(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
05 June 2025 (05.06.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/117683 A1

(51) International Patent Classification:
A61K 31/045 (2006.01) *A61P 3/10* (2006.01)
A61K 35/39 (2015.01) *C12N 5/071* (2010.01)
A61L 27/54 (2006.01) *A61B 17/00* (2006.01)
A61P 1/18 (2006.01)

(21) International Application Number:
PCT/US2024/057672

(22) International Filing Date:
27 November 2024 (27.11.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/603,878 29 November 2023 (29.11.2023) US
63/662,055 20 June 2024 (20.06.2024) US

(71) Applicant: **UNIVERSITY OF PITTSBURGH-OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION** [US/US]; 1st Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US).

(72) Inventors: **RINEHARDT, Hannah**; 1st Floor Gardner Steel Conference Center (GSCC), 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **GITTES, George, K.**; 2203 S Villa Dr, Gibsonia, Pennsylvania 15044 (US).

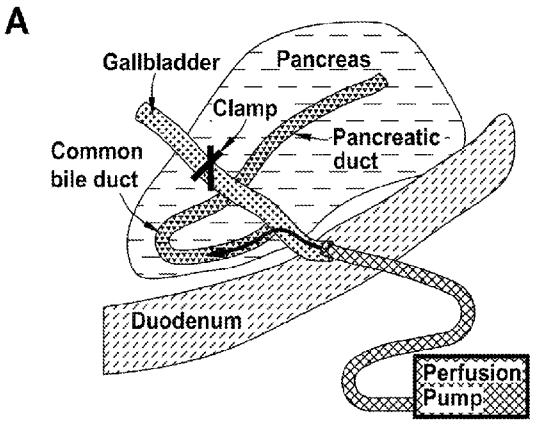
(74) Agent: **SMITH, Amanda** et al.; Meunier Carlin & Curfman LLC, 999 Peachtree Street, NE, Suite 1300, Atlanta, Georgia 30309 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: COMPOSITIONS AND METHODS FOR CHEMICAL PANCREATECTOMY FOR PANCREAS TRANSPLANTATION



(57) Abstract: Provided is a method of preparing a donor pancreas tissue for transplantation comprising sourcing a pancreas tissue that is suitable for transplantation and infusing the pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid plus a contrast agent to ablate, and track ablation of, an exocrine portion of the pancreas tissue. Also provided is a method of transplantation comprising obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function and implanting the donor pancreas tissue into a recipient. The mixed composition may also be used to treat the pancreas of a patient.

WO 2025/117683 A1

COMPOSITIONS AND METHODS FOR CHEMICAL PANCREATECTOMY FOR PANCREAS TRANSPLANTATION

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application 63/603,878, filed November 29th, 2023, and U.S. Provisional Application 63/622,055, filed June 20, 2024, each of which is incorporated by reference herein in its entirety and for all purposes.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under DK120698 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0003] Pancreatic transplantation is a complex procedure, typically reserved for individuals who have specific medical conditions that severely affect the pancreas. The most common indication for pancreatic transplant is severe and uncontrollable type I diabetes or diabetes (type I or type II) that is complicated by end-stage renal disease or severe metabolic complications. Other indications would include less severe type I diabetes in a patient either with or requiring a kidney transplant. Also, pancreatogenic diabetes, which can be secondary to chronic pancreatitis or cystic fibrosis or other. The pancreas for transplantation is typically obtained from a deceased organ donor, though living donor segmental pancreas donation is an option. In the donor operating room, a surgical team performs a pancreatectomy, which involves the removal of the pancreas from the donor's body. The surgical technique may vary depending on the specific circumstances, but it typically involves careful dissection of the blood vessels (e.g., superior mesenteric artery and vein), the pancreatic duct, and the duodenum. Since diabetes often damages both the kidney and the pancreas, some patients may be candidates for a simultaneous kidney-pancreas transplant.

[0004] After excision of the pancreas, the organ is carefully preserved to maintain its viability during transportation from the donor to the recipient's hospital. The most common

method of preservation is cold storage. The pancreas is cooled to a low temperature and placed in a sterile preservation solution to minimize metabolic activity and prevent organ damage until the transplantation procedure.

[0005] Once the recipient is prepared for transplantation, the surgical team performs the pancreas transplantation procedure. Throughout the entire process, meticulous attention is given to maintaining sterility, minimizing ischemic time (the time the organ is without blood flow), and ensuring proper tissue handling to maximize the viability and function of the transplanted pancreas. The recipient's abdomen is opened, and the native (recipient's) pancreas is carefully dissected and removed. The donor pancreas is then prepared for implantation. This involves preparing the blood vessels (arteries and veins) of the recipient to ensure a successful connection with the donor pancreas. The surgeon makes careful anastomoses (connections) between the recipient's blood vessels and those of the donor pancreas to establish blood flow to the transplanted organ. The surgeon may also connect the transplant pancreas to the recipient's digestive or urinary system for exocrine drainage, as discussed in greater detail below. The surgical incisions are closed, and the transplant procedure is completed.

[0006] When successful, a pancreatic transplant can dramatically improve a patient's quality of life, ending the need for glucose monitoring, insulin injections and food restrictions. However, a pancreatic transplant comes with high risks for complications. The body naturally rejects the foreign pancreas, and as such the transplant recipient will need to take immunosuppressive medications to minimize inflammatory damage to the transplant.

[0007] The need for an exocrine drainage system is another complicating factor. The transplant pancreas is typically excised with the donor's duodenum attached to it. This facilitates anastomosis of the transplant to the recipient's digestive or urinary system, providing a pathway for excreted digestive enzymes. Historically, bladder drainage was commonly used due to ease of monitoring the success of the pancreas transplant (i.e., through urinalysis). However, the high rate of urological and metabolic complications led the field to adopt enteric drainage as the preferred technique in recent years. Various surgical techniques for enteric drainage have been developed, but complications still occur in 2%-20% of cases, with intra-abdominal infections being a serious concern. Despite efforts to minimize complications, no universally standardized technique for exocrine pancreatic drainage has been established (1). Cell based therapies might one day pose a clinical alternative to full pancreatic transplantation. However, this area of

research has been burdened with tissue scarcity, the need for chronic immunosuppression, high loss of transferred islet cells, ethical and regulatory issues. As such, improvements in the field of pancreatic transplantation are still highly relevant and desirable.

SUMMARY

[0008] The current disclosure aims to address the problems discussed above by ablating exocrine portions of the donor pancreas tissue prior to transplantation. The ablation of exocrine portions advantageously reduces the antigen load to the recipient, thereby reducing the immune response. However, a donor pancreatic tissue that has been subjected to exocrine ablation retains healthy islet cells and normal levels of endocrine function and insulin production. Exocrine ablation also reduces or eliminates the secretion of digestive enzymes, which can eliminate the need for an exocrine drainage system. Normally, drainage is accomplished by anastomosing the donor duodenum to the recipient intestinal or urinary system. However, foreign intestinal tissue is one of the more potent immune system triggers. The need to include the duodenum for exocrine drainage undermines the immunosuppressant drugs, reducing their effectiveness as compared to other types of transplanted organs. If no digestive enzymes are secreted, there is no need to include donor duodenum in the first place.

[0009] In some aspects, the techniques described herein relate to a method of preparing a donor pancreas tissue for transplantation including: sourcing a pancreas tissue that is suitable for transplantation; and infusing the pancreas tissue with an effective amount of a composition including ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

[0010] In some aspects, the techniques described herein relate to a method, wherein the step of infusing the pancreas tissue is performed in situ within a cadaver.

[0011] In some aspects, the techniques described herein relate to a method, further including explanting infused pancreas tissue from the cadaver.

[0012] In some aspects, the techniques described herein relate to a method, wherein the pancreas tissue has been explanted from a cadaver, and the step of infusing the pancreas tissue is performed ex vivo relative to the cadaver.

[0013] In some aspects, the techniques described herein relate to a method, further including inserting a catheter at least partially into the pancreatic tissue.

[0014] In some aspects, the techniques described herein relate to a method, wherein the step of infusing the pancreas tissue includes infusing the pancreas tissue through a pancreatic duct.

[0015] In some aspects, the techniques described herein relate to a method, wherein the pancreas tissue is a whole pancreas.

[0016] In some aspects, the techniques described herein relate to a method, further including separating a duodenal tissue from the pancreas tissue.

[0017] In some aspects, the techniques described herein relate to a method, wherein the composition includes ethanol in a concentration of from 30% to 100%.

[0018] In some aspects, the techniques described herein relate to a method, wherein the composition includes acetic acid in a concentration of from 0.1 % to 5%.

[0019] In some aspects, the techniques described herein relate to a method, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

[0020] In some aspects, the techniques described herein relate to a method, wherein the composition is infused into the pancreas tissue at a constant rate for from 1 minute to 5 minutes.

[0021] In some aspects, the techniques described herein relate to a method, wherein the composition is infused at an effective infusion pressure of from 100 centimeters to 2000 centimeters of water.

[0022] In some aspects, the techniques described herein relate to a method, wherein the step of infusing the pancreas tissue at least partially chemically ablates the pancreas tissue.

[0023] In some aspects, the techniques described herein relate to a method of transplantation including: obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function; and implanting the donor pancreas tissue into a recipient.

[0024] In some aspects, the techniques described herein relate to a method, further including removing a native pancreas from the recipient before implanting the donor pancreas tissue.

[0025] In some aspects, the techniques described herein relate to a method, wherein the recipient is diabetic.

[0026] In some aspects, the techniques described herein relate to a method, wherein the step of obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function comprises infusing a pancreas tissue with an effective amount of a composition

comprising ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

[0027] In some aspects, the methods include a step of performing an ex vivo functionality analysis on the donor pancreas tissue to assess levels of endocrine function and levels of exocrine function prior to implanting the donor pancreas tissue into a recipient.

[0028] In some aspects, the methods include assessing the endocrine function of the donor pancreas tissue by evaluating the endocrine function of a cadaver from which the donor pancreas tissue is sourced and/or reviewing the health history of the cadaver. Normal levels of endocrine function can include a fasting blood glucose level of less than about 100 mg/dL, a glycated hemoglobin (HbA1c) concentration of less than about 5.7%, and/or a 75 g oral glucose tolerance test (OGTT) result of less than about 140 mg/dL.

[0029] In some aspects, the methods include assessing the exocrine function of the donor pancreas tissue by evaluating the exocrine function of a cadaver from which the donor pancreas tissue is sourced after ablating the exocrine portion of the pancreas tissue. Low levels of exocrine function include a serum 25 hydroxy vitamin D concentration of less than about 20 ng/mL and/or a 72 hour stool fecal fat level of above about 7 g/day.

[0030] In some aspects, the techniques described herein relate to a method of decreasing secretions from exocrine tissues, the method including; advancing a distal portion of a catheter into a pancreatic duct of the subject, delivering an effective amount of a composition including ethanol and/or acetic acid and a contrast agent to the pancreatic duct via the catheter at an effective infusion pressure, wherein the amount and infusion pressure are effective to decrease the secretion of digestive enzymes from one or more exocrine tissues of the pancreas, and limiting backflow of the composition out of the pancreatic duct.

[0031] In some aspects, the techniques described herein relate to a method, further including advancing a distal portion of the catheter through an ampulla of Vater and into a pancreatic duct of the subject.

[0032] In some aspects, the techniques described herein relate to a method, further including advancing an endoscope through an esophagus, a stomach, and a duodenum of the subject and advancing the catheter out a distal port of the endoscope and through the ampulla of Vater.

[0033] In some aspects, the techniques described herein relate to a method, further including advancing a guidewire into a pancreatic duct and advancing the catheter over the guidewire.

[0034] In some aspects, the techniques described herein relate to a method, further including creating tension on a steering wire that attaches to the distal portion of the catheter, and steering the catheter into the pancreatic duct.

[0035] In some aspects, the techniques described herein relate to a method, wherein the composition includes ethanol in a concentration of from 40% to 70%.

[0036] In some aspects, the techniques described herein relate to a method, wherein the composition includes acetic acid in a concentration of from 0.1% to 5%.

[0037] In some aspects, the techniques described herein relate to a method, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

[0038] In some aspects, the techniques described herein relate to a method, wherein the effective infusion pressure is from 100 centimeters to 2000 centimeters of water.

[0039] In some aspects, the techniques described herein relate to a method, further including visualizing the location of the catheter using the composition.

[0040] In some aspects, the techniques described herein relate to a method, further including modulating the effective infusion pressure while the catheter is in the pancreatic duct.

[0041] In some aspects, the techniques described herein relate to a method, wherein limiting backflow of the composition out of the pancreatic duct includes limiting backflow of the composition from the pancreatic duct into a biliary tree, an ampulla of Vater, and/or a duodenum.

[0042] In some aspects, the techniques described herein relate to a method, wherein limiting backflow of the composition further includes activating one or both of an occluding mechanism and/or an aspiration system.

[0043] In some aspects, the techniques described herein relate to a method, wherein activating an occluding mechanism includes pushing a fluid through an occluding mechanism lumen of the catheter and inflating a balloon.

[0044] In some aspects, the techniques described herein relate to a method either, wherein activating an occluding mechanism includes increasing the size of a distal portion of the catheter.

[0045] In some aspects, the techniques described herein relate to a method, wherein activating an occluding mechanism includes advancing or retracting a distal portion of a sheath over the catheter.

[0046] In some aspects, the techniques described herein relate to a method, wherein activating an aspiration system includes creating a negative pressure in an aspiration lumen of the catheter.

[0047] In some aspects, the techniques described herein relate to a method, wherein limiting backflow of the composition further includes maintaining activation of an occluding mechanism for a dwell time of from 3 to 30 minutes.

[0048] In some aspects, the techniques described herein relate to a method, wherein limiting backflow of the composition further includes maintaining activation of an occluding mechanism for a dwell time of from 5 to 15 minutes.

[0049] In some aspects, the techniques described herein relate to a method, wherein the backflow is limited for a time between from 3 to 30 minutes.

[0050] Other systems, methods, features and/or advantages will be or may become apparent to one with skill in the art upon examination of the following drawings and detailed description. It is intended that all such additional systems, methods, features and/or advantages be included within this description and be protected by the accompanying claims.

BRIEF DESCRIPTION OF DRAWINGS

[0051] The components in the drawings are not necessarily to scale relative to each other.

[0052] Figures 1A-1F show the results of pancreatic infusion with green fluorescent protein (GFP). (A) Schematic of the infusion model. (B-D) Retrograde infusion was performed with an adeno-associated virus serotype 8 (AAV) carrying a GFP expression sequence (AAV-GFP). One week after infection, the pancreas was broadly infected, as shown by the gross images (B and C) and by pancreatic sections (D and E) for GFP. Ductal cells are labeled with Dolichus Biflorus Agglutinin (DBA), and cell nuclei are labeled with Hoechst (HO). (F) Quantification of infection efficiency 1 week after infusion of virus. S: spleen; I: intestine. Scale bar is 50 micrometers.

[0053] Figures 2A-2O show the results of mouse pancreatic duct infusion with 100% ethanol at various time points after infusion. Post ethanol infusion pancreas at (A) 6-months showing preserved white islets (arrows). Amylase (AMY) staining is absent at all time points in ethanol-infused pancreas, but insulin (INS) positive β-cells and glucagon (GCG) positive α-cells persist (B: 1 month, C: 3 months, D: 6 months, E: 9 months). (F-I) Sham operated controls show intact islets and AMY-positive acinar tissue (F: 1 month, G: 3 months, H: 6 months, I: 9 months). HO: Hoescht nuclear stain, scale bar is 50 microns (J) Fasting blood glucose shows no difference at multiple time points after ethanol infusion compared to sham-operated mice. (K-N) There was no difference in glucose tolerance testing between ethanol-infused mice as compared to sham-

operated at all time points. (O) The ethanol-infused and sham-operated mice gained weight at a similar rate, with both groups on an elemental diet.

[0054] Figures 3A-3E show that β-cell mass and endocrine function are preserved after infusion of 100% ethanol. (A) There is no difference in β-cell mass in the pancreatic tail between sham-operated and ethanol-infused mice across all time points, suggesting preservation of islets. (B) Blood vessels (CD31 staining), including islet vessels are maintained after ethanol infusion at 9 months. scale bar is 50 micrometers (C) Blood ethanol levels rise quickly after pancreatic ductal ethanol infusion. (D) In vivo and (E) in vitro glucose stimulated insulin secretion (GSIS) show no difference between sham-operated and ethanol-infused mice/islets at the 9-month time point.

[0055] Figure 4 shows histology one week after pancreatic duct ligation (PDL). Control head of the pancreas (left image) shows normal islets (labeled by insulin antibody staining: Ins) and no CD45+ inflammatory cells (labeled by CD45 antibody staining: CD45). Cell nuclei are labeled with Hoechst (HO). After PDL (center image) there is extensive inflammation (CD45), but islets (Ins) are intact. The image at the right shows the normal head (H) and ligated tail (T) after 4 weeks showing the loss of exocrine tissue, but still white dots of islets in the tail.

[0056] Figures 5A-5J are progressive images after PDL that show a loss of islets between week 4 and 12. Ethanol infusion was performed at 8 weeks as an intervention to prevent islet loss. A-E) insulin staining at 0, 1, 4, 12, and 24 weeks after ligation, with islets labeled with DAB for insulin (dark coloring). F-J) Fluorescent immunohistochemistry staining at 0, 1, 4, 12 and 24 weeks after ligation, with islets labeled with insulin (Ins), acinar cells labeled with amylase (Amy), and cell nuclei labeled with Hoechst (HO).

[0057] Figures 6A-6H show the data gathered following PDL, reflecting the persistence of the islet tissue with ethanol infusion. (A-C) Fasting blood glucose levels and glucose tolerance testing are no different among PDL, PDL + ethanol-infused, and sham operated mice at 24-weeks, likely due to the normal islets in the unligated head of the pancreas. (D) In the ligated tail pancreas, no regeneration of exocrine tissue is seen in the PDL model at 24 weeks. There are also very few islets seen. (INS = insulin, AMY = amylase, HO = Hoescht) scale bar is 50 micrometers (E) PDL + ethanol infusion preserves the islets in the ligated tail, while preventing regeneration of exocrine tissue. (F) Sham-operated mice show islets surrounded by exocrine tissue. (G) β-cell mass in the tail is significantly diminished 24-weeks after PDL as compared to sham-operated. Infusion of ethanol at 8-weeks post-PDL prevents β-cell loss. PDL + ethanol-infused mice show no difference

in β-cell mass as compared to sham-operated. (H) Insulin secretion by islets from the pancreatic tail is diminished after PDL per 200 islets, with either low or high glucose concentration exposure, compared to sham-operated tail islets. The PDL + ethanol-infused tail islets have a normal insulin secretion pattern compared to sham-operated control islets.

[0058] Fig. 7 shows a photograph of a pancreas 6 months after infusion with 1% acetic acid. White islets (marked by arrows) are preserved.

[0059] Figures 8A-8B show histology and immunohistochemistry of a pancreas treated with 1% acetic acid. (A) Exocrine pancreatic tissue has been replaced with fat cells, but the islets have remained intact. (B) The tissue is insulin positive and amylase negative, indicating that the exocrine tissue has been ablated.

[0060] Figures 9A-9B show data from behavioral studies that demonstrate that the treatment of mouse pancreas with 1% acetic acid does not cause pain. (A) The distance traveled in meters by mice in the treatment group was not significantly different than the distance traveled by mice in the sham group (B) The rearing, measured in time pressed, was also not significantly different between the treatment and sham groups.

[0061] Figure 10 shows the anatomy of the pancreas and surrounding tissues.

[0062] Figure 11 shows photographs from necropsy of an 8 kg Cynomolgus monkey. (A) Opened duodenum shows the normal location of the opening to the pancreatico-biliary duct (ampulla of Vater) identical to human anatomy. (B) The ERCP catheter is inserted through the ampulla and specifically into the main pancreatic duct. C) Ink injection through the ERCP catheter into the pancreatic duct demonstrates complete perfusion of the entire pancreas (circled dark-stained tissue).

[0063] Figures 12A-12B show fluoroscopic images during the surgery. Fig. 12A shows a catheter in the pancreatic duct (tip of catheter shown by the arrow) and a clamp on the bile duct (arrowhead), and Fig. 12B shows the same shot after infusion of a contrast dye into the pancreatic duct and secondary ducts (arrows).

[0064] Figures 13A-13E show histologic images of a monkey pancreas three weeks after infusion of 2% acetic acid. (A) H&E shows intact islets (i) and fatty degeneration (f) of the exocrine tissue. Immunohistochemistry for insulin (green) and amylase (red) in the pancreatic head (B), body (C), and tail (D), and in a control pancreas from a streptozotocin (insulin-negative islet)

treated monkey pancreas (E). d, duct structure. In (D) the transition point where the infusion was inadequate to ablate the exocrine tissue more distally is shown (dotted line).

[0065] Figure 14 shows an endoscope in the duodenum of a subject, with the catheter entering the pancreatic duct via the ampulla of Vater.

[0066] Figure 15 shows a guidewire and catheter exiting the distal port of an endoscope. The occluding mechanism is activated in this view. Line A-A shows the position of the cross-sectional view depicted in Figure 19.

DETAILED DESCRIPTION

[0067] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate aspects, can also be provided in combination with a single aspect. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single aspect, can also be provided separately or in any suitable subcombination. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure.

[0068] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

[0069] Throughout the description and claims of this specification, the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and are not intended to exclude, for example, other additives, segments, integers, or steps. Furthermore, it is to be understood that the terms comprise, comprising, and comprises as they relate to various aspects, elements, and features of the disclosed invention also include the more limited aspects of "consisting essentially of" and "consisting of."

[0070] As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes aspects having two or more such polymers unless the context clearly indicates otherwise.

[0071] The terms "about" and "approximately" are defined as being "close to" as understood by one of ordinary skill in the art. In one non-limiting embodiment the terms are defined to be within 10%. In another non-limiting embodiment, the terms are defined to be within 5%. In still another non-limiting embodiment, the terms are defined to be within 1%.

[0072] Ranges can be expressed herein as from "about" one particular value and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It should be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

[0073] As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0074] For the terms "for example" and "such as," and grammatical equivalences thereof, the phrase "and without limitation" is understood to follow unless explicitly stated otherwise.

[0075] The terms "treat," "treating," "treatment," and grammatical variations thereof as used herein, include partially or completely delaying, alleviating, mitigating or reducing the intensity of one or more attendant symptoms of a disorder or condition and/or alleviating, mitigating or impeding one or more causes of a disorder or condition. Treatments according to the invention may be applied preventively, prophylactically, pallatively or remedially. Prophylactic treatments are administered to a subject prior to onset of a disease or condition, during early onset, or after an established development of a disease or condition. Prophylactic administration can occur for several days to years prior to the manifestation of symptoms of the disease or condition.

[0076] The terms "prevent," "preventing," "prevention," and grammatical variations thereof as used herein, refer to a method of partially or completely delaying or precluding the onset or recurrence of a disorder or conditions and/or one or more of its attendant symptoms or barring a subject from acquiring or reacquiring a disorder or condition or reducing a subject's risk of acquiring or reacquiring a disorder or condition or one or more of its attendant symptoms. For example, the transplant may prevent the recurrence of diabetes in the recipient.

[0077] References to "donors," "recipients," "patients," or "subjects" can include animals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like.

[0078] As used herein, "pancreatic duct" refers to the main or major pancreatic duct, which is also known as the duct of Wirsung. The pancreatic duct joins the common bile duct just prior to

the ampulla of Vater, after which both ducts perforate the medial side of the second portion of the duodenum at the major duodenal papilla.

[0079] In an aspect, provided is a method of preparing a donor pancreas tissue for transplantation comprising: sourcing a pancreas tissue that is suitable for transplantation; and infusing the pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid to ablate an exocrine portion of the pancreas tissue. For example, the pancreas tissue can be "sourced" from an organ procurement organization, a viable or a non-viable animal (e.g., human), and/or from a bioengineered source (e.g., a lab-grown pancreas tissue). As used herein, the term "suitable for transplantation" refers to a tissue that would be deemed transplantable to a recipient host by a medical practitioner or transplant expert. Factors affecting whether a pancreas tissue is suitable for transplantation can include (but are not limited to): the potential donor's age, size, lifestyle, immunologic compatibility with the recipient, diseases or disorders that may affect the pancreatic tissue function, and or levels of biological markers pertaining to pancreatic tissue function. In some aspects, the pancreas tissue is a whole pancreas. In some aspects, the pancreas tissue is a portion of a whole pancreas.

[0080] As noted above, the methods include a step of infusing the pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid and contrast agent to ablate, and track ablation of, an exocrine portion (which can include the secreting tissue and the ducts) of the pancreas tissue. In some aspects, the step of infusing the pancreas tissue partially or totally chemically ablates the an exocrine portion of the pancreas tissue. An "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages. To "ablate" means to reduce the functionality. For example, treatment with the compositions disclosed herein ablate one or more exocrine portions of the pancreas tissue, meaning that it decreases the secretion of digestive enzymes from one or more exocrine portions of the pancreas tissue. The term "ablate" and grammatical variations thereof as used herein can indicate a partial reduction in functionality or a total reduction in functionality. The term "exocrine tissue" indicates tissue that produces and secretes substances onto an epithelial surface by way of a duct. "Exocrine tissue" also encompasses the ducts through which the secretions are delivered to the rest of the body. In the pancreas, the exocrine tissue is tissue that secretes and delivers digestive enzymes to the

gastrointestinal tract. The cells of the exocrine pancreatic tissue include acinar cells, which produce and secrete digestive enzymes, and duct cells, which produce and secrete bicarbonate.

[0081] In some aspects, the step of infusing the pancreas tissue is performed *in situ* within a cadaver. As used herein, the term "cadaver" refers to a human or other animal that has undergone cardiac death and/or brain death. Under some circumstances, performing the infusion while the donor pancreas tissue is still *in situ* (for example, within a cadaver) can improve the ablation of exocrine tissue. In those cases, the infused donor pancreas tissue is explanted after the infusion step. However, some circumstances may require that the donor pancreas tissue be explanted prior to the infusion step. In those circumstances, the step of infusing the pancreas tissue is performed *ex vivo* relative to the cadaver. Some circumstances where the donor pancreas was infused *in situ* may require additional infusion steps after explanation (*ex vivo* relative to the cadaver).

[0082] The pancreas tissue may be explanted from a cadaver alone or surrounded by nearby anatomical parts, such as, but not limited to, kidney, duodenum and spleen, superior mesenteric artery, celiac axis, and aortic cuff. Some aspects include a step of separating the duodenal tissue from the pancreas tissue and not transplanting the separated duodenal tissue into the recipient. This is a departure from conventional technique. Duodenal tissue is often included with transplanted pancreas tissue because it serves as the drainage system for the pancreas tissue after transplantation. Currently, the intestinal connection required to include the duodenal tissue could result in anastomotic leaks, sepsis, pancreatic fistula, pseudocysts, and/or abscesses, any of which could result in rejection of the pancreas tissue or endanger the wellbeing of the recipient. However, foreign intestinal tissue can trigger a strong immune response that has to be managed with significantly higher doses of immunosuppressants than is typically used for organ transplantation, making the recipient especially vulnerable to illness or disease. This is a result of a large amount of exocrine pancreas tissue and duodenum, especially the Peyer's patches in the duodenum that contain highly immunogenic dendritic cells and B lymphocytes putting the patient at higher risk for rejection and ultimately graft failure. Importantly, the ablation of exocrine tissue eliminates the fluid generated by the pancreas tissue that the duodenal tissue does not need to be included for drainage. As such, the risks of fluid buildup, transplant rejection, and other consequences of transplantation are all minimized by the present disclosure.

[0083] Some delivery systems for performing the methods disclosed herein are described in U.S. Patent No. 11,071,550, which is hereby incorporated by reference in its entirety and for all

purposes. In some aspects, the method of preparing a donor pancreas tissue for transplantation further comprises inserting a catheter at least partially into the pancreatic tissue. In some aspects, the catheter can be inserted into the pancreatic duct. For example, the catheter can be advanced through the ampulla of Vater. And Backflow of the infused composition can be limited, for example, by an occluding system, an aspiration system, or both. For example, an occluding system might include an occluding mechanism that protrudes radially outward from the catheter such that it contacts the walls of the pancreatic duct to physically block fluid exiting the catheter from moving past it in a proximal direction. In some aspects, the methods further include infusing a contrast fluid into the pancreatic duct and visualizing the location of the catheter.

[0084] While the examples disclosed herein discuss compositions comprising ethanol or acetic acid for ablation of the pancreatic exocrine tissue and contrast agent for tracking, other compositions might comprise other substances for ablation of the pancreatic exocrine tissue. For example, an effective amount of a composition comprising formaldehyde, propyl alcohol, hydrochloric acid, acrolein, chromic acid and/or acetone may also be delivered to the pancreatic duct, in place of or in combination with ethanol and/or acetic acid, at an infusion pressure effective to decrease the secretion of digestive enzymes from one or more exocrine tissues of the pancreas.

[0085] In some embodiments, the concentration of ethanol in the composition being delivered into the pancreatic duct can be, for example, from 30% to 100% volume/volume, including from 40% to 90%, from 50% to 80%, from 60% to 70%, from 30% to 60%, from 40% to 50%, from 70% to 100%, or from 80% to 90% volume/volume. In some embodiments, the composition comprises 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% ethanol. The percentages are given as percent volume/volume in water.

[0086] In some embodiments, the concentration of acetic acid in the composition being delivered into the pancreatic duct can be, for example, from 0.1% to 5% volume/volume, including from 0.1% to 1%, from 0.5% to 4.5%, from 1% to 4%, from 1% to 3%, from 1% to 2%, from 2% to 5%, from 2% to 4%, from 2% to 3%, from 3% to 5%, or from 4% to 5% volume/volume. In some embodiments, the composition comprises 0.1%, 0.5%, 1%, 1.5%, 2%, 2.5%, or 3% acetic acid. The percentages are given as percent volume/volume in water.

[0087] In some embodiments, the composition being delivered into the pancreatic duct can be a mixture of ethanol, acetic acid and/or any other substance that decreases the secretion of digestive enzymes from one or more exocrine tissues of the pancreas. For example, the composition can

contain a mixture of from 10 to 99.9% volume/volume ethanol and from 0.1% to 5% volume/volume acetic acid. However, in some embodiments, a composition containing ethanol is not mixed with acetic acid or any other substances that decrease the secretion of digestive enzymes. In some embodiments, a composition containing acetic acid is not mixed with ethanol or any other substances that decrease the secretion of digestive enzymes.

[0088] The infusion pressure can be, for example, from 100 to 2000 centimeters of water, including from 300 to 1700 centimeters of water, from 300 to 1500 centimeters of water, from 300 to 1200 centimeters of water, or from 500 to 1000 centimeters of water. In some embodiments, the infusion pressure can be 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, or 1400 centimeters of water. In some embodiments, the infusion pressure can be modulated while the catheter is in the pancreatic duct, for example, to change the pressure of the composition as it is being delivered to the pancreatic duct.

[0089] The dwell time refers to a period after the infusion during which backflow of the composition out of the pancreatic tissue is limited (i.e., by an occluding system). Sufficient dwell time allows the pancreatic tissue to absorb the composition. The dwell time can be, for example, from 3 to 30 minutes, including from 5 to 25 minutes, or from 5 to 20 minutes, or from 5 to 15 minutes, including 5 minutes, 6 minutes, 7 minutes, 8 minutes, 9 minutes, 10 minutes, 11 minutes, 12 minutes, 13 minutes, 14 minutes or 15 minutes of dwell time. In some aspects, the composition is infused into the pancreas tissue at a constant rate over a duration of, for example, from 1 minute to 5 minutes, including from 1 minute to 2 minutes, from 2 minutes to 3 minutes, from 3 minutes to 4 minutes, from 4 minutes to 5 minutes, from 1 minute to 3 minutes, from 2 minutes to 4 minutes, from 3 minutes to 5 minutes, from 1.5 minutes to 4.5 minutes, from 2.5 minutes to 3.5 minutes, from 1.5 minutes to 2.5 minutes, or from 3.5 minutes to 4.5 minutes. In some aspects, the composition is infused into the pancreas tissue at a constant rate for 1 minute, 1.5 minutes, 2 minutes, 2.5 minutes, 3 minutes, 3.5 minutes, 4 minutes, 4.5 minutes, or 5 minutes.

[0090] In another aspect, provided is a method of transplantation comprising: obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function; and implanting the donor pancreas tissue into a recipient. The "donor" pancreas tissue is any whole or portion of a pancreas that is external to a recipient, which can be achieved via explantation from a viable or non-viable animal or by bioengineering (i.e., lab-grown pancreas tissue). The "recipient" is any subject into whom the donor pancreas tissue is surgically implanted.

[0091] In some aspects, the method of transplantation further comprises removing a native pancreas from the recipient before implanting the donor pancreas tissue. In some aspects, the native pancreas has been previously removed from the recipient.

[0092] In some aspects, the recipient has a disease or condition that could benefit from pancreas transplantation including, but not limited to, diabetes (type I or type II), hypoglycemia, pancreatitis, pancreatic cancer, cystic fibrosis (or any other causes of pancreatogenic diabetes), pancreatic tumors, autoimmune pancreatitis, congenital insulin deficiency, or hyperinsulinism. In some aspects, the transplant treats the disease or condition and provides relief of symptoms to the recipient. In some aspects, the transplant acts prophylactically to prevent further progression or recurrence of the disease or condition.

[0093] In some aspects, the donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function is obtained by infusing a pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid and contrast agent to ablate, and track ablation of, an exocrine portion of the pancreas tissue.

[0094] The donor pancreas tissue can be assessed to determine if it has normal levels of endocrine function prior to implanting the donor pancreas tissue into a recipient. In some aspects, levels of endocrine function are determined by an ex vivo functionality analysis of the donor pancreas tissue prior to transplantation. In some aspects, levels of endocrine function are determined by evaluating the endocrine function of a cadaver (for example, a brain-dead cadaver) from which the donor pancreas tissue is sourced. Alternatively, or in addition, the health history of a cadaver (brain-dead and/or cardiac-dead) can be reviewed to evaluate previous endocrine function. In both of these scenarios, normal levels of endocrine function can be defined by the standard non-diabetic ranges: a fasting blood glucose level of less than about 100 mg/dL, a glycated hemoglobin (HbA1c) concentration of less than about 5.7%, and/or a 75 g oral glucose tolerance test (OGTT) result of less than about 140 mg/dL). In some situations, however, a donor pancreas tissue may be sufficiently normal to be acceptable for transplant despite having endocrine function in prediabetic ranges. For example, in some situations, a fasting blood glucose level between 100 mg/dL and 125 mg/dL, a glycated hemoglobin (HbA1c) concentration between 5.7% and 6.4%, and/or a 75 g oral glucose tolerance test (OGTT) result between 140 mg/dL and 199 mg/mL can be sufficiently normal for use in the methods disclosed herein.

[0095] In some aspects, normal levels of endocrine function include a fasting blood glucose level of less than about 100 mg/dL, or less than about 95 mg/dL, or less than about 90 mg/dL, or less than about 85 mg/dL, or less than about 80 mg/dL, or less than about 75 mg/dL. In some aspects, normal levels of endocrine function include a glycated hemoglobin (HbA1c) concentration of less than 5.7%, or less than about 5.6%, or less than about 5.5%, or less than about 5.4%, or less than about 5.2%, or less than about 5%, or less than about 4.8%, or less than about 4.6%, or less than about 4.4%, or less than about 4.2%, or less than about 4%. In some aspects, normal levels of endocrine function include a 75 g oral glucose tolerance test (OGTT) result of less than about 140 mg/dL, or less than about 135 mg/dL, or less than about 130 mg/dL, or less than about 125 mg/dL, or less than about 120 mg/dL, or less than about 115 mg/dL, or less than about 110 mg/dL, or less than about 105 mg/dL, or less than about 100 mg/dL, or less than about 95 mg/dL, or less than about 90 mg/dL, or less than about 85 mg/dL.

[0096] The donor pancreas tissue can be assessed to determine if it has low levels of exocrine function (for example, after ablation of the exocrine portion of the pancreas tissue). In some aspects, levels of exocrine function are determined by an ex vivo functionality analysis of the donor pancreas tissue prior to transplantation. In some aspects, levels of exocrine function are determined by evaluating the exocrine function of a cadaver (such as, for example, a brain-dead cadaver) from which the donor pancreas tissue is sourced. In this scenario, levels of exocrine function can be considered "low" with a serum 25 hydroxy vitamin D concentration of less than about 20 ng/mL and/or a 72 hour stool fecal fat level of above about 7 g/day.

[0097] In some aspects, low levels of exocrine function include a serum 25 hydroxy vitamin D concentration of less than about 20 ng/mL, or less than about 18 ng/mL, or less than about 16 ng/mL, or less than about 14 ng/mL, or less than about 12 ng/mL, or less than about 10 ng/mL. In some aspects, low levels of exocrine function include a 72 hour stool fecal fat level of above about 7 g/day, or above about 7.5 g/day, or above about 8 g/day, or above about 8.5 g/day, or above about 9 g/day, or above about 9.5 g/day, or above about 10 g/day.

[0098] In another aspect, method of preparing a donor pancreas tissue for transplantation is provided. The method includes sourcing a pancreas tissue that is suitable for transplantation. Also, infusing the pancreas tissue with an effective amount of a composition comprising an ablation composition combined with a contrast agent. For example, the composition may include one or both of an ethanol and/or acetic acid mixed with a contrast agent. In this manner, the contrast agent

can facilitate tracking of ablation of an exocrine portion of the pancreas tissue. By adding a radiographic contrast agent to the ablation composition, the perfusion of the ablation composition can be tracked with the contrast agent.

[0099] The composition may be provided separately from the method or the method may include creating the composition. For example, the ablation compound may be combined with the contrast agent in the operating room relatively contemporaneous with the preparation of the donor pancreas tissue for transplantation. The contrast agent and the ablation compound may be mixed together by hand or by using a mixer. In any case, after infusion of the pancreas tissue with the composition the contrast agent can facilitate tracking of the ablation, such as by using radiography to track the contrast agent. Since the contrast agent is mixed with the ablation compound its infusion corresponds with that of the ablation compound and thus provides a visual indication of the extent of ablation. The composition may also be mixed separately and supplied in convenient containers for use during the procedure.

[0100] In one example, Figures 12A-12B illustrate the extent of ablation when the compound includes a combination of the ablation compound and the contrast agent. In this example, the ablation would be effective coextensive with the contrast dye in the pancreatic tissue shown in Fig. 12B. In another example, rather than an ink injection the composition with the contrast agent could be injected into the pancreatic duct to demonstrate complete perfusion of the entire pancreas.

[0101] As noted above, an "effective amount" of composition comprising ethanol and/or acetic acid and contrast agent includes partially or totally chemically ablating an exocrine portion of the pancreas tissue. The "effective amount" is the amount sufficient to effect beneficial or desired results. When preparing the mixed composition of contrast agent and ablation compound, the method may include calculating the dilution of the ablation compound to ensure maintenance of the effective amount in the overall composition. For example, if the contrast agent halves the concentration of the ablation compound then the original concentration of the ablation compound may be doubled per unit of volume.

[0102] In another aspect, the composition including the ablation compound and the contrast agent is used to treat a subject. A distal portion of a catheter is advanced into a pancreatic duct of the subject. An effective amount of the mixed composition (for example a mixture of ethanol and/or acetic acid and contrast agent) is delivered to the pancreatic duct via the catheter at an effective infusion pressure. The amount and infusion pressure are effective to decrease the

secretion of digestive enzymes from the exocrine tissues of the pancreas. In addition, the backflow of the composition out of the pancreatic duct is limited, such as by use of an occluding mechanism.

[0103] The method can also include advancing a distal portion of the catheter through an ampulla of Vater and into a pancreatic duct of the subject.

[0104] The method can also include advancing an endoscope through an through an esophagus, a stomach, and a duodenum of the subject and advancing the catheter out a distal port of the endoscope and through the ampulla of Vater.

[0105] The method may further include advancing a guidewire into a pancreatic duct and advancing the catheter over the guidewire. The method may also include creating tension on a steering wire that attaches to the distal portion of the catheter, and steering the catheter into the pancreatic duct.

[0106] The method may also include visualizing the location of the catheter using the composition.

EXAMPLE 1

[0107] Retrograde infusion of ethanol in mouse pancreatic duct: In the methods described herein, ethanol is introduced to the mouse pancreas following a procedure that was initially developed for retrograde intraductal infusion of virus for gene therapy purposes (2). In that gene therapy experiment, the pancreatic infusion transfected the tissue with green fluorescent protein (GFP). Results of that study are included here, as Figure 1, to demonstrate that pancreatic infusion enables complete or nearly complete access to the pancreatic tissue. Fig.1A is a schematic of the infusion path. Figs. 1B and 1C are photographs demonstrating that GFP fluoresces throughout the pancreas 1 week after transfection. Figs. 1D and 1E are immunofluorescence images showing the successful GFP transfection on a microscopic level. Fig. 1F graphs the infection efficiency of various cell types using the pancreatic infusion method.

[0108] In a study analyzing the results of pancreatic duct infusion with ethanol, infusion was followed by sacrifice at 1-month, 3-months, 6-months, and 9-months. In this example, the ethanol concentration is 100%. Fig. 2A shows a representative photograph of the treated pancreas tissue 6-months post-treatment. The islets are visible as small white areas (labeled by white arrows). These islets are not normally visible due to the opaque overlying acinar tissue. Upon sacrifice,

there is no evidence of pancreatic acinar tissue, but the pancreatic endocrine tissue, including both β-cells and the glucagon-producing alpha cells, is well-preserved. See Figs. 2B-2E, where amylase (AMY) staining is absent at all time points in ethanol-infused pancreas, but insulin (INS) positive β-cells and glucagon (GCG) positive α-cells persist (B: 1 month, C: 3 months, D: 6 months, E: 9 months). In Figs. 2F-2I, sham operated controls show intact islets and AMY-positive acinar tissue (F: 1 month, G: 3 months, H: 6 months, I: 9 months).

[0109] Fasting glucose levels and glucose tolerance tests show no difference between ethanol infused mice and sham-operated controls at all time points (Figs. 2J-2N), suggesting that β-cell function remains intact. Body weight of these mice is also not different from controls (Fig. 2O), but an elemental diet is required to avoid malabsorption.

[0110] There is also no significant difference in β-cell mass at any time point (Fig. 3A). A possible explanation is that exocrine destruction is due to direct exposure of the exocrine ducts and acini to the ethanol. Further diffusion of ethanol beyond the exocrine pancreas into the stroma of the pancreas and near the islets may be accompanied by dilution of the ethanol by tissue fluids, plus rapid removal of the ethanol by lymphatic and blood flow, thus sparing the islets (Fig. 3B). Significant levels of ethanol are found in the blood within 5 minutes of infusion (Fig. 3C), confirming that the ethanol rapidly exits from the pancreas. In addition to a normal β-cell mass, endocrine function also appears normal, as shown by in vivo measurements of insulin levels during glucose tolerance testing, as well as in vitro glucose-stimulated insulin secretion (GSIS) at the 9-month time point (Figs. 3D-3E). Consistent with this normal function, the islet vasculature appears to be intact (CD31 staining, Fig. 3B). Taken together, these data show ablation of the exocrine pancreas, without significant loss of β-cell mass or endocrine function.

[0111] Mouse pancreatic duct ligation (PDL) yields a model that is reflective of chronic pancreatitis with progressive loss of islet tissue. In the PDL procedure, the pancreatic duct is ligated at the mid-point of the pancreas (Fig. 4, right image). Thus, only the distal half (tail) of the pancreas is affected since the ligation is positioned at the mid-point of the duct. Initially (weeks 0-8 after ligation), there is near total destruction of the exocrine ductal and acinar cells in the ligated tail, but with preservation of β-cell mass and glucose tolerance (Fig. 4, left and center images). Figs. 5A-5J demonstrate that twelve weeks after PDL, the distal pancreatic islets are nearly absent, likely due to secondary injury stemming from the death of the exocrine cells. Figs. 5A-5E show insulin staining using DAB, whereas Figs. 5F-5J show insulin and amylase staining

using immunofluorescence (with a Hoescht counterstain for labeling cell nuclei). The condition is thus reflective of chronic pancreatitis-related diabetes. Mice maintain a normal fasting blood glucose level and glucose tolerance, even after 24 weeks of PDL, presumably due to the normal islets in the unligated head of the pancreas (Figs. 6A-6B). In the absence of ethanol infusion, , a substantial loss of islets and β-cell mass occurred specifically in the PDL-tail compared with sham-controls (0.11 ± 0.01 milligrams vs 0.72 ± 0.01 milligrams, $p<0.05$) (Fig. 3G). This islet loss is in line with the islet loss seen in subjects with chronic pancreatitis related diabetes (CPRD).

[0112] The mouse PDL model is used to determine whether an ethanol infusion shows a similar exocrine ablation and islet sparing in the setting of chronic pancreatitis, and if this selective exocrine ablation can protect the islets to prevent CPRD. Infusion of ethanol into the distal pancreatic duct (starting at a point just beyond the ligation) at the 8-week time point post-PDL prevents the loss of islets in the pancreatic tail, with no detectable recurrent inflammation and no detectable regeneration of acinar cells (as demonstrated by immunofluorescent staining for insulin and amylase, shown in Figs. 6D-6F). Jaundice rates are less than 5% (jaundice being an indicator of biliary stricturing and/or obstruction). The β-cell mass in the ligated tail after PDL and ethanol infusion shows no difference from the β-cell mass in the same anatomical distribution (tail) of sham-operated controls (0.61 ± 0.01 milligrams vs 0.72 ± 0.01 milligrams). This preservation of β-cell mass is in contrast to the loss of β-cell mass in the ligated portion of the pancreas after PDL without ethanol infusion (0.11 ± 0.01 milligrams vs 0.61 ± 0.01 milligrams, $p<0.05$) (Fig. 6G). In vitro GSIS by islets harvested from the tail show that the insulin secretion specifically from the isolated tail is low in the setting of PDL alone (low number of islets, so required pooling of specimens) as compared to the controls or to PDL with ethanol infusion (Fig. 6H). The negative effects of a pancreatitis milieu on β-cell function are well known (8). Taken together, these data show that ethanol infusion at 8 weeks prevents PDL related islet destruction and improves β-cell function, and thus suggest that ethanol infusion may prevent CPRD in humans. Other potential benefits of the ethanol infusion procedure could include decreased chronic pain, fewer pancreatic cancers, and a reduction of the other life-threatening complications of chronic pancreatitis.

[0113] Methods: *Mouse manipulation:* All mouse experiments are approved by the Animal Research and Care Committee at the Children's Hospital of Pittsburgh and the University of Pittsburgh IACUC. C57BL/6 mice are all 10 week-old-males purchased from Jackson Laboratory (Bar Harbor, ME, USA). Pancreatic ductal infusion technique is performed as described (2, 9, 10),

however infusion is 100% ethanol at a catheter rate of 10 microliters/min to a total volume of 100 microliters. PDL is performed and validated as previously described (6, 7, 9). Intervention, to prevent β-cell loss following PDL, is performed at 8-weeks post-PDL with 100% ethanol as described above. All groups receive elemental diet to counteract the lack of pancreatic enzymes in the ethanol and PDL models.

[0114] *Glucose Stimulated Insulin Secretion (GSIS):* For in vivo GSIS, after 16-hour overnight fast, 9-month post-ethanol infused, 9-month sham operated, 24-week post-PDL, and 24-week post-PDL/16-week post-ethanol mice receive glucose by intraperitoneal injections (1 milligram/gram as a 10% solution). Blood samples are obtained from tail-tip bleedings and blood glucose levels are measured. Plasma insulin levels are determined by ELISA (ALPCO, Salem, NH, USA). For in vitro static GSIS, digestion and islet isolation is performed as previously described (6, 7, 9) for each condition. Mouse islets are cultured in Ham's F10 medium (Life Technologies, St. Louis, MO, USA) supplemented with 0.5% BSA (Sigma-Aldrich, St. Louis, MO, USA), 2 millimoles/liter glutamine, 2 millimoles/liter calcium, and 5 millimoles/liter glucose at 37 degrees Celsius, 95% air/5% CO2. After overnight culture, 200 islets per condition are transferred to new plates and treated with low glucose (2.8 millimoles/liter) and high glucose (16.7 millimoles/liter) conditions. Islets are pelleted by centrifugation and lysed in acid ethanol for assessment of insulin in media and islets by radioimmunoassay (Linco Research Inc., St. Charles, Missouri, USA). Results are reported as insulin secreted (nanograms/milliliter) per hour normalized to number of islets.

[0115] *Histology and Immunohistochemistry*: All pancreas samples are fixed and cryo-protected in 30% sucrose overnight before freezing, as described before (7, 9, 12). Primary antibodies for immunostaining are: guinea pig polyclonal antiinsulin (Dako, Carpinteria, CA, USA), goat polyclonal anti-glucagon (Santa Cruz Biotechnology, Dallas, Texas, USA), rat polyclonal anti-CD31 (BD Biosciences, San Jose, California, USA), and rabbit polyclonal anti-amylase (Santa Cruz Biotechnology, Dallas, Texas, USA). Secondary antibodies for indirect fluorescent staining are Cy2, Cy3, and Cy5-conjugated guinea pig and goat-specific (Jackson ImmunoResearch Labs, West Grove, PA, USA). Nuclear staining is performed with Hoechst solution (Becton-Dickinson Biosciences). Staining and imaging sections are performed as previously described (7). Histological quantification is performed on the basis of at least 10

sections that are 100 micrometers apart for each mouse. Quantification of β-cell mass is performed as has been previously described (9, 12).

[0116] *Data analysis:* GraphPad Prism 6.0 (GraphPad Software, Inc. La Jolla, CA) is used for statistical analyses. All values are depicted as mean ± standard error of the mean. Five repeats are analyzed in each condition. All data are statistically analyzed using one-way ANOVA with a Bonferroni correction, followed by Fisher's Exact Test to compare two groups. Significance is considered when $p < 0.05$.

EXAMPLE 2

Retrograde infusion of acetic acid in mouse pancreatic duct

[0117] The pancreatic infusion methods described in Example 1 were performed in mice with 1% acetic acid. Fig. 7 shows ablation of the exocrine tissue with visible intact islets, demonstrating that the 1% acetic acid infusion allowed endocrine tissue to be preserved. Fig. 8A shows a histology image of treated pancreatic tissue. Exocrine pancreatic tissue has been replaced with fat cells, but the islets have remained intact. Fig. 8B shows immunohistochemistry of treated pancreatic tissue. The tissue is insulin positive and amylase negative, indicating that the exocrine tissue has been ablated. The mixture of acetic acid and ethanol does not cause diabetes. Fasting glucose levels and glucose tolerance tests show no difference between ethanol infused mice and sham operated controls at all time points. Figs. 9A and 9B are the results of open field testing, which quantitatively tracks mouse movements in different ways that reflect the degree of pain that they are experiencing. The distance traveled in meters by mice in the treatment group was not significantly different than the distance traveled by mice in the sham group (Fig. 9A). The rearing, measured in time pressed, was also not significantly different between the treatment and sham groups (Fig. 9B). These results demonstrate that the treatment does not cause pain.

EXAMPLE 3

Retrograde infusion of acetic acid in Cynomologus pancreatic duct

[0118] The primate pancreas has a more rigid structure and lower tissue compliance than the mouse pancreas. For reference, Figure 10 shows an anatomical schematic of the human pancreas 1, duodenum 3, liver 5, ampulla of Vater 9, pancreatic duct 11, bile duct 13, cystic duct 15, left hepatic duct 17, right hepatic duct 19, and common hepatic duct 21.

[0119] Cynomologus monkeys can be used to study the retrograde infusion protocol in primates. All procedures are performed in accordance with the regulations specified by the University of Pittsburgh IACUC. The Cynomologus monkeys are first quarantined for 30 days, then transferred to the primate facility and given a 1 to 2-week acclimatization period before operating. After acclimatization, the animals undergo a laparotomy and duodenotomy with cannulation of the ampulla of Vater and temporary clamping of the common bile duct to prevent perfusion of the liver (additional details below).

[0120] A necropsy of an 8 kilogram Cynomologus monkey demonstrated that the related anatomical structures are similar to humans (Fig. 11). For example, there is a major papilla and a minor papilla. The major papilla drains the bile and most of the pancreatic juice. The common bile duct fuses with the main pancreatic duct (Duct of Wirsung in humans) to form a short common channel (approximately 1-1.5cm). In Fig. 11A, the location of the ampulla of Vater is visible through the opened duodenum in a position that is similar to the human anatomy. Fig. 11B shows an endoscopic retrograde cholangiopancreatography (ERCP) catheter being inserted through the ampulla of Vater, where it is routed into the main pancreatic duct. Fig. 11C shows the results of an ink injection through the ERCP catheter into the pancreatic duct, demonstrating complete perfusion of the entire pancreas (dark-stained tissue within the oval).

[0121] Acetic acid (2%) and contrast fluid is then infused at a specified rate, pressure, and volume via a pressure-regulated infusion pump. For example, an 8 to 9 kilogram Cynomolgus can receive 7 milliliters of 2% acetic acid, at a pressure of 500 centimeters of water. Fluoroscopic dye can also be infused to confirm the location and positioning of the catheter (Fig. 12A and 12B). The volume and pressure of the infusion can be varied to balance the ablation of the exocrine tissue with the retention of the islet tissue (increasing the volume and/or pressure ablates additional exocrine tissue, whereas decreasing the volume and/or pressures retains additional islet tissue) and tracking of the ablation using radiographic processes. The catheter and clamp are then removed and the surgery completed. The Cynomologus monkeys recover well from this procedure.

[0122] The pancreas is harvested 3 to 6 weeks later. Figures 13A-13E shows histologic images of a monkey pancreas three weeks after infusion of 2% acetic acid. This perfusion resulted in ablation of the exocrine pancreas in the head and body of the pancreas, and part of the tail.

[0123] Methods

[0124] *Cynomologus infusion procedure details*: After induction of general anesthesia, the abdomen is prepped and draped and a 10 to 12 centimeter upper abdominal midline incision created. The duodenum is fully mobilized out of the retroperitoneum and a non-crushing clamp applied to the common bile duct to prevent the composition from perfusing the bile duct and liver. A two centimeter duodenotomy is then created to expose the ampulla of Vater, which is cannulated with a 2.8 French double lumen umbilical artery catheter. A clamp is then placed on the minor papilla and catheter to prevent back leaking of the composition. Radio-opaque contrast is then infused into the smaller channel of the catheter (or remains from the mixed composition) under fluoroscopic guidance to confirm filling of the pancreatic duct, and no filling of the bile duct. Once confirmed, the infusion pump is connected to the other channel of the catheter and the pancreas is infused, followed by the 10-minute dwell time with the clamps and catheter left in place. The clamps and catheter are then removed and the duodenum and abdomen closed. This infusion surgery is well tolerated by Cynomologus monkeys.

[0125] The pancreas is harvested 3 to 6 weeks later. In some cases, or for some test groups, multiple infusions can be performed over the course of the study to ensure complete ablation of the exocrine pancreatic tissue.

[0126] During the 3 to 6-week period between the procedure and the sacrifice, Cynomologus monkeys are supplied with CREON enzymes as a dietary supplement to avoid malabsorption due to loss of acinar enzyme production by the pancreas. Random blood glucose checks are performed two to three times per week to confirm euglycemia. One day prior to sacrifice, a standard oral glucose tolerance test is performed. Throughout the 3 to 6-week period, the Cynomologus monkeys are monitored for scleral icterus as a sign of possible biliary obstruction due to bile duct structuring caused by the infusion.

[0127] At harvest, the pancreas and duodenum are examined grossly in situ, and then removed en bloc along with the common bile duct. The common bile duct and ampulla of Vater are opened to inspect for strictures. The pancreas is examined for the presence of intact acinar tissue, which is easily discernible with only simple 2 to 3 x loupe magnification. At this time, if the acinar/exocrine tissue is gone, the islets are visible as small white spheres, as shown in Fig. 2A (these islets are not normally visible due to the opaque overlying acinar tissue). The pancreas is then processed for histologic analysis to confirm the presence or absence of acinar tissue and ducts, to confirm the presence of islets, and to confirm normal morphometry of the islets. In addition,

beta cell mass is calculated based on the percent insulin positive area on histology along with the gross weight of the pancreas. The experimental values are compared to the normal range for Cynomologus NHP pancreas beta cell mass (3) to determine whether the infusion has decreased beta cell mass significantly.

EXAMPLE 4

Chemical pancreatectomy and transplantation

[0128] Pancreas transplantation is being applied with increasing frequency in the treatment of diabetes mellitus Type 1 and selected cases of Type 2. It is known that pancreas transplantation can consistently establish normoglycemic insulin-independent state. Due to the increased use of different pancreas transplantation models in rats for studying the metabolic function of the transplanted pancreas, reviewing the various techniques in pancreas transplant is necessary.

[0129] *Chemical pancreatectomy:* A rat can be prepared for surgery, given isoflurane anesthesia. Once the animal is anesthetized, it can be placed on a temperature-controlled stage to maintain normothermia. The skin is sterilized using three betadine swabs and three 70% ethanol swabs prior toward making an incision. An incision measuring about 2 cm is made in the upper midline of the abdomen. The skin is sterilized using three betadine swabs and three 70% ethanol swabs prior toward making an incision. The duodenum is isolated to expose the common bile duct, after which a microclamp can be placed on the common bile duct above the branching of the pancreatic duct. A 31-gauge blunt-ended catheter can then be inserted into the common bile duct transduodenally through the sphincter of Oddi, which is then clamped with another microclamp to prevent backflow. The other end of the catheter is connected to a micro-infusion apparatus, which delivers precise volumes of acetic acid and contrast agent at a controlled rate. 1 % acetic acid is injected using a 31 Gauge catheter at a constant rate for 2-3 minutes.

[0130] *Pancreas transplant:* The donor rat can be prepared for surgery, given isoflurane anesthesia and monitored. The anesthetized donor rat can undergo midline laparotomy with an upward displacement of the liver and exposure of the common bile duct for temporary clamping. A duodenotomy with a 30-gauge needle can be performed followed by the advancement of a 31-gauge blunt catheter inserted into the pancreatic duct and clamped in place. Saline at an appropriate volume for pancreatic size can be infused at a rate of 50 μL/minute. Systemic heparin can be administered. The aorta can be cross-clamped, the cava incised, and arterial infusion of cold

heparinized lactated ringers can be followed by procurement of the pancreas with duodenum and spleen, superior mesenteric artery, celiac axis, and aortic cuff. This can then be transplanted into the recipient retroperitoneum by midline laparotomy of the anesthetized recipient rat after left nephrectomy. Venous anastomosis of the portal vein graft to the recipient's left renal vein can be performed over a polyester cuff. Arterial anastomosis of the graft aorta to the recipient's left renal artery can be performed over a polyester cuff. A hand-sewn anastomosis of the graft duodenum to the recipient's bladder in an end-to-side fashion can be performed for exocrine drainage.

[0131] Graft splenectomy can be performed after reperfusion. A surgical drain adjacent to the bladder anastomosis can be left in place to bulb suction. The abdomen and skin are then closed and the rat is allowed to recover.

[0132] Alternatively, a chemical pancreatectomy can be performed on the donor pancreas prior to procurement. For chemical pancreatectomy, anesthetized donor rats can undergo chemical pancreatectomy as described above. Then, heparinization and cross-clamping of the aorta can be performed. These procedures can be followed by the same steps described above. The pancreas can then be procured without the duodenum and transplanted as described above, and the anastomosis of the duodenum to the recipient's bladder can be eliminated. The blood vessels of the pancreas can be attached to the iliac vessels.

[0133] Surgical drain output and drain amylase can be measured on post-operative day 3 and 5 to assess the post-operative condition. All surgical drains can be removed on post-operative day 5.

EXAMPLE 5

Infusion procedure and devices for performing the same

[0134] This example describes an infusion procedure. Fig. 10 displays the relevant anatomy for the following discussion. Briefly, an endoscope, for example, a duodenoscope, is routed through a subject's digestive tract and into the duodenum 3 until it is adjacent with the ampulla of Vater 9. The ampulla of Vater 9 is inspected using the endoscope. As shown in Fig. 14R, a catheter 33 (such as the one shown in Figure 15) is routed through the endoscope 25, out a distal port 27 at a distal portion 23 of the endoscope 25, through the ampulla of Vater 9, and into the pancreatic duct 11. The distal end of the catheter is placed into the pancreatic duct 11, about 1 to 2 centimeters from the proximal end of the pancreatic duct 11, as shown in Fig. 14. The catheter

can deliver a composition including an ablation compound and a contrast liquid, for example, a radiopaque dye, into the pancreatic duct 11 for visualization by an imaging system, for example, a fluoroscopic imaging system.

[0135] As shown in Fig. 15, the distal portion of the catheter can include an occluding system that includes an occluding mechanism 36a, which is activated to seal the proximal portion of the pancreatic duct 11 prior to infusion of the composition. This limits the extent that the composition can escape the pancreatic duct 11 to contact and thus damage the biliary tree or the duodenum 3. The distal portion of the catheter 33 can also (or alternatively) include an aspiration system that creates a negative suction to remove proximally travelling fluid through aspiration port 45, further limiting the extent that the composition can leak into the biliary tree or the digestive tract. In some embodiments, the composition is completely prevented from entering tissue structures other than the pancreatic duct by the occluding mechanism 36a, the aspiration port 45, or a combination thereof. Once the occluding mechanism 36a and/or aspiration port 45 are activated, pressurized fluid is delivered to the pancreatic duct 11 via infusion fluid port 32. The occluding mechanism 36a and/or aspiration port(s) 45 are then deactivated, the catheter 33 retracted back into the endoscope 25, and the endoscope 25 is retracted from the subject.

[0136] Fig. 15 shows the distal portion 23 of an endoscope 25. The endoscope 25 can include a distal port 27, a camera 29, and a light 31. Catheter 33 exits the endoscope via distal port 27, and may be routed over guidewire 34 for steering purposes. An occluding mechanism 36a is used to limit the extent that the composition can leak proximally during the procedure. In some embodiments, the occluding mechanism 36a is positioned less than 50 millimeters from the distal end of the catheter 33, including less than 50, less than 40, less than 30, and less than 20 millimeters from the distal end of the catheter 33. For example, the occluding mechanism can be placed from 5 to 15 millimeters proximal to the distal end of the catheter 33. The occluding mechanism 36a can be joined to the catheter 33, or it can be a separate component from the catheter 33. In the embodiment shown in Fig. 15, the occluding mechanism 36a is a balloon that can contact the walls of the pancreatic duct 11 to prevent backflow of the composition.

EXAMPLE CLAUSES

[0137] Aspect 1. A method of preparing a donor pancreas tissue for transplantation comprising: sourcing a pancreas tissue that is suitable for transplantation; and infusing the pancreas

tissue with an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

[0138] Aspect 2. The method of aspect 1, further comprising mixing the contrast agent with ethanol and/or acetic acid to create the composition.

[0139] Aspect 3. The method of either of aspects 1 or 2, further comprising tracking the ablation of the exocrine portion of the pancreas tissue.

[0140] Aspect 4. The method of aspect 3, wherein tracking the ablation includes tracking filling of the pancreas tissue by the composition using the contrast agent.

[0141] Aspect 5. The method of any one of aspects 1-4, wherein the step of infusing the pancreas tissue is performed in situ within a cadaver.

[0142] Aspect 6. The method of any one of aspects 1-5, further comprising explanting infused pancreas tissue from the cadaver.

[0143] Aspect 7. The method of any one of aspects 1-6, wherein the pancreas tissue has been explanted from a cadaver, and the step of infusing the pancreas tissue is performed ex vivo relative to the cadaver.

[0144] Aspect 8. The method of any one of aspects 1-7, further comprising inserting a catheter at least partially into the pancreatic tissue.

[0145] Aspect 9. The method of any one of aspects 1-8, wherein the step of infusing the pancreas tissue comprises infusing the pancreas tissue through a pancreatic duct.

[0146] Aspect 10. The method of any one of aspects 1-9, wherein the pancreas tissue is a whole pancreas.

[0147] Aspect 11. The method of any one of aspects 1-10, further comprising separating a duodenal tissue from the pancreas tissue.

[0148] Aspect 12. The method of any one of aspects 1-11, wherein the composition comprises ethanol in a concentration of from 30% to 50%.

[0149] Aspect 13. The method of any one of aspects 1-12, wherein the composition comprises acetic acid in a concentration of from 0.1 % to 5%.

[0150] Aspect 14. The method of any one of aspects 1-13, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

[0151] Aspect 15. The method of any one of aspects 1-14, wherein the composition is infused into the pancreas tissue at a constant rate over a duration of from 1 minute to 5 minutes.

[0152] Aspect 16. The method of any one of aspects 1-15, wherein the composition is infused at an effective infusion pressure of from 100 centimeters to 2000 centimeters of water.

[0153] Aspect 17. The method of any one of aspects 1-16, wherein the step of infusing the pancreas tissue at least partially chemically ablates the pancreas tissue.

[0154] Aspect 18. A method of decreasing secretions from exocrine tissues, the method comprising; advancing a distal portion of a catheter into a pancreatic duct of a subject, delivering an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to the pancreatic duct via the catheter at an effective infusion pressure, wherein the amount and infusion pressure are effective to decrease the secretion of digestive enzymes from one or more exocrine tissues of the pancreas, and limiting backflow of the composition out of the pancreatic duct.

[0155] Aspect 19. The method of aspect 18, further comprising advancing a distal portion of the catheter through an ampulla of Vater and into a pancreatic duct of the subject.

[0156] Aspect 20. The method of either aspects 18 or 19, further comprising advancing an endoscope through an esophagus, a stomach, and a duodenum of the subject and advancing the catheter out a distal port of the endoscope and through the ampulla of Vater.

[0157] Aspect 21. The method of any one of aspects 18-20, further comprising advancing a guidewire into a pancreatic duct and advancing the catheter over the guidewire.

[0158] Aspect 22. The method of any one of aspects 18-20, further comprising creating tension on a steering wire that attaches to the distal portion of the catheter, and steering the catheter into the pancreatic duct.

[0159] Aspect 23. The method of any one of aspects 18-22, wherein the composition comprises ethanol in a concentration of from 40% to 70%.

[0160] Aspect 24. The method of any one of aspects 18-23, wherein the composition comprises acetic acid in a concentration of from 0.1% to 5%.

[0161] Aspect 25. The method of any one of aspects 18-24, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

[0162] Aspect 26. The method of any one of aspects 18-25, wherein the effective infusion pressure is from 100 centimeters to 2000 centimeters of water.

[0163] Aspect 27. The method of any one of aspects 18-26, further comprising visualizing the location of the catheter using the composition.

[0164] Aspect 28. The method of any one of aspects 18-27, further comprising modulating the effective infusion pressure while the catheter is in the pancreatic duct.

[0165] Aspect 29. The method of any one of aspects 18-28, wherein limiting backflow of the composition out of the pancreatic duct comprises limiting backflow of the composition from the pancreatic duct into a biliary tree, an ampulla of Vater, and/or a duodenum.

[0166] Aspect 30. The method of any one of aspects 18-29, wherein limiting backflow of the composition further comprises activating one or both of an occluding mechanism and/or an aspiration system.

[0167] Aspect 31. The method of aspect 30, wherein activating an occluding mechanism comprises pushing a fluid through an occluding mechanism lumen of the catheter and inflating a balloon.

[0168] Aspect 32. The method either of aspects 30 or 31, wherein activating an occluding mechanism comprises increasing the size of a distal portion of the catheter.

[0169] Aspect 33. The method of any one of aspects 30-32, wherein activating an occluding mechanism comprises advancing or retracting a distal portion of a sheath over the catheter.

[0170] Aspect 34. The method of any one of aspects 30-33, wherein activating an aspiration system comprises creating a negative pressure in an aspiration lumen of the catheter.

[0171] Aspect 35. The method of any one of aspects 30-34, wherein limiting backflow of the composition further comprises maintaining activation of an occluding mechanism for a dwell time of from 3 to 30 minutes.

[0172] Aspect 36. The method of aspect 35, wherein limiting backflow of the composition further comprises maintaining activation of an occluding mechanism for a dwell time of from 5 to 15 minutes.

[0173] Aspect 37. The method of any one of aspects 18-36, wherein the backflow is limited for a time between from 3 to 30 minutes.

[0174] Aspect 38. A method of transplantation comprising: obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function; and implanting the donor pancreas tissue into a recipient.

[0175] Aspect 39. The method of aspect 38, further comprising removing a native pancreas from the recipient before implanting the donor pancreas tissue.

[0176] Aspect 40. The method of any one of aspects 38-39, wherein the recipient is diabetic.

[0177] Aspect 41. The method of any one of aspects 38-40, wherein the step of obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function comprises infusing a pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

[0178] Aspect 42. The method of any one of aspects 38-41, further comprising performing an ex vivo functionality analysis on the donor pancreas tissue to assess levels of endocrine function and/or levels of exocrine function prior to implanting the donor pancreas tissue into a recipient.

[0179] Aspect 43. The method of any one of aspects 38-42, further comprising assessing the endocrine function of the donor pancreas tissue by evaluating the endocrine function of a cadaver from which the donor pancreas tissue is sourced and/or reviewing the health history of the cadaver.

[0180] Aspect 44. The method of aspect 43, wherein normal levels of endocrine function include a fasting blood glucose level of less than about 100 mg/dL, a glycated hemoglobin (HbA1c) concentration of less than about 5.7%, and/or a 75 g oral glucose tolerance test (OGTT) result of less than about 140 mg/dL.

[0181] Aspect 45. The method of any one of aspects 38-44, further comprising assessing the exocrine function of the donor pancreas tissue by evaluating the exocrine function of a cadaver from which the donor pancreas tissue is sourced after ablating the exocrine portion of the pancreas tissue.

[0182] Aspect 46. The method of aspect 45, wherein low levels of exocrine function include a serum 25 hydroxy vitamin D concentration of less than about 20 ng/mL and/or a 72 hour stool fecal fat level of above about 7 g/day.

[0183] The following patents, applications and publications as listed below and throughout this document are hereby incorporated by reference in their entirety herein.

Reference list

1. Ferrer-Fabrega *et al.*, Exocrine drainage in pancreas transplantation: Complications and management World J Transplant 2020; 10(12): 392-403.

2. Xiao X, Guo P, Prasadan K, Shiota C, Peirish L, Fischbach S, Song Z, Gaffar I, Wiersch J, El-Gohary Y, Husain SZ, Gittes GK. Pancreatic cell tracing, lineage tagging and targeted genetic

manipulations in multiple cell types using pancreatic ductal infusion of adeno-associated viral vectors and/or cell-tagging dyes. Nat Protoc. 2014 Dec;9(12):2719-24.

3. Saisho Y, Butler AE, Manesso E, Galasso R, Zhang L, Gurlo T, Toffolo GM, Cobelli C, Kavanagh K, Wagner JD, Butler PC. Relationship between fractional pancreatic beta cell area and fasting plasma glucose concentration in monkeys. Diabetologia. 2010 Jan;53(1):111-4.

4. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24(3):349-358.

5. Pan FC, Bankaitis ED, Boyer D, et al. Spatiotemporal patterns of multipotentiality in Ptf1a-expressing cells during pancreas organogenesis and injury-induced facultative restoration. Development. 2013;140(4):751-764.

6. Xiao X, Chen Z, Shiota C, et al. No evidence for beta cell neogenesis in murine adult pancreas. J Clin Invest. 2013;123(5):2207-2217.

7. Xiao X, Wiersch J, El-Gohary Y, et al. TGFbeta receptor signaling is essential for inflammation-induced but not beta-cell workload-induced beta-cell proliferation. Diabetes. 2013;62(4):1217-1226.

8. Levy P, Dominguez-Munoz E, Imrie C, Lohr M, Maisonneuve P. Epidemiology of chronic pancreatitis: burden of the disease and consequences. United European Gastroenterol J. 2014;2(5):345-354.

9. Xiao X, Gaffar I, Guo P, et al. M2 macrophages promote beta-cell proliferation by upregulation of SMAD7. Proc Natl Acad Sci U S A. 2014;111(13):E1211-1220.

10. Xiao X, Prasadan K, Guo P, et al. Pancreatic duct cells as a source of VEGF in mice. Diabetologia. 2014;57(5):991-1000.

11. Xiao X, Guo P, Shiota C, et al. Neurogenin3 activation is not sufficient to direct duct-to-beta cell transdifferentiation in the adult pancreas. J Biol Chem. 2013;288(35):25297-25308.

12. Xiao X, Guo P, Chen Z, et al. Hypoglycemia reduces vascular endothelial growth factor A production by pancreatic beta cells as a regulator of beta cell mass. J Biol Chem. 2013;288(12):8636-8646.

What is claimed is:

1. A method of preparing a donor pancreas tissue for transplantation comprising:

sourcing a pancreas tissue that is suitable for transplantation; and

infusing the pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

2. The method of claim 1, further comprising mixing the contrast agent with ethanol and/or acetic acid to create the composition.

3. The method of either of claims 1 or 2, further comprising tracking the ablation of the exocrine portion of the pancreas tissue.

4. The method of claim 3, wherein tracking the ablation includes tracking filling of the pancreas tissue by the composition using the contrast agent.

5. The method of any one of claims 1-4, wherein the step of infusing the pancreas tissue is performed *in situ* within a cadaver.

6. The method of any one of claims 1-5, further comprising explanting infused pancreas tissue from the cadaver.

7. The method of any one of claims 1-6, wherein the pancreas tissue has been explanted from a cadaver, and the step of infusing the pancreas tissue is performed *ex vivo* relative to the cadaver.

8. The method of any one of claims 1-7, further comprising inserting a catheter at least partially into the pancreatic tissue.

9. The method of any one of claims 1-8, wherein the step of infusing the pancreas tissue comprises infusing the pancreas tissue through a pancreatic duct.

10. The method of any one of claims 1-9, wherein the pancreas tissue is a whole pancreas.

11. The method of any one of claims 1-10, further comprising separating a duodenal tissue from the pancreas tissue.

12. The method of any one of claims 1-11, wherein the composition comprises ethanol in a concentration of from 30% to 50%.

13. The method of any one of claims 1-12, wherein the composition comprises acetic acid in a concentration of from 0.1 % to 5%.

14. The method of any one of claims 1-13, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

15. The method of any one of claims 1-14, wherein the composition is infused into the pancreas tissue at a constant rate over a duration of from 1 minute to 5 minutes.

16. The method of any one of claims 1-15, wherein the composition is infused at an effective infusion pressure of from 100 centimeters to 2000 centimeters of water.

17. The method of any one of claims 1-16, wherein the step of infusing the pancreas tissue at least partially chemically ablates the pancreas tissue.

18. A method of decreasing secretions from exocrine tissues, the method comprising;

advancing a distal portion of a catheter into a pancreatic duct of a subject,

delivering an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to the pancreatic duct via the catheter at an effective infusion pressure,

wherein the amount and infusion pressure are effective to decrease the secretion of digestive enzymes from one or more exocrine tissues of the pancreas, and

limiting backflow of the composition out of the pancreatic duct.

19. The method of claim 18, further comprising advancing a distal portion of the catheter through an ampulla of Vater and into a pancreatic duct of the subject.

20. The method of either claims 18 or 19, further comprising advancing an endoscope through an esophagus, a stomach, and a duodenum of the subject and advancing the catheter out a distal port of the endoscope and through the ampulla of Vater.

21. The method of any one of claims 18-20, further comprising advancing a guidewire into a pancreatic duct and advancing the catheter over the guidewire.

22. The method of any one of claims 18-20, further comprising creating tension on a steering wire that attaches to the distal portion of the catheter, and steering the catheter into the pancreatic duct.

23. The method of any one of claims 18-22, wherein the composition comprises ethanol in a concentration of from 40% to 70%.

24. The method of any one of claims 18-23, wherein the composition comprises acetic acid in a concentration of from 0.1% to 5%.

25. The method of any one of claims 18-24, wherein the effective amount of the composition is from 3 milliliters to 50 milliliters.

26. The method of any one of claims 18-25, wherein the effective infusion pressure is from 100 centimeters to 2000 centimeters of water.

27. The method of any one of claims 18-26, further comprising visualizing the location of the catheter using the composition.

28. The method of any one of claims 18-27, further comprising modulating the effective infusion pressure while the catheter is in the pancreatic duct.

29. The method of any one of claims 18-28, wherein limiting backflow of the composition out of the pancreatic duct comprises limiting backflow of the composition from the pancreatic duct into a biliary tree, an ampulla of Vater, and/or a duodenum.

30. The method of any one of claims 18-29, wherein limiting backflow of the composition further comprises activating one or both of an occluding mechanism and/or an aspiration system.

31. The method of claim 30, wherein activating an occluding mechanism comprises pushing a fluid through an occluding mechanism lumen of the catheter and inflating a balloon.

32. The method either of claims 30 or 31, wherein activating an occluding mechanism comprises increasing the size of a distal portion of the catheter.

33. The method of any one of claims 30-32, wherein activating an occluding mechanism comprises advancing or retracting a distal portion of a sheath over the catheter.

34. The method of any one of claims 30-33, wherein activating an aspiration system comprises creating a negative pressure in an aspiration lumen of the catheter.

35. The method of any one of claims 30-34, wherein limiting backflow of the composition further comprises maintaining activation of an occluding mechanism for a dwell time of from 3 to 30 minutes.

36. The method of claim 35, wherein limiting backflow of the composition further comprises maintaining activation of an occluding mechanism for a dwell time of from 5 to 15 minutes.

37. The method of any one of claims 18-36, wherein the backflow is limited for a time between from 3 to 30 minutes.

38. A method of transplantation comprising:

obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function; and

implanting the donor pancreas tissue into a recipient.

39. The method of claim 38, further comprising removing a native pancreas from the recipient before implanting the donor pancreas tissue.

40. The method of any one of claims 38-39, wherein the recipient is diabetic.

41. The method of any one of claims 38-40, wherein the step of obtaining a donor pancreas tissue having normal levels of endocrine function and low levels of exocrine function comprises infusing a pancreas tissue with an effective amount of a composition comprising ethanol and/or acetic acid and a contrast agent to ablate an exocrine portion of the pancreas tissue.

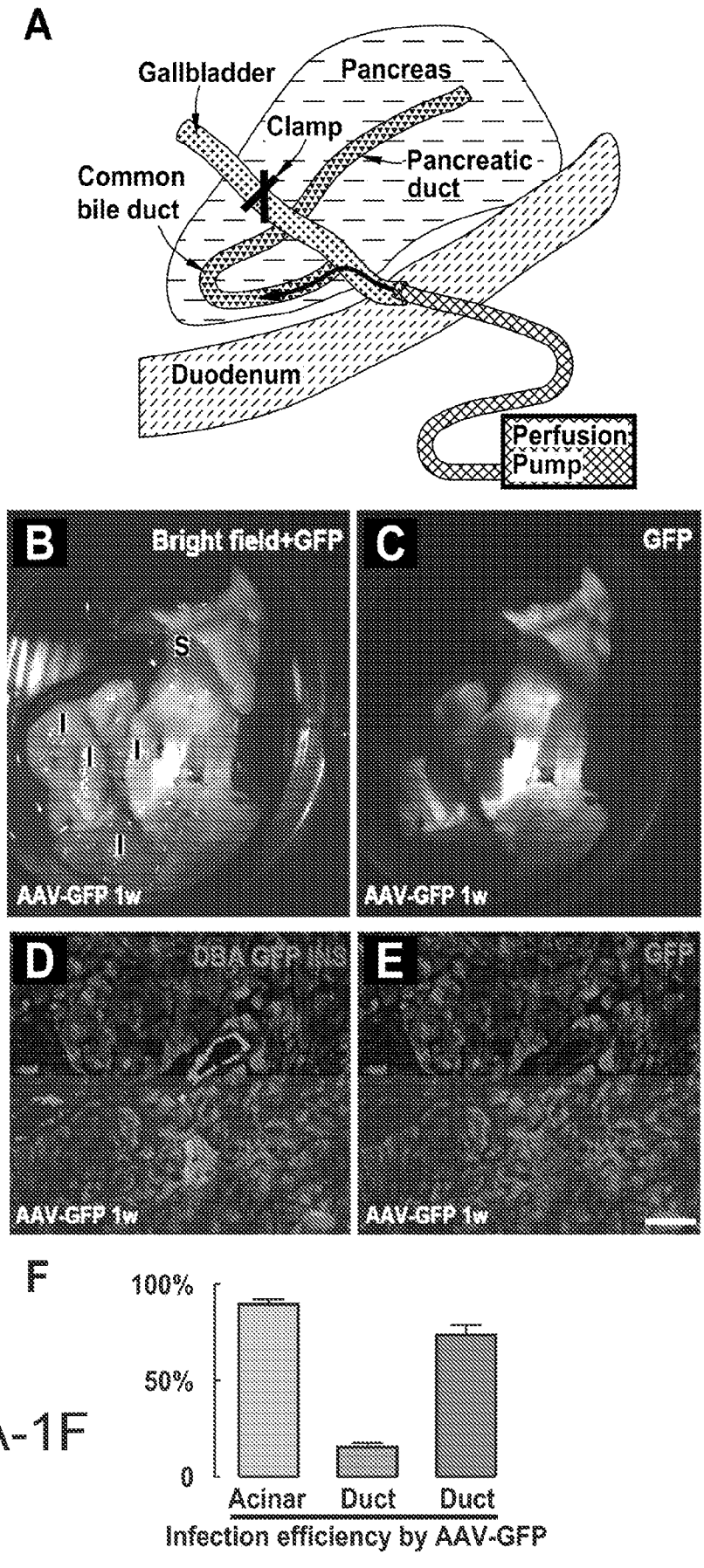
42. The method of any one of claims 38-41, further comprising performing an ex vivo functionality analysis on the donor pancreas tissue to assess levels of endocrine function and/or levels of exocrine function prior to implanting the donor pancreas tissue into a recipient.

43. The method of any one of claims 38-42, further comprising assessing the endocrine function of the donor pancreas tissue by evaluating the endocrine function of a cadaver from which the donor pancreas tissue is sourced and/or reviewing the health history of the cadaver.

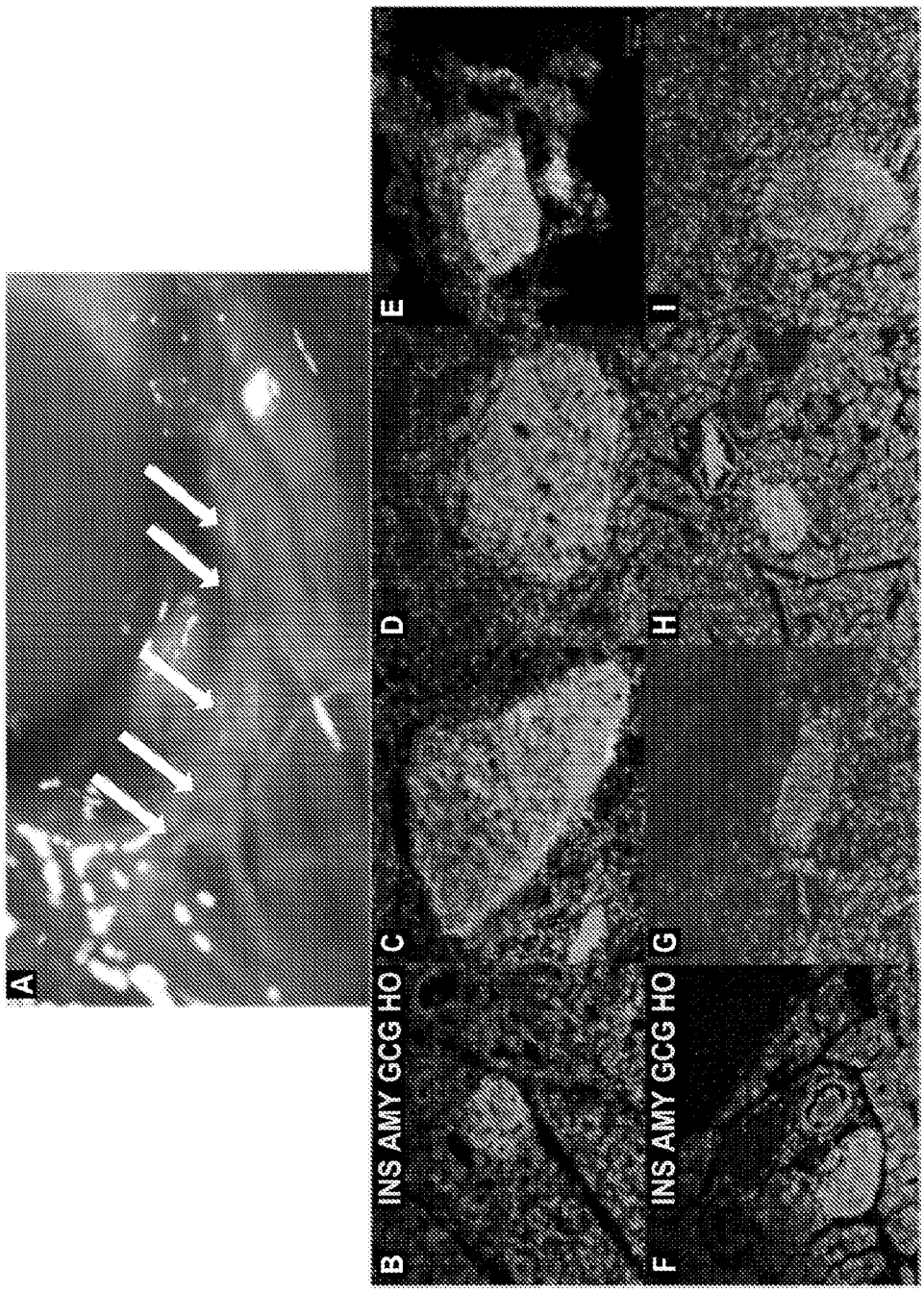
44. The method of claim 43, wherein normal levels of endocrine function include a fasting blood glucose level of less than about 100 mg/dL, a glycated hemoglobin (HbA1c) concentration of less than about 5.7%, and/or a 75 g oral glucose tolerance test (OGTT) result of less than about 140 mg/dL.

45. The method of any one of claims 38-44, further comprising assessing the exocrine function of the donor pancreas tissue by evaluating the exocrine function of a cadaver from which the donor pancreas tissue is sourced after ablating the exocrine portion of the pancreas tissue.

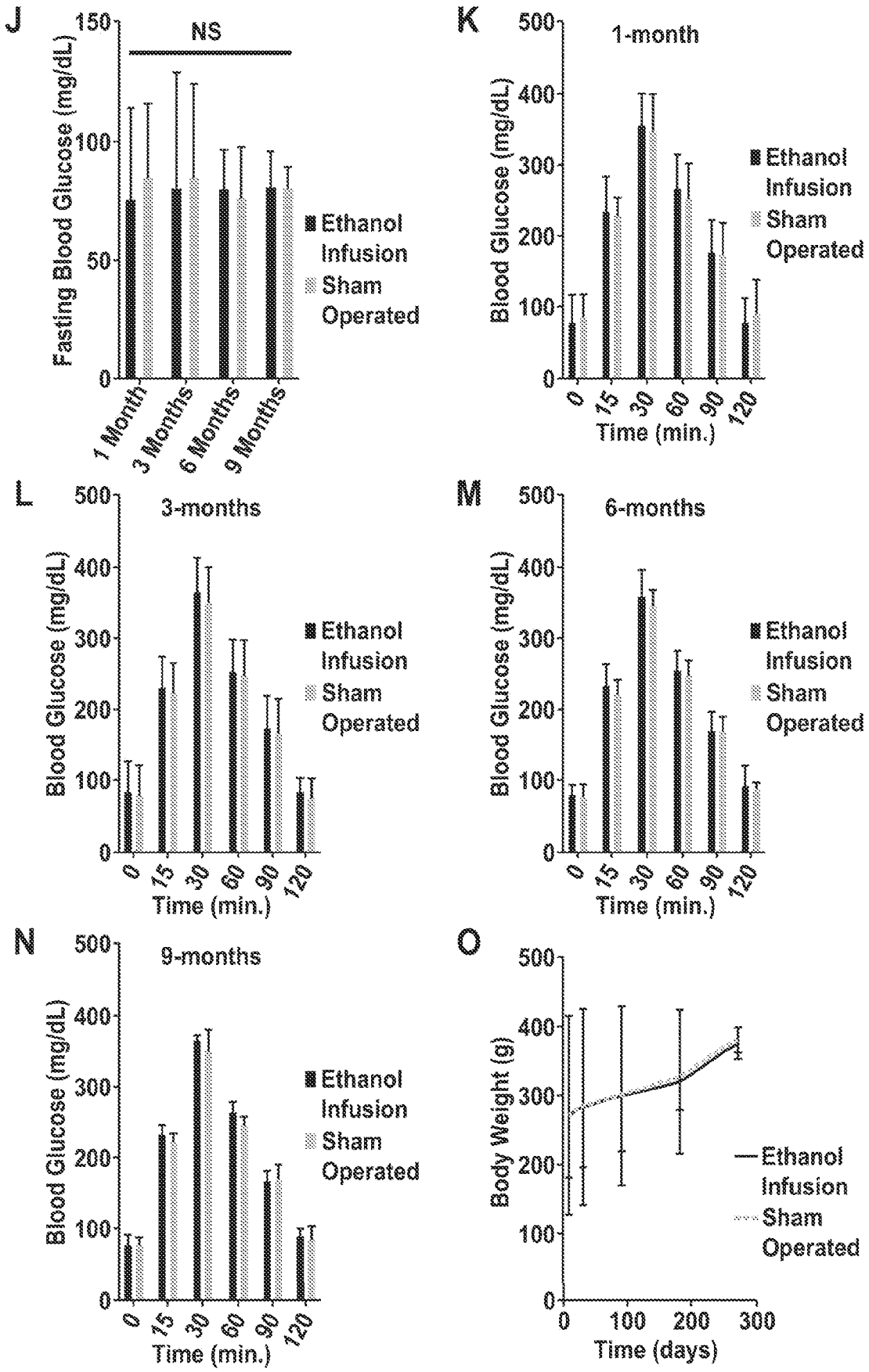
46. The method of claim 45, wherein low levels of exocrine function include a serum 25 hydroxy vitamin D concentration of less than about 20 ng/mL and/or a 72 hour stool fecal fat level of above about 7 g/day.


A
Gallbladder
Pancreas
Clamp
Pancreatic duct
Common bile duct
Duodenum
Perfusion Pump
B
Bright field+GFP
S
I
AAV-GFP 1w
C
GFP
AAV-GFP 1w
D
AAV-GFP 1w
E
GFP
AAV-GFP 1w
F
100%
50%
0
Acinar
Duct
Duct
Infection efficiency by AAV-GFP

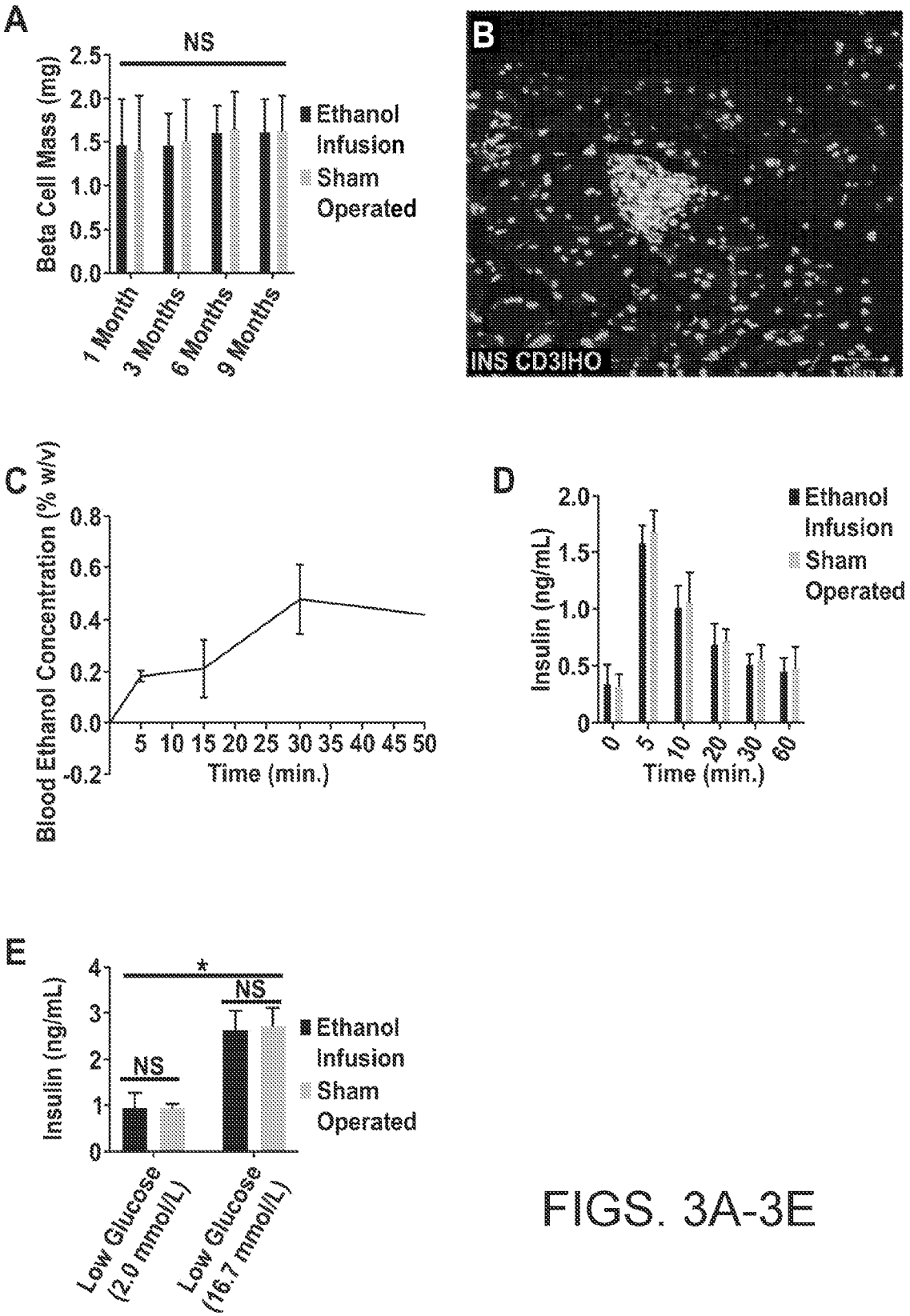
FIGS. 1A-1F



FIGS. 2A-2I


J
NS
Fasting Blood Glucose (mg/dL)
150
100
50
0
1 Month
3 Months
6 Months
9 Months
Ethanol Infusion
Sham Operated
K
1-month
Blood Glucose (mg/dL)
500
400
300
200
100
0
0
15
30
60
90
120
Time (min.)
Ethanol Infusion
Sham Operated
L
3-months
Blood Glucose (mg/dL)
Time (min.)
Ethanol Infusion
Sham Operated
M
6-months
Blood Glucose (mg/dL)
Time (min.)
Ethanol Infusion
Sham Operated
N
9-months
Blood Glucose (mg/dL)
Time (min.)
Ethanol Infusion
Sham Operated
O
Body Weight (g)
500
400
300
200
100
0
0
100
200
300
Time (days)
Ethanol Infusion
Sham Operated

FIGS. 2J-2O


A
NS
Beta Cell Mass (mg)
2.5
2.0
1.5
1.0
0.5
0.0
1 Month
3 Months
6 Months
9 Months
Ethanol Infusion
Sham Operated
B
INS CD3IHO
C
Blood Ethanol Concentration (% w/v)
0.8
0.6
0.4
0.2
0.0
-0.2
5 10 15 20 25 30 35 40 45 50
Time (min.)
D
Insulin (ng/mL)
2.0
1.5
1.0
0.5
0
0 5 10 20 30 60
Time (min.)
Ethanol Infusion
Sham Operated
E
Insulin (ng/mL)
4
3
2
1
0
*
NS
NS
Low Glucose (2.0 mmol/L)
Low Glucose (16.7 mmol/L)
Ethanol Infusion
Sham Operated

FIGS. 3A-3E

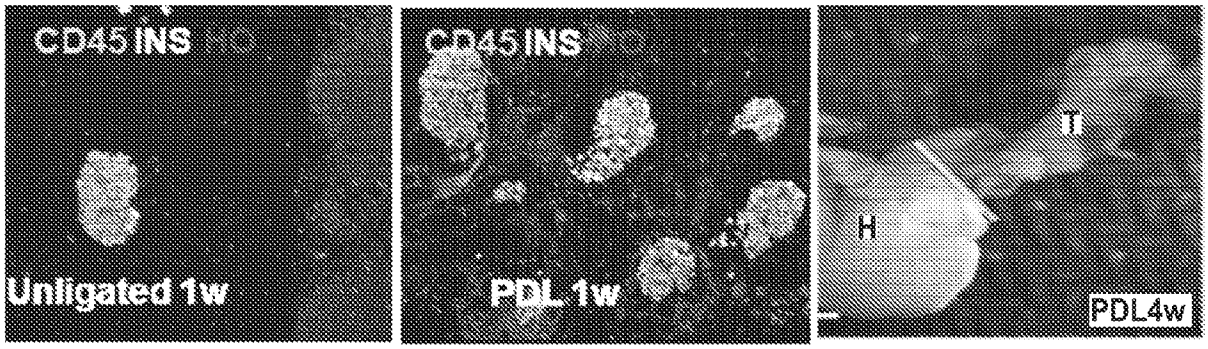
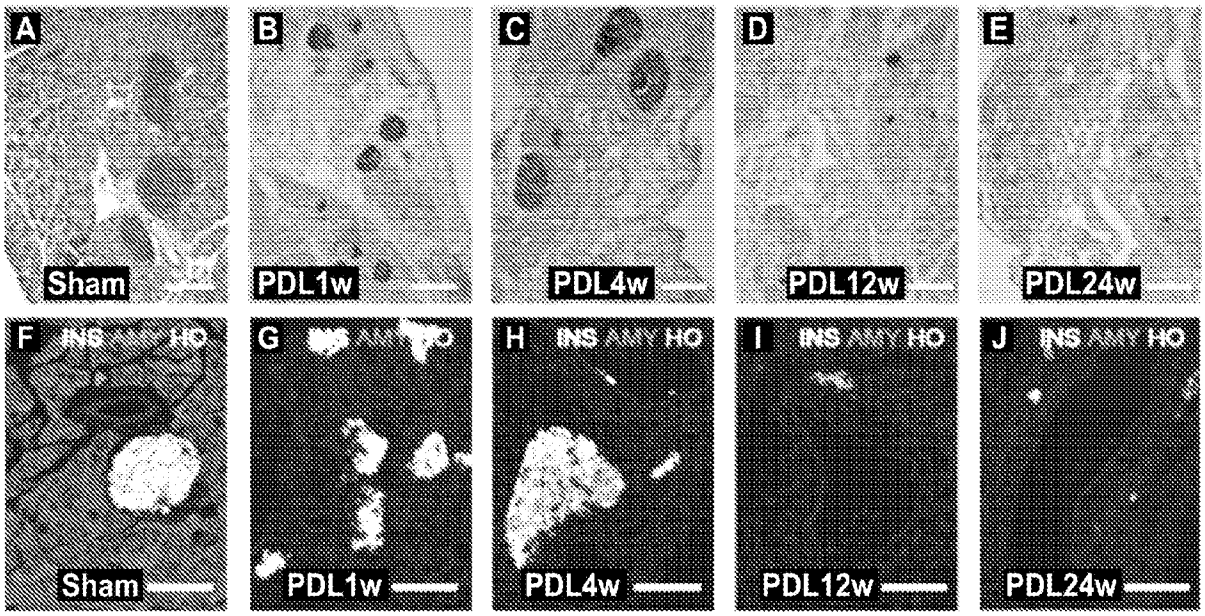
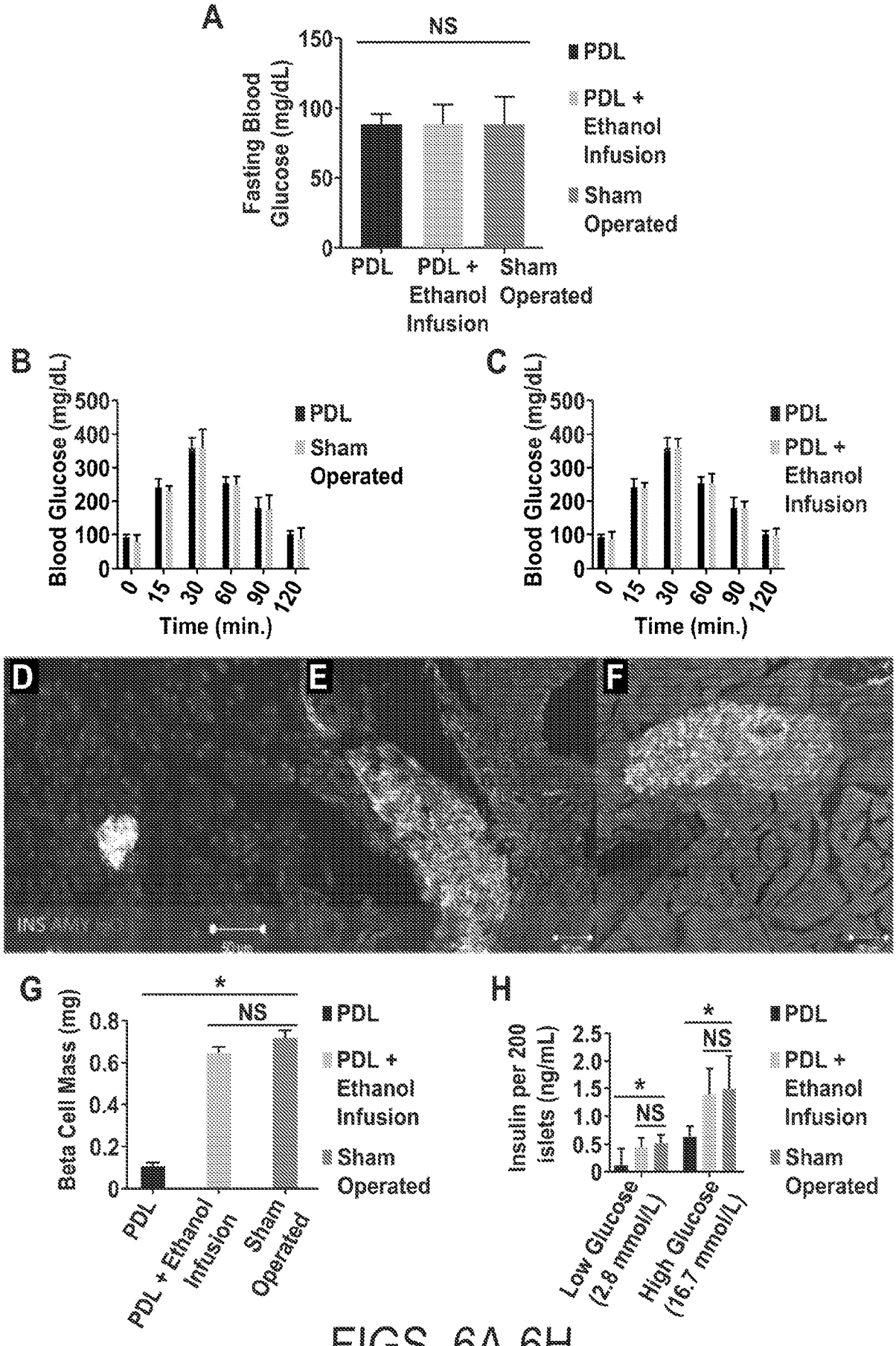


FIG. 4



FIGS. 5A-5J


A
NS
Fasting Blood Glucose (mg/dL)
150
100
50
0
PDL
PDL + Ethanol Infusion
Sham Operated
B
Blood Glucose (mg/dL)
500
400
300
200
100
0
0 15 30 60 90 120
Time (min.)
PDL
Sham Operated
C
Blood Glucose (mg/dL)
Time (min.)
PDL
PDL + Ethanol Infusion
D
E
F
INS
G
*
NS
Beta Cell Mass (mg)
0.8
0.6
0.4
0.2
0
PDL
PDL + Ethanol Infusion
Sham Operated
H
Insulin per 200 islets (ng/mL)
2.5
2.0
1.5
1.0
0.5
0
*
NS
*
NS
Low Glucose (2.8 mmol/L)
High Glucose (16.7 mmol/L)
PDL
PDL + Ethanol Infusion
Sham Operated

FIGS. 6A-6H

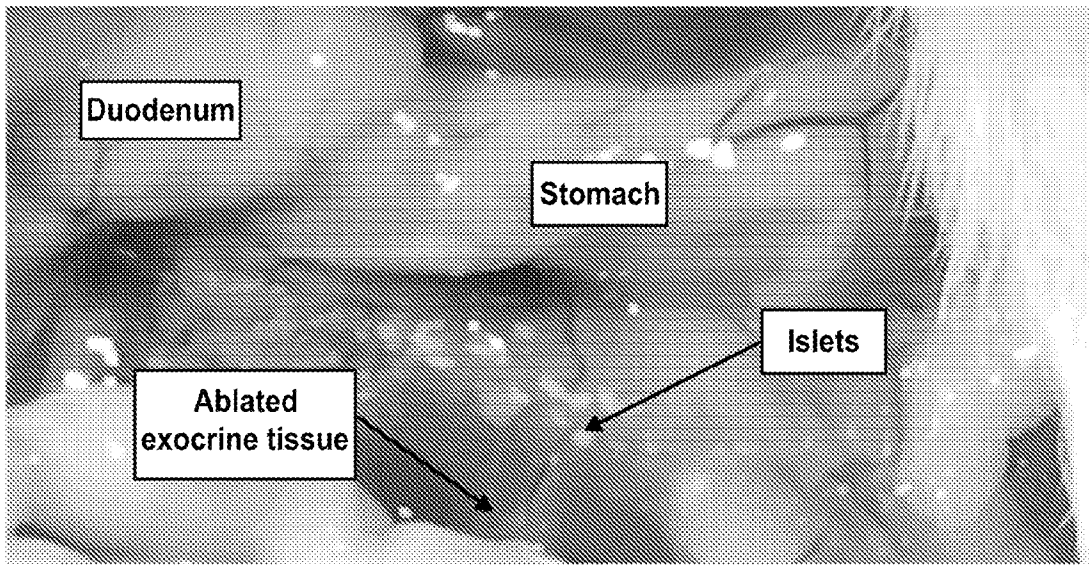

Duodenum
Stomach
Islets
Ablated exocrine tissue

FIG. 7

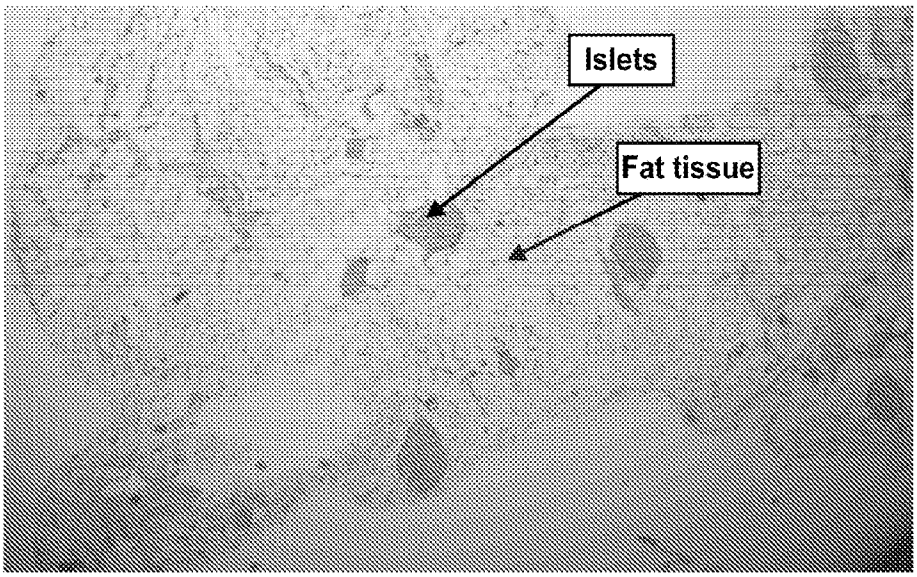

Islets
Fat tissue

FIG. 8A

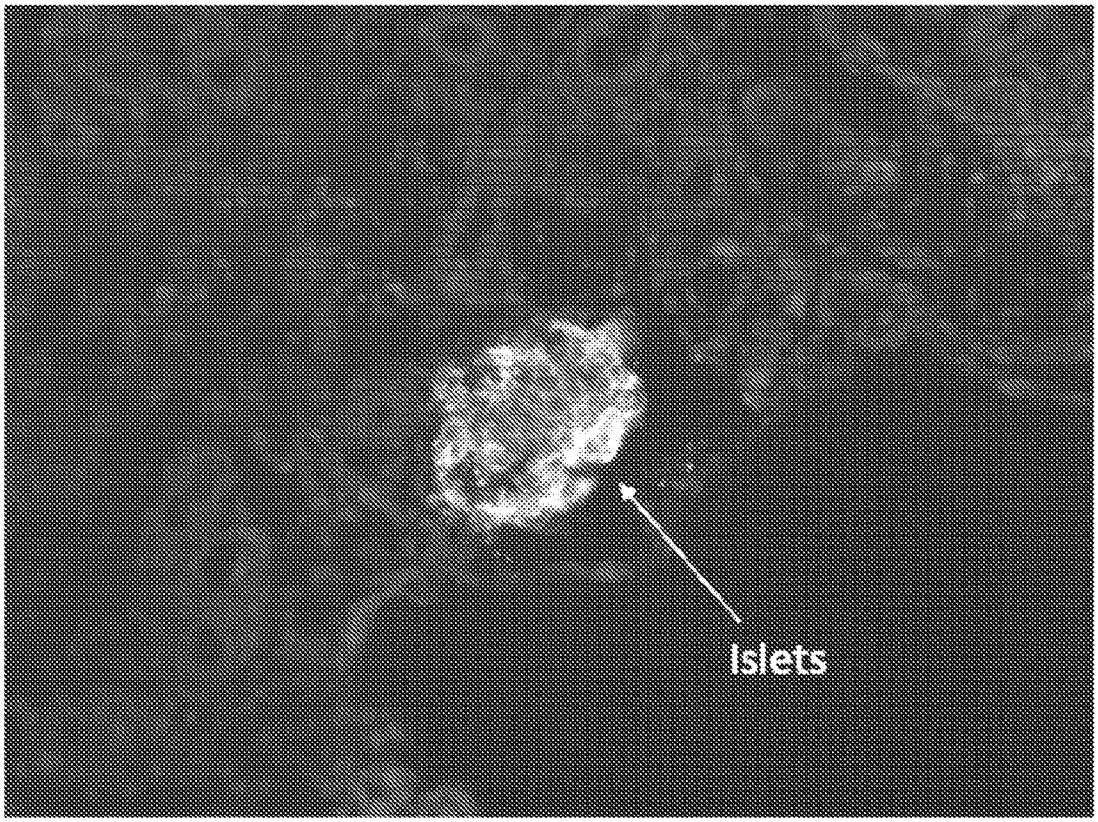


FIG. 8B

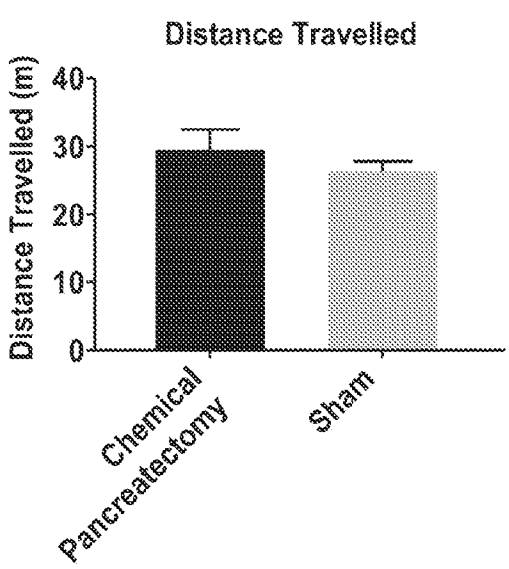


FIG. 9A

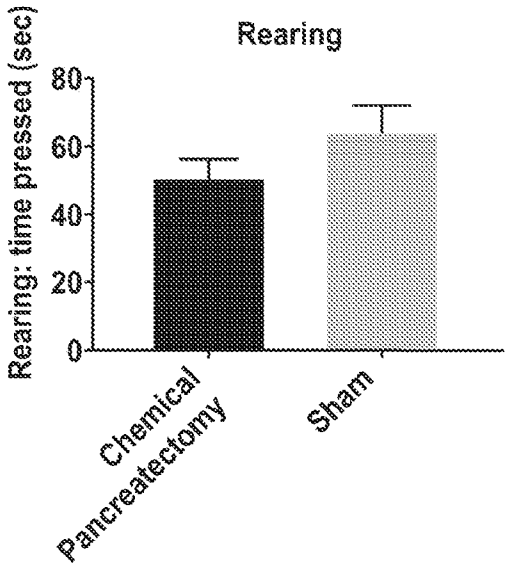


FIG. 9B

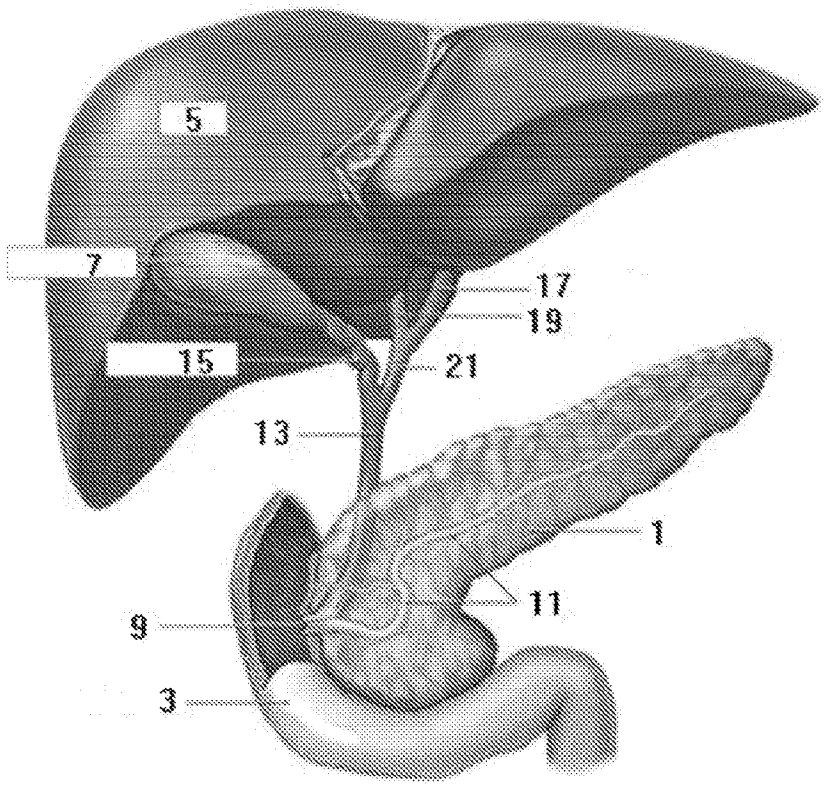
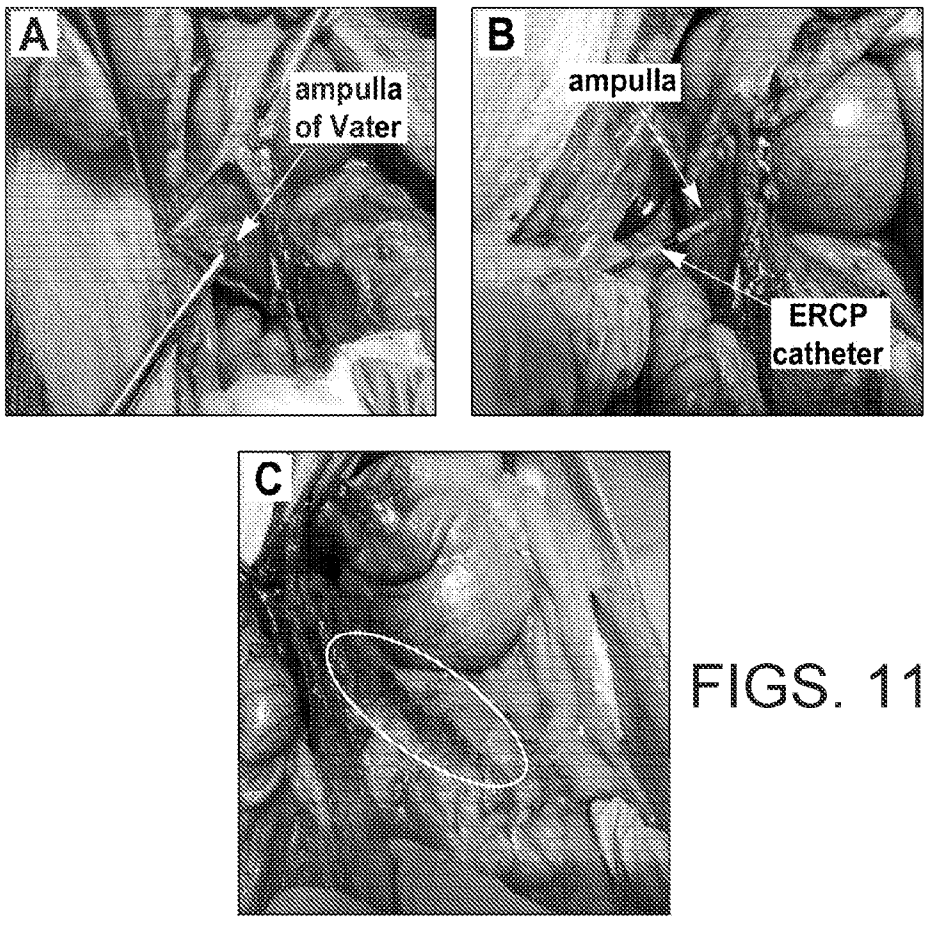


FIG. 10



FIGS. 11A-11C

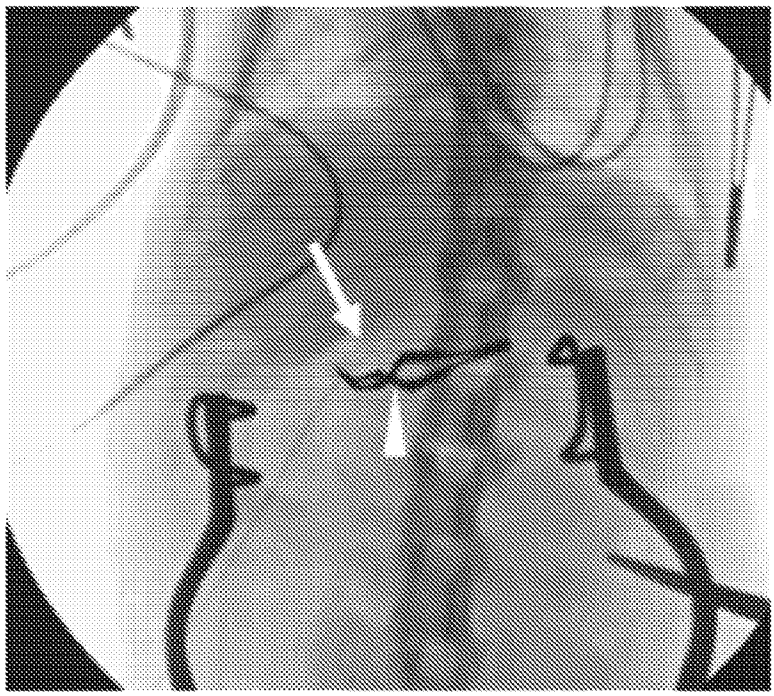


FIG. 12A

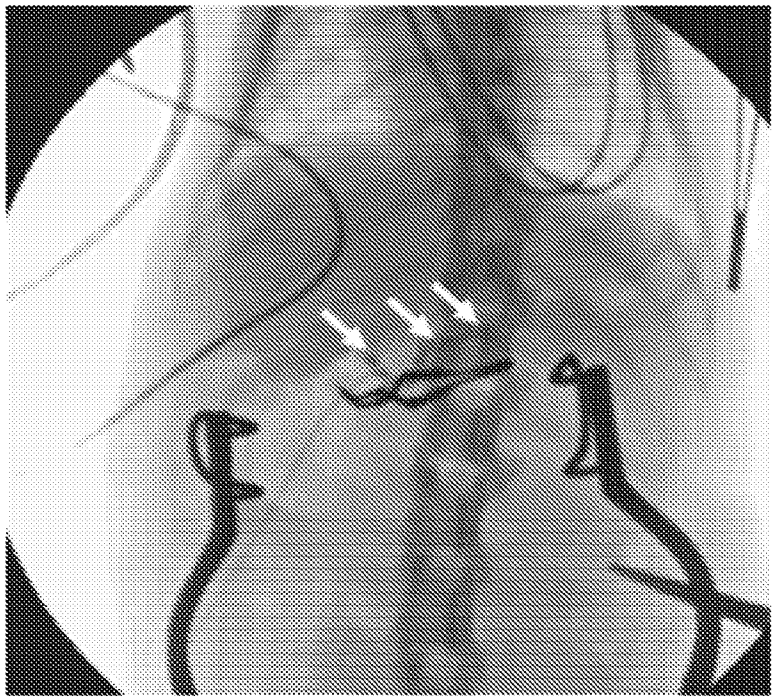
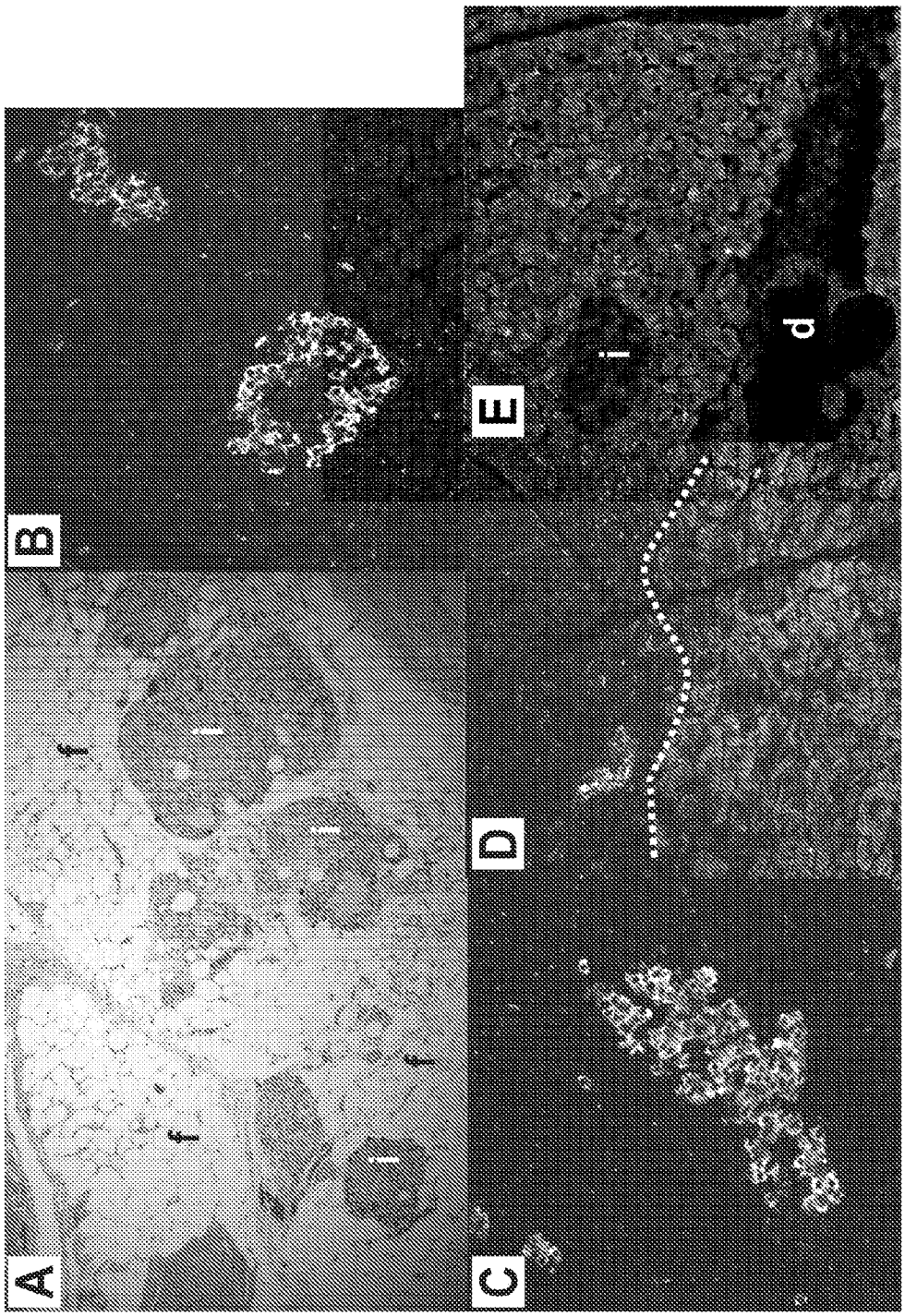


FIG. 12B



FIGS. 13A-13E

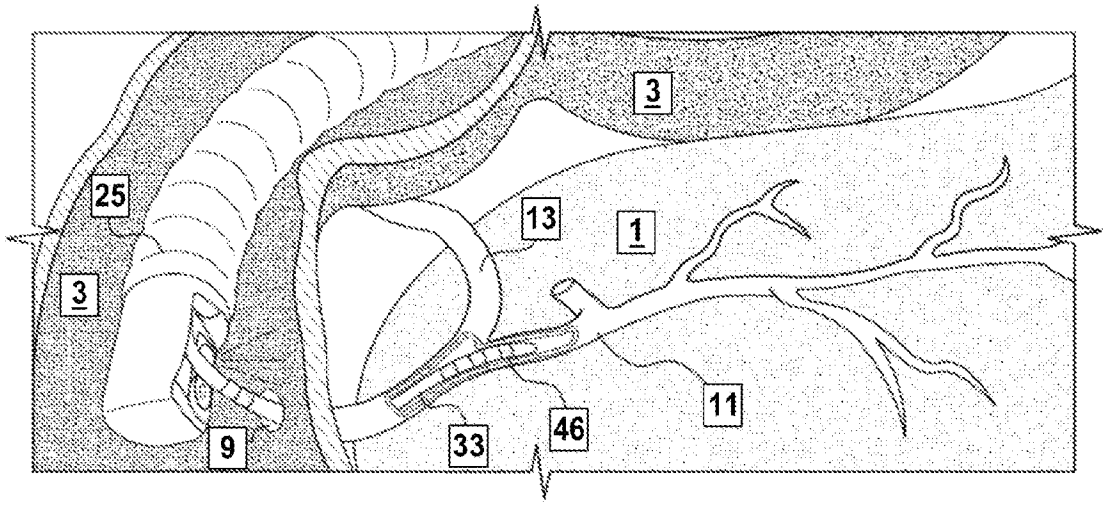


FIG. 14

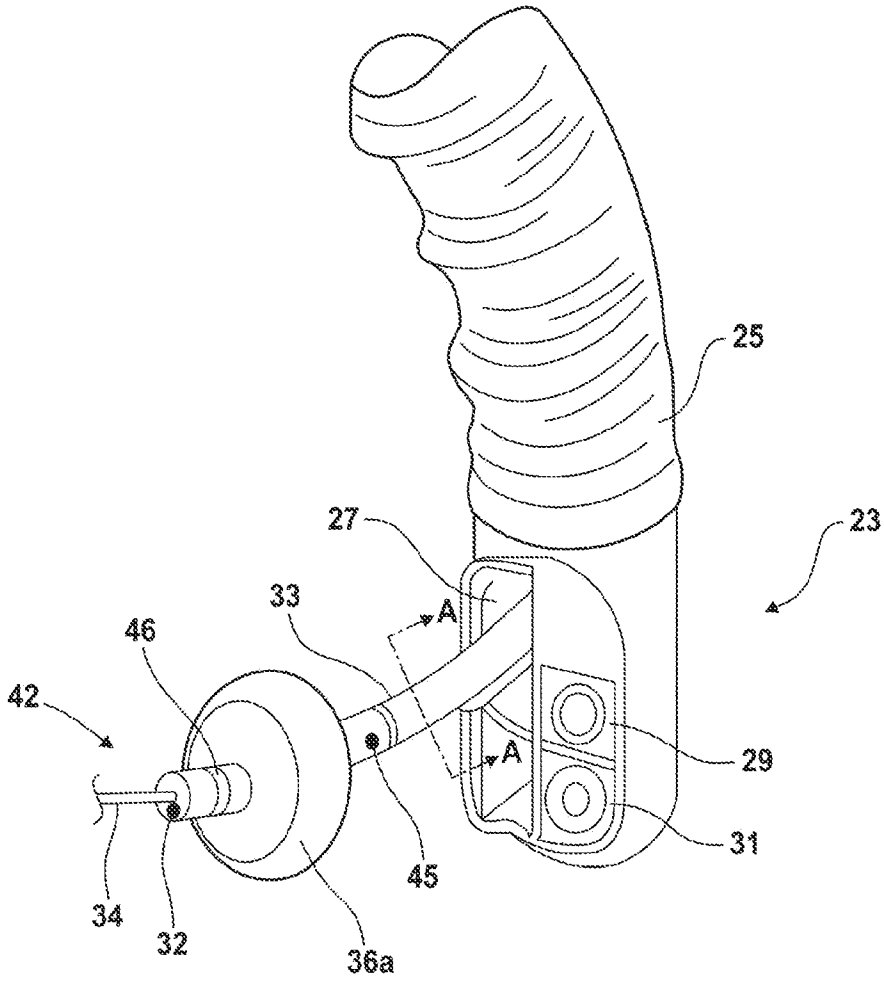


FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/057672

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/045*** (2025.01); ***A61K 35/39*** (2025.01); ***A61L 27/54*** (2025.01); ***A61P 1/18*** (2025.01); ***A61P 3/10*** (2025.01); ***C12N 5/071*** (2025.01); ***A61B 17/00*** (2025.01)

CPC: ***A61K 31/045; A61L 27/54; A61P 1/18; A61P 3/10; A61B 17/00; A61K 35/39;*** *A61B 2017/00743; A61B 2017/00818*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 2020/0214715 A1 (UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION) 09 July 2020 (09.07.2020)	
X	Entire document	18-20
Y	Entire document	1-3, 38-40
	US 2003/0044391 A1 (ELLIOTT et al.) 06 March 2003 (06.03.2003)	
Y	Entire document	1-3, 38-40
	US 2020/0360446 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA et al.) 19 November 2020 (19.11.2020)	
A	Entire document	1-4, 18-20, 38-40
	US 6,479,283 B1 (MANSSON et al.) 12 November 2002 (12.11.2002)	
A	Entire document	1-4, 18-20, 38-40
	US 9,533,013 B2 (UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL et al.) 03 January 2017 (03.01.2017)	
A	Entire document	1-4, 18-20, 38-40

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 January 2025 (05.01.2025)	**16 January 2025 (16.01.2025)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	**TAINA MATOS**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/057672

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CERISE et al. Pancreas transplantation following total pancreatectomy for chronic pancreatitis, Clin Transplant., 8 Nov 2019, Vol. 33(12):e13731, Pgs. 1-17. Entire document	39, 40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/057672

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **5-17, 21-37, 41-46**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).