other reports suggest Genipin, a naturally occurring crosslinking agent to replace GA and for an optimal scaffolding [41-43]. Recently, Yujia Wang et al. [44] in their study with porcine liver transplants suggest that Genipin could significantly reduce the immunogenicity compared with GA (Figure. 6).

Various nanotechnology based approaches has been suggested for better biomolecular conjugation. Andreas M. Nyström et al.[45] reports the conjugation of Thiol-functionalized shell crosslinked knedel-like (SCK) nanoparticles with bovine serum albumin (BSA). I. M. El-Sherbiny et al.[46] suggest the copolymerization of polyethylene glycol(PEG) with N-phthaloyl chitosan (NPHCs) to be used as respirable alginate hydrogel microspheres for an optimal pulmonary drug delivery. Alginate hydrogels are also reported to be effective crosslinking drug carriers in stomach [47].
Tania Betancourt et al. [48] recommend pH-responsive hydrogels of poly-itaconic acid-g-ethylene glycol for oral drug delivery. Recently, Qinmei Wang et al. [49] reports an injectable hydrogel composed of oxidized alginate(OA) crosslinking gelatin with electroactive tetra-aniline –graft OA-nanoparticles (nEOAs).

Hydrogel formations with hyaluronate [50], nanofibers [51] are reported to be effective for bone regeneration and arterial scaffolding, respectively. Hyaluronan scaffolds are also reported to be involved in smooth muscle cell (SMC) regeneration [52].

6. VASCULARIZATION:

Vascularization signifies the preliminary adaptation of the cells into the molecular niche after transplantation. The formation of blood vessels ensures the traffic of nutrients, growth and survival of the cells. Thyroidectomy- induced devascularization is reported to cause islet infiltration in rabbits [53].

Cara E Ellis et al. [54] reports an artificial vascularization matrix made up of collagen crosslinked with 1-ethyl-3- carbodiimide and N-hydroxysuccinimide and chondroitin-6-sulfate, chitosan, and laminin. This study was performed with neonatal porcine islets (NPIs) transplanted subcutaneously upon immunoincompetent B6.Rag−/− mice. The combination of the co-polymers ensured the function, survival and vascularization of the islets post-transplantation (Figure. 7).
FIGURE 7: **Right**: Dark field images of NPIs embedded in Collagen alone (C) (A) Collagen-Chitosen (CC) (B), Collagen-Chitosen-Chondroitin (CCC) (C) and Collagen-Chitosen-Chondroitin–Laminin (CCCL) (D) after the matrices were cultured for 7 days (Scale bars: 400 μm for (A) and (B) and 1.6 mm for (C and D). **Left**: Morphology of NPIs in the CCCL gels and transplanted in immunocompromised B6.Rag−/− mice. Circles indicate visible islets; arrows indication visible vasculature of pre-transplant (A) and after 4 (B), 21 (C) and 28 (D) days. Scale bars are 400 μm (Adopted from Cara E Ellis et al.).

Similar to this study is the recent report by Edward A. Phelps et al. [55] which suggest the use of polyethylene glycol maleimide (PEG-MAL) hydrogels for the encapsulation of islets. The grafted cells functioned properly and secreted insulin. This addition of vascular endothelial growth factor (VEGF), the primary molecular of vascularity, resulted in optimal vascularization of the grafted cells (Figure. 8). VEGF is also reported to cause lymphangiogenesis, in corneal allogeneic transplantations on murine model [56].

FIGURE 8: Islet transplantation with PEG-MAL and alginate. A Hydrogels were cross-linked directly onto the tissue surface of the mesentery. B Macroscopic images of implant site at 0, 1, and 4 weeks. C Whole mount immunostain for insulin of explanted hydrogel at 4 weeks. D Quantification of islets in immunostained explants. (Adopted from Edward A. Phelps et al.).
7. OTHER BENEFICIAL FACTORS:
Nathalie M. Fiaschi-Taesch et al. [57] in their study with non human primate (NHP) islets, reports that hepatocyte growth factor (HGF) could enhance the survival rate of islets post-transplantation (Figure. 9).

**FIGURE 9:** Photomicrographs of adenoviral transduction of 500 NHP islet equivalents (IEs) with murine HGF. (Adopted from Nathalie M. Fiaschi-Taesch et al.)

Another complementary study [58] with porcine islets suggests the property of adenosine in preserving pancreas for islet transplantation (Figure. 10).

**FIGURE 10:** DTZ staining of islet yields with different perfusates. A. Control group with University of Wisconsin (UW) perfusion. B. Experimental group with UW added with adenosine perfusion solution (Adopted from W.Q. Song et al.).

Other molecules such as anti-CD40 antibody [59] and Ribonuclease (RNase) [60] also are reported to be associated with graft survival in heart transplantation model.

8. ALTERNATIVE TRANSPLANTATION ROUTES:
Morteza Abouzaripour et al.[61] ,in their two months study with mice reports a novel intravenous transplantation of very small embryonic like stem cells(VSELs).The transplanted cells were cultured with mouse embryonic fibroblast (MEF) cells and exhibited significant survival rates and proper hypoglycaemic activity in the pancreas (Figure. 11). The VSELs are also reported to be contributing to the regeneration of pancreas [62].
In addition, Juliana Navarro Ueda Yaochite et al., 2015 [63] with their study with adipose-derived mesenchymal stem cells (ADMSCs) report a successful delivery and functioning of cells, via intrasplenic (I.Sp) and intrapancreatic (I.Pc) routes (Figure 12).

FIGURE 12: Days after (A) Intrapancreatic and (B) Intrasplenic ADMSC\textsuperscript{Lac+} injection. Ex vivo bioluminescent imaging of the pancreas, liver and spleen 48 hours after injected with ADMSC\textsuperscript{Lac+}. (C) (Adopted from Juliana Navarro Ueda Yaochite et al.).

9. AGEING:

The transplantation of pancreatic β cells and their subsequent adaptation and functioning within the host tissue/vascular microenvironment, in regard to ageing is an important technical aspect to be considered. Studies on microcellular niche were conducted in muscle [64], skin [65] and neuronal cells [66]. Ageing is also associated with inflammation [67] and fibrosis [68] of pancreatic islets.
One of the interesting works is the heterochronic and isochronic transplant study by Seth. J. Salpeter et al. [69]. They transplanted β cells between young and aged mice. The proliferation rates were measured by the markers Insulin, Ki67 and Nkx6.1. The results indicated that β cells of both young and old mice proliferated significantly, when each of them were transplanted into young mice. In contrast, the cells exhibited attenuated proliferation rates when transplanted into old mice (Figure 13).

**FIGURE 13**: Proliferation results of transplanted β cells with the markers Insulin, Nkx6.1 and Ki67 colored in green, maroon and blue, respectively.

10. CONCLUSION:

Various practically available interventions such as insulin, digestion regulators and insulin potentiators are relatively cheaper and could give a temporary remedy way before the acute failure of islets. All these factors, along with the costs of treatments make pancreatic islet replacement stand behind kidney, liver and heart transplantations. The reports on islet ageing strictly necessitate more research on cadaveric and xenotransplantation strategies and anticipate complementary gerontologic interventions. Attention must be given to the encapsulation and crosslinking materials, as they must remain inert in the long run and should not lead to any immune responses. Considerable evidences suggest [70-78] the association of pancreatic β cells with other networks, indicating certain ‘cross-talks’ among the heterodermal derivatives. These studies warn that the islets, albeit unique, are not isolated entities, but are in continuous equilibrium with other physiological systems. Any of our transplantation measures must be in harmony with these networks, to be optimally effective lest they elicit serious interdermal complications.
REFERENCES:

[1] Poitout, Vincent, and R Paul Robertson, Glucolipotoxicity: Fuel excess and β-cell dysfunction. Endocrine Reviews 2008; 29: 351–66.

[2] S. Jitrapakdee, A. Wutthisathapornchai, J. C. Wallace, and M. J. MacDonald, Regulation of insulin secretion: role of mitochondrial signaling. Diabetologia 2010; 53, 1019–32.

[3] Jingbo Pi, Qiang Zhang, Jingqi Fu, Courtney G. Woods, Yongyong Hou, Barbara E Corkey, Sheila Collins, and Melvin E. Andersen, ROS signaling, oxidative stress and Nrf2 in pancreatic beta-cell function. Toxicology and Applied Pharmacology 2011; (244), 77–83.

[4] Carl Jorgen Hedeskov and Kirsten Capito, The Pentose Cycle and Insulin Release in Isolated Mouse Pancreatic Islets during Starvation. Biochemical Journal 1975;152: 571-576.

[5] M. J. Shapiro, J. R. T. Lakey, E. A. Ryan et al., Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. The New England Journal of Medicine 2000; vol. 343, no. 4, pp. 230–238.

[6] Chand S, A J Mcknight, S Shabir, W Chan, J A Mccaughan, A P Maxwell, and others, Analysis of Single Nucleotide Polymorphisms Implicate mTOR Signalling in the Development of New-Onset Diabetes after Transplantation. BBACL1 2016; 5: 41–45.

[7] Bijkerk Roel, Pieter Van Der Pol, and Meriem Khairoun, Simultaneous Pancreas – Kidney Transplantation in Patients with Type 1 Diabetes Reverses Elevated MBL Levels in Association with MBL2 Genotype and VEGF Expression. Diabetologia 2016; 853–58.

[8] Nicholls Susan, Ricardo Pong-wong, Louisa Mitchard, Ross Harley, Alan Archibald, Andrew Dick, and others, Genome-Wide Analysis in Swine Associates Corneal Graft Rejection with Donor-Recipient Mismatches in Three Novel Histocompatibility Regions and One Locus Homologous to the Mouse H-3 Locus. PLoS ONE 2016; 1–12.

[9] Torren Cornelis R Van Der, Arnaud Zaldumbide, Dave L Roelen, Gaby Duinkerken, Simone H Brand-schaaf, Mark Peakman, and others, Innate and Adaptive Immunity to Human Beta Cell Lines : Implications for Beta Cell Therapy. Diabetologia 2016; 170–75.

[10] Zhang Xiaohai, Nicole M Valenzuela, and Elaine F Reed, HLA class I antibody-mediated endothelial and smooth muscle cell activation. Curr Opin Organ Transplant 2012; August: 17(4).

[11] Harper Ines G, Jason M Ali, Simon J F Harper, Menna R Clatworthy, Thomas M Conlon, Gavin J Pettigrew, and others, Augmentation of Recipient Adaptive Alloimmunity by Donor Passenger Lymphocytes within the Transplant Article Augmentation of Recipient Adaptive Alloimmunity by Donor Passenger Lymphocytes within the Transplant. Cell Reports 2016; 1–14.

[12] Wang Nan, Narendiran Rajasekaran, Tieying Hou, Claudia Macaubas, and D Mellins, Immunological Basis for Rapid Progression of Diabetes in Older NOD Mouse Recipients Post BM-HSC Transplantation. PLoS ONE 2015; 1–16.

[13] Rodríguez-castelán Julia, Margarita Martínez-gómez, Francisco Castelán, and Estela Cuevas, Hypothyroidism Affects Vascularization and Promotes Immune Cells Infiltration into Pancreatic Islets of Female Rabbits. International Journal of Endocrinology 2015; 19–21.

[14] Malihe-Sadat Poormasjedi-Meibod, Raza B. Jalili, Azadeh Hosseini-Tabatabaei, Ryan Hartwell, Aziz Ghabary, Immuno-Regulatory Function of Indoleamine 2,3 Dioxygenase through Modulation of Innate Immune Responses. PLoS ONE 2013; Volume 8, Issue 8, e71044.

[15] Zhan Yang, Yeming Han, Hukui Sun, Ting Liang, Chao Zhang, and Jing Song, T Cells Prolongs Allograft Survival. Oncotarget 2016; 767491.
[16] Nagy Nadine, Gernot Kaber, Pamela Y Johnson, John A Gebe, Anton Preisinger, Ben A Falk, and others, Inhibition of Hyaluronan Synthesis Restores Immune Tolerance during Autoimmune Insulitis. The Journal of Clinical Investigation 2015; Volume 125 Number 10.

[17] Bogdani Marika, Pamela Y Johnson, Susan Potter-perigo, Nadine Nagy, and Anthony J Day, Hyaluronan and Hyaluronan- Binding Proteins Accumulate in Both Human Type 1 Diabetic Islets and Lymphoid Tissues and Associate With Inflammatory Cells in Insulitis. Diabetes 2014; 63:2727–2743.

[18] Bogdani Marika, Charmaine Simeonovic, Nadine Nagy, Pamela Y Johnson, K Chan, and Thomas N Wight, The Detection of Glycosaminoglycans in Pancreatic Islets and Lymphoid Tissues. Methods Mol Biol 2015; 1229: 413–430.

[19] Paudel Suresh, Ioannis M Zacharioudakis, Fainareti N Zervou, Panayiotis D Ziakas, and Eleftherios Mylonakis, Prevalence of Clostridium difficile Infection among Solid Organ Transplant Recipients : A Meta-Analysis of Published Studies. PLoS ONE 2015; 1–16.

[20] Kim Sung-Han, Hyun-jeong Lee, Sun-mi Kim, Joo Hee Jung, Sung Shin, Young Hoon Kim, and others, Diagnostic Usefulness of Cytomegalovirus (CMV) - Specific T Cell Immunity in Predicting CMV Infection after Kidney Transplantation : A Pilot Proof-of-Concept Study. Infect Chemother 2015; 47(2):105-110.

[21] Sue Paul K, Nora Pisanic, Christopher D Heaney, Michael Forman, Alexandra Valsamakis, Annette M Jackson, and others, Hepatitis E Virus Infection Among Solid Organ Transplant Recipients at a North American Transplant Center. Open Forum Infectious Diseases 2012; 1–8.

[22] Chedid Marcio F, Leandro A Scaffaro, Aljamir D Chedid, Antonio C Maciel, Carlos Thadeu S Cerski, Matheus J Reis, and others, Transarterial Embolization and Percutaneous Ethanol Injection as an Effective Bridge Therapy before Liver Transplantation for Hepatitis C-Related Hepatocellular Carcinoma. Gastroenterology Research and Practice 2016; Article ID 9420274, 5 pages.

[23] Saab Sammy, Justin Rheem, Melissa Jimenez, Sherona Bau, Gina Choi, Francisco Durazo, and others, Curing Hepatitis C in liver transplant recipients is associated with changes in Immunosuppressant use. Journal of Clinical and Translational Hepatology 2016; 4:32–38.

[24] Alan D. Agulnick, Dana M. Ambruzs, Mark A. Moorman, Anindita Bhouthik,Rosemary M. Cesario, Janice K. Payne, Jonathan R. Kelly, Carl Haakmeester, Robert Srijemac,Alistair Z. Wilson, Justin Kerr, Mauro A. Frazier, Evert J. Kroon, Kevin A. D’amour, Tissue Engineering and Regenerative Medicine, Insulin-Producing Endocrine Cells Differentiated In Vitro From Human Embryonic Stem Cells Function in Macrocapsulation Devices In Vivo. Stem Cells Translational Medicine 2015; 4:1214–1222.

[25] Pepper Andrew R, Rena Pawlick, Boris Gala-lopez, Amanda Macgillivary, Delfina M Mazzuca, David J G White, and others, Diabetes Is Reversed in a Murine Model by Marginal Mass Syngeneic Islet Transplantation Using a Subcutaneous Cell Pouch Device. Transplantation 2015; 99: 2294–2300.

[26] Yap Woon Teck, Xiaomin Zhang, Zachary G Bannon, Dixon B Kaufman, William L Lowe, and Lonnie D Shea, Collagen IV-Modified Scaffolds Improve Islet Survival and Function and Reduce Time to Euglycemia. Tissue Engineering: Part A 2013; Volume 19, Numbers 21 and 22.

[27] McBane Joanne E, Branka Vulesevic, Donna T Padavan, Kimberly A Mcewan, S Gregory, and Erik J Suuronen, Evaluation of a Collagen-Chitosan Hydrogel for Potential Use as a Pro-Angiogenic Site for Islet Transplantation. PLoS ONE 2013;8:1–15.

[28] Ehrhart Friederike, Esther Mettler, Thomas Böse, Matthias Max Weber, and Julio Alberto Vásquez, Biocompatible Coating of Encapsulated Cells Using Ionotropic Gelation. PLoS ONE 2013; 8: 1–9.
[29] Kuehn Carina, Jonathan R T Lakey, Morgan W Lamb, and Patrick Vermette, Young Porcine Endocrine Pancreatic Islets Cultured in Fibrin Show Improved Resistance toward Hydrogen Peroxide. Islets 2013; 207–15

[30] Guerreiro Luiz Henrique, Mariana F A N Gutерres, Bruno Melo-ferreira, Luiza C S Erthal, Silva Rosa, Daniela Lourenço, and others, Preparation and Characterization of PEGylated Amylin. AAPS Pharm.SciTech 2013; Vol. 14, No. 3.

[31] Yamashita Shingo, Kazuo Ohashi, Rie Utoh, Teruo Okano, and Masakazu Yamamoto, Human Laminin Isotype Coating for Creating Islet Cell Sheets. Cell Medicine 2015; 8: 39–46.

[32] Willenberg Bradley J, Jose Oca-cossio, Yunqing Cai, Alicia R Brown, William L Clapp, Dale R Abrahamson, and others, Repurposed Biological Scaffolds: Kidney to Pancreas. Organogenesis 2015; 47–57.

[33] Okawa Hiroko, Hiroki Kayashima, Jun-ichi Sasaki, Jiro Miura, Yuya Kamano, Yukihiro Kosaka, and others, Scaffold-Free Fabrication of Osteoinductive Cellular Constructs Using Mouse Gingiva-Derived Induced Pluripotent Stem Cells. Stem Cells International 2016; Article ID 6240794, 11 pages.

[34] Sayed-Hadi Mirmalek-Sani, Giuseppe Orlando, John McQuilling, Rajesh Pareta, David Mack, Marcus Salvatori, Alan C Farney, Robert J Stratta, Anthony Atala, Emmanuel C Opara, and Shay Soker, Porcine pancreas extracellular matrix as a platform for endocrine pancreas bioengineering. Biomaterials 2013; July; 34(22): 5488–5495.

[35] Johansson Ulrika, Massimiliano Ria, Å Karin, and Nancy Dekki Shalaly, Pancreatic Islet Survival and Engraftment Is Promoted by Culture on Functionalized Spider Silk Matrices. PLoS ONE 2015; 1–21.

[36] Wu Di, Jian Wan, Yan Huang, Yibing Guo, Tianxin Xu, Mingyan Zhu, and others, 3D Culture of MIN-6 Cells on Decellularized Pancreatic Scaffold: In Vitro and In Vivo Study. BioMed Research International 2015; Article ID 432645, 8 pages.

[37] Schmidt CE, Baier JM., Acellular vascular tissues: Natural biomaterials for tissue repair and tissue engineering. Biomaterials 2000; Nov. 21(22):2215-31.

[38] Cavallo J A, S C Greco, J Liu, M M Frisella, C R Deeken, and B D Matthews, Remodeling characteristics and biomechanical properties of a crosslinked versus a non-crosslinked porcine dermis scaffolds in a porcine model of ventral hernia repair. Hernia 2015; April ; 19(2): 207–218.

[39] Dardik H, Miller N, Dardik A, Ibrahim I, Sussman B, Berry SM, Wolodiger F, Kahn M, Dardik IA decade of experience with the glutaraldehyde-tanned human umbilical cord vein graft for revascularization of the lower limb. J Vasc Surg 1988; Feb;7(2):336–46.

[40] Saeromi Jeong, Eun Jung Yoon, Hong Gook Lim, Si Chan Sung, and Yong Jin Kim, The Effect of Space Fillers in the Cross-Linking Processes of Bioprosthesis. BioResearch Open Access 2013;Vol :2, 2.

[41] Chang Y,Tsai CC,Liang HC,Sung HW,In Vivo evaluation of cellular and acellular pericardia fixed with a naturally occurring crosslinking agent (Genipin).Biomaterials 2002;Jun;23(12):2447-57.

[42] Jiang T, Ren XJ, Tang JL, Yin H, Wang KJ, Zhou CL,Preparation and characterization of Genipin-crosslinked rat acellular spinal cord scaffolds. Mater Sci Eng C Mater Biol Appl 2013; Aug 1;33(6):3514-21.

[43] Thomas Vinoy, Danna Nozik, Harsh Patel, Raj K Singh, Yogesh K Vohra, and Avenue South, Biohybrid Fibro-Porous Vascular Scaffolds: Effect of Crosslinking on Properties. Mater Res Soc Symp Proc. 2015; 1718.
[44] Wang Yujia, Ji Bao, Xiujuan Wu, Qiong Wu, Yi Li, Yongjie Zhou, and others, Genipin Crosslinking Reduced the Immunogenicity of Xenogeneic Decellularized Porcine Whole-Liver Matrices through Regulation of Immune Cell Proliferation and Polarization. Scientific Reports 2016; 1–16. DOI: 10.1038/srep24779.

[45] Andreas M. Nyström and Karen L. Wooley, Thiol-functionalized shell crosslinked knedel-like (SCK) nanoparticles: A versatile entry for their conjugation with biomacromolecules. Tetrahedron 2008; September 1; 64(36): 8543–8552.

[46] M. El-Sherbiny and H. D. C. Smyth, Biodegradable nano-micro carrier systems for sustained pulmonary drug delivery: (I)Self-assembled nanoparticles encapsulated in respirable/swellable semi-IPN microspheres. Int J Pharm 2010; August 16; 395.

[47] Tripathi Rahul, and Brahmeshwar Mishra, Development and Evaluation of Sodium Alginate–Polyacrylamide Graft – Co-Polymer- Based Stomach Targeted Hydrogels of Famotidine . AAPS 2012; 13.

[48] Tania Betancourt, Juan Pardo, Ken Soo, and Nicholas A. Peppas, Characterization of pH-Responsive Hydrogels of Poly(itaconic acid-g-Ethylene Glycol) Prepared by UV-Initiated Free Radical Polymerization as Biomaterials for Oral Delivery of Bioactive Agents. J Biomed Mater Res A 2010; April ; 93(1): 175–188.

[49] Wang Qinmei, and Qiong Wang, Hydrogels Containing Conductive Polymer Nanoparticles for Biomedical Applications. International Journal of Nanomedicine 2016;11: 131–145.

[50] Yeom Junseok, Byung Woo Hwang, Dong Jun Yang, Hong-in Shin, and Sei Kwang Hahn, Effect of Osteoconductive Hyaluronate Hydrogels on Calvarial Bone Regeneration. Biomaterials Research 2014; 18:8.

[51] Mark T. McClendon and Samuel I. Stupp, Tubular Hydrogels of Circumferentially Aligned Nanofibers to Encapsulate and Orient Vascular Cells. Biomaterials 2012; August ; 33(23): 5713–5722.

[52] Chandrasekhar R. Kothapalli, Patricia M. Taylor, Ryszard T. Smolenski, Magdi H. Yacoub, and Anand Ramamurthi, Transforming Growth Factor Beta 1 and Hyaluronan Oligomers Synergistically Enhance Elastin Matrix Regeneration by Vascular Smooth Muscle Cells. Tissue Engineering: Part A, 2009; Volume 15, Number 3.

[53] Rodriguez-castelán, Julia, Margarita Martínez-gómez, Francisco Castelán, and Estela Cuevas, Hypothyroidism Affects Vascularization and Promotes Immune Cells Infiltration into Pancreatic Islets of Female Rabbits. International Journal of Endocrinology 2015; 19–21.

[54] Ellis, Cara E, Branka Vulesevic, Erik Suuronen, Telford Yeung, Karen Seeberger, and Gregory S Korbett, Bioengineering a Highly Vascularized Matrix for the Ectopic Transplantation of Islets. Islets 2013; 5:5, 216–225.

[55] Phelps, Edward A, Kellie L Templeman, and Veterans Affairs, Engineered VEGF-releasing PEG-MAL hydrogel for pancreatic islet vascularization. Drug Deliv Transl Res 2015;April ; 5(2): 125–136.

[56] Chen, Wei-sheng, Zhiyi Cao, Satoshi Sugaya, Maria J Lopez, Victor G Sendra, Nora Laver, and others, Pathological Lymphangiogenesis Is Modulated by Galectin-8-Dependent Crosstalk between podoplanin and integrin-associated VEGFR-3. Nature Communications 2016;7: 1–17.

[57] Fiaschi-taesch, Nathalie M, Dora M Berman, Brian M Sicari, and Karen K Takane, Hepatocyte Growth Factor Enhances Engraftment and Function of Nonhuman Primate Islets. Diabetes 2008; 57.

[58] Song, W Q, D Z Fu, Y Cheng, and Y F Liu, Influence of Adenosine on Preservation of Porcine Pancreas in Islet Transplantation. Genetics and Molecular Research 2015; 14: 18293–301.
Mohiuddin, Muhammad M, Avneesh K Singh, Philip C Corcoran, Marvin L Thomas Iii, Tannia Clark, Billeta G Lewis, and others, Chimeric 2C10R4 Anti-CD40 Antibody Therapy Is Critical for Long-Term Survival of GTKO.hCD46.hTBM Pig-to-Primate Cardiac Xenograft. Nature Communications 2016;7:1–10.

Eike Kleinert, Martin C. Langenmayer, Bruno Reichart, Jana Kindermann, Barbara Griemert, Andreas Blutke, Kerstin Troidl, Tanja Mayr, Tobias Grantzow, Fatih Noyan, Jan-Michael Abicht, Silvia Fischer, Klaus T. Preissner, Ruediger Wanke, Elisabeth Deindl, Sonja Guethoff, Ribonuclease (RNase) Prolongs Survival of Grafts in Experimental Heart Transplantation. Journal of the American Heart Association 2016; 1–14.

Morteza Abouzaripour, Iraj Ragerdi Kashani, Parichehr Pasbakhsh, and Nader Atlasy, Intravenous Transplantation of Very Small Embryonic Like Stem Cells in Treatment of Diabetes Mellitus. Avicenna J Med Biotech 2015; 7(1): 22–31.

Deepa Bhartiya and Hiren Patel, Very small embryonic-like stem cells are involved in pancreatic regeneration and their dysfunction with age may lead to diabetes and cancer. Stem Cell Research & Therapy 2015; 6:96.

Juliana Navarro Ueda Yaohite, Carolina Caliari-Oliveira, Lucas Eduardo Botelho de Souza, Lourenço Sbragia Neto, Patricia Vianna Bonini Palma, Dimas Tadeu Covas, Kelen Cristina Ribeiro Malmegrim, Julio César Voltarelli and Eduardo António Donadi, Therapeutic efficacy and biodistribution of allogeneic mesenchymal stem cells delivered by intrasplenic and intrapancreatic routes in streptozotocin-induced diabetic mice. Stem Cell Research & Therapy 2015; 6:31.

Song SY, Jung JE, Jeon YR, Tark KC, Lew DH, Determination of adipose-derived stem cell application on photo-aged fibroblasts, based on paracrine function. Cytotherapy 2011; Mar:13(3):378-84.

S. A. Villeda, J. Luo, K. I. Mosher, B. Zou, M. Britschgi, T. M. Stan, N. Fainberg, Z. Ding, A. Eggel, M. Kurt, E. Czirr, J. Park, S. Couillard-després, L. Aigner, E. R. Peskind, J. A. Kaye, J. F. Quinn, and D. R. Galasko, The aging systemic milieu negatively regulates neurogenesis and cognitive function. Nature 2012; vol. 477, no. 7362, pp. 90–94.

Masako Imaoka, Toshimasa Jindo, and Wataru Takasaki, The Process and Development Mechanism of Age-related Fibrosis in the Pancreatic Islets of Sprague-Dawley Rats: Immunohistochemical Detection of Myofibroblasts and Suppression Effect by Estrogen Treatment. J Toxicol Pathol 2013; 26: 1–10.

Salpeter SJ, Khalaileh A, Weinberg-corem N, Ziv O, Glaser B, Systemic Regulation of the Age-Related Decline of Pancreatic β-Cell Replication. Diabetes 2013; 62(August):2843–8.

Medina A, Yamada S, Hara A, Hamamoto K, Kojima I. Involvement of the parasympathetic nervous system in the initiation of regeneration of pancreatic β-cells. Endocrine Journal 2013; 60(5):687–96.

M. M. Feng, Y. Xiang, S. Wang, and W. Lu, An autocrine γ-aminobutyric acid signaling system exists in pancreatic β-cell progenitors of fetal and postnatal mice. International Journal of Physiology, Pathophysiology and Pharmacology 2013; vol. 5, no. 2, pp. 91–101.
Biankin A V, Waddell N, Kassahn KS et al., Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. NIH Public Access pathway genes 2012; 491(7424):399–405.

B. S. Pourcain, R. A. M. Cents, A. J. O. Whitehouse et al., Common variation near ROBO2 is associated with expressive vocabulary in infancy. Nature communications 2014; pp. 1–9.

T. A. Evans, C. Santiago, E. Arbeille, and G. J. Bashaw, Robo2 acts in trans to inhibit Slit-Robo1 repulsion in pre-crossing commissural axons. eLife 2015; pp. 1–26.

G. Harburg, J. Compton, W. Liu, N. Iwai, S. Zada, R. Marlow, P. Strickland, Y. A. Zeng, and L. Hinck, SLIT/ROBO2 Signaling Promotes Mammary Stem Cell Senescence by Inhibiting Wnt Signaling. Stem Cell Reports 2014; vol. 3, no. 3, pp. 385–393.

H. A. N. Al-wadei, M. H. Al-wadei, M. F. Ullah, and H. M. Schuller, Celecoxib and GABA Cooperatively Prevent the Progression of Pancreatic Cancer In-Vitro and in Xenograft Models of Stress-Free and Stress-Exposed Mice. PLoS ONE 2012; vol. 7, no. 8, pp:11.

Chen, Yi-ju, Stacy R Finkbeiner, Daniel Weinblatt, Matthew J Emmett, Feven Tameire, Maryam Yousefi, Chenghua Yang, et al. De Novo Formation of Insulin-Producing “Neo-β Cell Islets” from Intestinal Crypts. Cell Reports 2013; no. 6: 1046–58. doi:10.1016/j.celrep.2014.02.013.

R. D. Hickey, F. Galivo, J. Schug, M. A. Brehm, A. Haft, Y. Wang, E. Benedetti, G. Gu, M. A. Magnuson, L. D. Shultz, E. Lagasse, D. L. Greiner, K. H. Kaestner, and M. Grompe, Generation of islet-like cells from mouse gall bladder by direct ex vivo reprogramming. Stem Cell Research 2013; vol. 11, no. 1, pp. 503–515.

DOI REFERENCES.

[1] Poitout, Vincent, and R Paul Robertson, Glucolipotoxicity: Fuel excess and β-cell dysfunction. Endocrine Reviews 2008; 29: 351–66.
10.1210/er.2007-0023

[2] S. Jitrapakdee, A. Wutthisathapornchai, J. C. Wallace, and M. J. MacDonald, Regulation of insulin secretion: role of mitochondrial signaling. Diabetologia 2010; 53, 1019–32.
10.1007/s00125-010-1685-0.

[3] Jingbo Pi, Qiang Zhang, Jingqi Fu, Courtney G. Woods, Yongyong Hou, Barbara E Corkey, Sheila Collins, and Melvin E. Andersen, ROS signaling, oxidative stress and Nrf2 in pancreatic beta-cell function. Toxicology and Applied Pharmacology 2011; (244), 77–83.
10.1016/j.taap.2009.05.025.

[6] Chand S, A J Mcknight, S Shabir, W Chan, J A Mccaughan, A P Maxwell, and others, Analysis of Single Nucleotide Polymorphisms Implicate mTOR Signalling in the Development of New-Onset Diabetes after Transplantation. BBACL 2016; 5: 41–45. 10.1016/j.bbacli.2015.12.004

[7] Bijkerk Roel, Pieter Van Der Pol, and Meriem Khairoun, Simultaneous Pancreas–Kidney Transplantation in Patients with Type 1 Diabetes Reverses Elevated MBL Levels in Association with MBL2 Genotype and VEGF Expression. Diabetologia 2016; 853–58. 10.1007/s00125-015-3858-3.

[8] Nicholls Susan, Ricardo Pong-wong, Louisa Mitchard, Ross Harley, Alan Archibald, Andrew Dick, and others, Genome-Wide Analysis in Swine Associates Corneal Graft Rejection with Donor-Recipient Mismatches in Three Novel Histocompatibility Regions and One Locus Homologous to the Mouse H-3 Locus. PLoS ONE 2016; 1–12. 10.1371/journal.pone.0152155.
[9] Torren Cornelis R Van Der, Arnaud Zaldumbide, Dave L Roelen, Gaby Duinkerken, Simone H Brand-schaaf, Mark Peakman, and others, Innate and Adaptive Immunity to Human Beta Cell Lines: Implications for Beta Cell Therapy. Diabetologia 2016; 170–75. 10.1007/s00125-015-3779-1.

[10] Zhang Xiaohai, Nicole M Valenzuela, and Elaine F Reed, HLA class I antibody-mediated endothelial and smooth muscle cell activation. Curr Opin Organ Transplant 2012; August: 17(4). 10.1097/MOT.0b013e328355f1c2.

[11] Harper Ines G, Jason M Ali, Simon J F Harper, Menna R Clatworthy, Thomas M Conlon, Gavin J Pettigrew, and others, Augmentation of Recipient Adaptive Alloimmunity by Donor Passenger Lymphocytes within the Transplant Article Augmentation of Recipient Adaptive Alloimmunity by Donor Passenger Lymphocytes within the Transplant. Cell Reports 2016; 1–14. 10.1016/j.celrep.2016.04.009

[12] Wang Nan, Narendiran Rajasekaran, Tieying Hou, Claudia Macaubas, and D Mellins, Immunological Basis for Rapid Progression of Diabetes in Older NOD Mouse Recipients Post BM-HSC Transplantation. PLoS ONE 2015; 1–16. 10.1371/journal.pone.0128494.

[13] Rodríguez-castelán Julia, Margarita Martinez-gómez, Francisco Castelán, and Estela Cuevas, Hypothyroidism Affects Vascularization and Promotes Immune Cells Infiltration into Pancreatic Islets of Female Rabbits. International Journal of Endocrinology 2015; 19–21. 10.1155/2015/917806.

[14] Malihe-Sadat Poormasjedi-Meibod, Raza B. Jalili, Azadeh Hosseini-Tabatabaei, Ryan Hartwell, Aziz Ghahary,Immuno-Regulatory Function of Indoleamine 2 , 3 Dioxygenase through Modulation of Innate Immune Responses. PLoS ONE 2013; Volume 8, Issue 8, e71044. 10.1371/journal.pone.0071044.

[15] Nagy Nadine, Gernot Kaber, Pamela Y Johnson, John A Gebe, Anton Preisinger, Ben A Falk, and others, Inhibition of Hyaluronan Synthesis Restores Immune Tolerance during Autoimmune Insulitis. The Journal of Clinical Investigation 2015; Volume 125 Number 10. 10.1172/JCI79271DS1

[16] Bogdani Marika, Pamela Y Johnson, Susan Potter-perigo, Nadine Nagy, and Anthony J Day, Hyaluronan and Hyaluronan- Binding Proteins Accumulate in Both Human Type 1 Diabetic Islets and Lymphoid Tissues and Associate With Inflammatory Cells in Insulitis. Diabetes 2014; 63:2727–2743 . 10.2337/db13-12658

[17] Bogdani Marika, Charmaine Simeonovic, Nadine Nagy, Pamela Y Johnson, K Chan, and Thomas N Wight, The Detection of Glycosaminoglycans in Pancreatic Islets and Lymphoid Tissues. Methods Mol Biol 2015; 1229: 413–430. 10.1007/978-1-4939-1714-3_32.

[18] Paudel Suresh, Ioannis M Zacharioudakis, Fainareti N Zervou, Panayiotis D Ziakas, and Eleftherios Mylonakis, Prevalence of Clostridium difficile Infection among Solid Organ Transplant Recipients: A Meta-Analysis of Published Studies. PLoS ONE 2015; 1–16 . 10.1371/journal.pone.0124483

[19] Kim Sung-Han, Hyun-jeong Lee, Sun-mi Kim, Joo Hee Jung, Sung Shin, Young Hoon Kim, and others, Diagnostic Usefulness of Cytomegalovirus ( CMV ) - Specific T Cell Immunity in Predicting CMV Infection after Kidney Transplantation: A Pilot Proof-of- Concept Study. Infect Chemother 2015; 47(2):105-110. 10.3947/ic.2015.47.2.105.
[21] Sue Paul K, Nora Pisanic, Christopher D Heaney, Michael Forman, Alexandra Valsamakis, Annette M Jackson, and others, Hepatitis E Virus Infection Among Solid Organ Transplant Recipients at a North American Transplant Center. Open Forum Infectious Diseases 2012; 1–8. 10.1093/ofid/ofw006.

[22] Chedid Marcio F, Leandro A Scaffaro, Aljamir D Chedid, Antonio C Maciel, Carlos Thadeu S Cerski, Matheus J Reis, and others, Transarterial Embolization and Percutaneous Ethanol Injection as an Effective Bridge Therapy before Liver Transplantation for Hepatitis C-Related Hepatocellular Carcinoma. Gastroenterology Research and Practice 2016; Article ID 9420274, 5 pages. 10.1155/2016/9420274

[23] Saab Sammy, Justin Rheem, Melissa Jimenez, Sherona Bau, Gina Choi, Francisco Durazo, and others, Curing Hepatitis C in liver transplant recipients is associated with changes in Immunosuppressant use. Journal of Clinical and Translational Hepatology 2016; 4:32–38. 10.14218/JCTH.2016.00001

[24] Alan D. Agulnick, Dana M. Ambruzs, Mark A. Moorman, Anindita Bhoumik, Rosemary M. Cesario, Janice K. Payne, Jonathan R. Kelly, Carl Haakmeester, Robert Srijemac, Alistair Z. Wilson, Justin Kerr, Mauro A. Frazier, Evert J. Kroon, Kevin A. D’amour, Tissue Engineering and Regenerative Medicine, Insulin-Producing Endocrine Cells Differentiated In Vitro From Human Embryonic Stem Cells Function in Macroporous Devices In Vivo. Stem Cells Translational Medicine 2015; 4:1214–1222. 10.1007/s00125-013-2955-4

[25] Pepper Andrew R, Rena Pawlick, Boris Gala-lopez, Amanda Macgillivray, Delfina M Mazzuca, David J G White, and others, Diabetes Is Reversed in a Murine Model by Marginal Mass Syngeneic Islet Transplantation Using a Subcutaneous Cell Pouch Device. Transplantation 2015; 99: 2294–2300. 10.1097/TP.0000000000000864

[26] Yap Woon Teck, Xiaomin Zhang, Zachary G Bannon, Dixon B Kaufman, William L Lowe, and Lonnie D She, Collagen IV-Modified Scaffolds Improve Islet Survival and Function and Reduce Time to Euglycemia. Tissue Engineering: Part A 2013; Volume 19, Numbers 21 and 22. 10.1089/ten.tea.2013.0033

[27] McBane Joanne E, Branka Vulesevic, Donna T Padavan, Kimberly A Mcewan, S Gregory, and Erik J Suuronen, Evaluation of a Collagen-Chitosan Hydrogel for Potential Use as a Pro-Angiogenic Site for Islet Transplantation. PLoS ONE 2013;8:1–15 . 10.1371/journal.pone.0077538

[28] Ehrhart Friederike, Esther Mettler, Thomas Böse, Matthias Max Weber, and Julio Alberto Vásquez, Biocompatible Coating of Encapsulated Cells Using Ionotropic Gelation. PLoS ONE 2013; 8: 1–9. 10.1371/journal.pone.0073498

[29] Kuehn Carina, Jonathan R T Lakey, Morgan W Lamb, and Patrick Vermette, Young Porcine Endocrine Pancreatic Islets Cultured in Fibrin Show Improved Resistance toward Hydrogen Peroxide. Islets 2013; 207–15 10.4161/isl.26989.

[30] Guerreiro Luiz Henrique, Mariana F A N Guteres, Bruno Melo-ferreira, Luiza C S Erthal, Silva Rosa, Daniela Lourenço, and others, Preparation and Characterization of PEGylated Amylin. AAPS Pharm.SciTech 2013; Vol. 14, No. 3. 10.1208/s12249-013-9987-4

[31] Yamashita Shingo, Kazuo Ohashi, Rie Utoh, Teruo Okano, and Masakazu Yamamoto, Human Laminin Isotype Coating for Creating Islet Cell Sheets. Cell Medicine 2015; 8: 39–46.
[32] Willenberg Bradley J, Jose Oca-cossio, Yunqing Cai, Alicia R Brown, William L Clapp, Dale R Abrahamson, and others, Repurposed Biological Scaffolds: Kidney to Pancreas. Organogenesis 2015; 47–57. 10.1080/15476278.2015.1067354

[33] Okawa Hiroko, Hiroki Kayashima, Jun-ichi Sasaki, Jiro Miura, Yuya Kamano, Yukihiro Kosaka, and others, Scaffold-Free Fabrication of Osteoinductive Cellular Constructs Using Mouse Gingiva-Derived Induced Pluripotent Stem Cells. Stem Cells International 2016; Article ID 6240794, 11 pages. 10.1155/2016/6240794

[34] Sayed-Hadi Mirmalek-Sani, Giuseppe Orlando, John McQuilling, Rajesh Pareta, David Mack, Marcus Salvatori, Alan C Farney, Robert J Stratta, Anthony Atala, Emmanuel C Opara, and Shay Soker, Porcine pancreas extracellular matrix as a platform for endocrine pancreas bioengineering. Biomaterials 2013; July; 34(22): 5488–5495. 10.1016/j.biomaterials.2013.03.054.

[35] Johansson Ulrika, Massimiliano Ria, Å Karin, and Nancy Dekki Shalaly, Pancreatic Islet Survival and Engraftment Is Promoted by Culture on Functionalized Spider Silk Matrices. PLoS ONE 2015; 1–21. 10.1371/journal.pone.0130169

[36] Wu Di, Jian Wan, Yan Huang, Yibing Guo, Tianxin Xu, Mingyan Zhu, and others, 3D Culture of MIN-6 Cells on Decellularized Pancreatic Scaffold: In Vitro and In Vivo Study. BioMed Research International 2015; Article ID 432645, 8 pages. 10.1155/2015/432645.

[38] Cavallo J A, S C Greco, J Liu, M M Frisella, C R Deeken, and B D Matthews, Remodeling characteristics and biomechanical properties of a crosslinked versus a non-crosslinked porcine dermis scaffolds in a porcine model of ventral hernia repair. Hernia 2015; April ; 19(2): 207–218. 10.1007/s10029-013-1070-2.

[40] Saeromi Jeong, Eun Jung Yoon, Hong Gook Lim, Si Chan Sung, and Yong Jin Kim, The Effect of Space Fillers in the Cross-Linking Processes of Bioprosthesis. BioResearch Open Access 2013;Vol :2, 2. 10.1089/biores.2012.0289.

[42] Jiang T, Ren XJ, Tang JL, Yin H, Wang KJ, Zhou CL, Preparation and characterization of Genipin-crosslinked rat acellular spinal cord scaffolds. Mater Sci Eng C Mater Biol Appl 2013; Aug 1;33(6):3514-21. 10.1016/j.msec.2013.04.046.

[44] Wang Yujia, Ji Bao, Xiujuan Wu, Qiong Wu, Yi Li, Yongjie Zhou, and others, Genipin Crosslinking Reduced the Immunogenicity of Xenogeneic Decellularized Porcine Whole-Liver Matrices through Regulation of Immune Cell Proliferation and Polarization. Scientific Reports 2016; 1–16 . 10.1038/srep24779.

[45] Andreas M. Nyström and Karen L. Wooley, Thiol-functionalized shell crosslinked knedel-like (SCK) nanoparticles: A versatile entry for their conjugation with biomacromolecules. Tetrahedron 2008; September 1; 64(36): 8543–8552. 10.1016/j.tet.2008.04.104.

[46] M. El-Sherbiny and H. D. C. Smyth, Biodegradable nano-micro carrier systems for sustained pulmonary drug delivery: (I)Self-assembled nanoparticles encapsulated in respirable/swellable semi-IPN microspheres. Int J Pharm 2010; August 16; 395. 10.1016/j.ijpharm.2010.05.032.
[47] Tripathi Rahul, and Brahmeshwar Mishra, Development and Evaluation of Sodium Alginate–Polyacrylamide Graft–Co-Polymer-Based Stomach Targeted Hydrogels of Famotidine. AAPS 2012; 13. 10.1208/s12249-012-9824-1

[48] Tania Betancourt, Juan Pardo, Ken Soo, and Nicholas A. Peppas, Characterization of pH-Responsive Hydrogels of Poly(lactic acid-g-Ethylene Glycol) Prepared by UV-Initiated Free Radical Polymerization as Biomaterials for Oral Delivery of Bioactive Agents. J Biomed Mater Res A 2010; April ; 93(1): 175–188. 10.1002/jbm.a.32510

[49] Wang Qinmei, and Qiong Wang, Hydrogels Containing Conductive Polymer Nanoparticles for Biomedical Applications. International Journal of Nanomedicine 2016;11: 131–145. 10.2147/IJN.S94777.

[50] Yeom Junseok, Byung Woo Hwang, Dong Jun Yang, Hong-in Shin, and Sei Kwang Hahn, Effect of Osteoconductive Hyaluronate Hydrogels on Calvarial Bone Regeneration. Biomaterials Research 2014; 18:8. 10.1186/2055-7124-18-8.

[51] Mark T. McClendon and Samuel I. Stupp, Tubular Hydrogels of Circumferentially Aligned Nanofibers to Encapsulate and Orient Vascular Cells. Biomaterials 2012; August ; 33(23): 5713–5722. 10.1016/j.biomaterials.2012.04.040.

[52] Chandrasekhar R. Kothapalli, Patricia M. Taylor, Ryszard T. Smolenski, Magdi H. Yacoub, and Anand Ramamurthi, Transforming Growth Factor Beta 1 and Hyaluronan Oligomers Synergistically Enhance Elastin Matrix Regeneration by Vascular Smooth Muscle Cells. Tissue Engineering: Part A, 2009; Volume 15, Number 3. 10.1089/ten.tea.2008.0040

[53] Rodríguez-castelán, Julia, Margarita Martínez-gómez, Francisco Castelán, and Estela Cuevas, Hypothyroidism Affects Vascularization and Promotes Immune Cells Infiltration into Pancreatic Islets of Female Rabbits. International Journal of Endocrinology 2015; 19–21. 10.1155/2015/917806

[54] Ellis, Cara E, Branka Vulesevic, Erik Suuronen, Telford Yeung, Karen Seeberger, and Gregory S Korbutt, Bioengineering a Highly Vascularized Matrix for the Ectopic Transplantation of Islets. Islets 2013; 5:5, 216–225. 10.4161/isl.27175.

[55] Phelps, Edward A, Kellie L Templeman, and Veterans Affairs, Engineered VEGF-releasing PEG-MAL hydrogel for pancreatic islet vascularization. Drug Deliv Transl Res 2015;April ; 5(2): 125–136. 10.1007/s13346-013-0142-2.

[56] Chen, Wei-sheng, Zhiyi Cao, Satoshi Sugaya, Maria J Lopez, Victor G Sendra, Nora Laver, and others, Pathological Lymphangiogenesis Is Modulated by Galectin-8-Dependent Crosstalk between podoplanin and integrin-associated VEGFR-3. Nature Communications 2016;7: 1–17. 10.1038/ncomms11302.

[57] Fiaschi-taesch, Nathalie M, Dora M Berman, Brian M Sicari, and Karen K Takane, Hepatocyte Growth Factor Enhances Engraftment and Function of Nonhuman Primate Islets. Diabetes 2008; 57. 10.2337/db08-1085.

[58] Song, W Q, D Z Fu, Y Cheng, and Y F Liu, Influence of Adenosine on Preservation of Porcine Pancreas in Islet Transplantation. Genetics and Molecular Research 2015; 14: 18293–301. 10.4238/2015.
[59] Mohiuddin, Muhammad M, Avneesh K Singh, Philip C Corcoran, Marvin L Thomas Iii, Tannia Clark, Billeta G Lewis, and others, Chimeric 2C10R4 Anti-CD40 Antibody Therapy Is Critical for Long-Term Survival of GTKO.hCD46.hTBM Pig-to-Primate Cardiac Xenograft. Nature Communications 2016;7:1–10. 10.1038/ncomms11138.

[60] Eike Kleinert, Martin C. Langenmayer, Bruno Reichart, Jana Kindermann, Barbara Griemert, Andreas Blutke, Kerstin Troidl, Tanja Mayr, Tobias Grantzow, Fatih Noyan, Jan-Michael Abicht, Silvia Fischer, Klaus T. Preissner, Ruediger Wanke, Elisabeth Deindl, Sonja Guethoff, Ribonuclease (RNase) Prolongs Survival of Grafts in Experimental Heart Transplantation. Journal of the American Heart Association 2016; 1–14. 10.1161/JAHA.116.003429.

[63] Juliana Navarro Ueda Yaochite, Carolina Caliari-Oliveira, Lucas Eduardo Botelho de Souza, Lourenço Sbragia Neto, Patrícia Vianna Bonini Palma, Dimas Tadeu Covas, Kelen Cristina Ribeiro Malmegrim, Julio César Voltarelli and Eduardo Antônio Donadi, Therapeutic efficacy and biodistribution of allogeneic mesenchymal stem cells delivered by intrasplenic and intrapancreatic routes in streptozotocin-induced diabetic mice. Stem Cell Research & Therapy 2015; 6:31. 10.1186/s13287-015-0017-1

[67] Ionel Sandovici, Constanze M. Hammerle, Wendy N. Cooper, Noel H. Smith, Jane L. Tarry-Adkins, Benjamin J. Dunmore, Julien Bauer, Simon R. Andrews, Giles S. H. Yeo, Susan E. Ozanne, Miguel Constâncio, Ageing is associated with molecular signatures of inflammation and type 2 diabetes in rat pancreatic islets. Diabetologia 2016; 59:502–511. 10.1007/s00125-015-3837-8

[68] Masako Imaoka, Toshimasa Jindo, and Wataru Takasaki, The Process and Development Mechanism of Age-related Fibrosis in the Pancreatic Islets of Sprague-Dawley Rats: Immunohistochemical Detection of Myofibroblasts and Suppression Effect by Estrogen Treatment. J Toxicol Pathol 2013; 26: 1–10. 10.1293/tox.26.1

[69] Salpeter SJ, Khalaileh A, Weinberg-corem N, Ziv O, Glaser B, Systemic Regulation of the Age-Related Decline of Pancreatic β -Cell Replication. Diabetes 2013; 62(August):2843– 8. 10.2337/db13-0160.

[76] H. A. N. Al-wadei, M. H. Al-wadei, M. F. Ullah, and H. M. Schuller, Celecoxib and GABA Cooperatively Prevent the Progression of Pancreatic Cancer In-Vitro and in Xenograft Models of Stress-Free and Stress-Exposed Mice. PLoS ONE 2012;vol. 7, no. 8, pp:1–11. 10.1371/journal.pone.0043376.

[77] Chen, Yi-ju, Stacy R Finkbeiner, Daniel Weinblatt, Matthew J Emmett, Feven Tameire, Maryam Yousefi, Chenghua Yang, et al. De Novo Formation of Insulin-Producing “Neo - β Cell Islets” from Intestinal Crypts. Cell Reports 2013;no. 6: 1046–58. 10.1016/j.celrep.2014.02.013.

[78] R. D. Hickey, F. Galivo, J. Schug, M. A. Brehm, A. Haft, Y. Wang, E. Benedetti, G. Gu, M. A. Magnuson, L. D. Shultz, E. Lagasse, D. L. Greiner, K. H. Kaestner, and M. Grompe, Generation of islet-like cells from mouse gall bladder by direct ex vivo reprogramming. Stem Cell Research 2013; vol. 11, no. 1, pp. 503–515. 10.1016/j.scr.2013.02.005.