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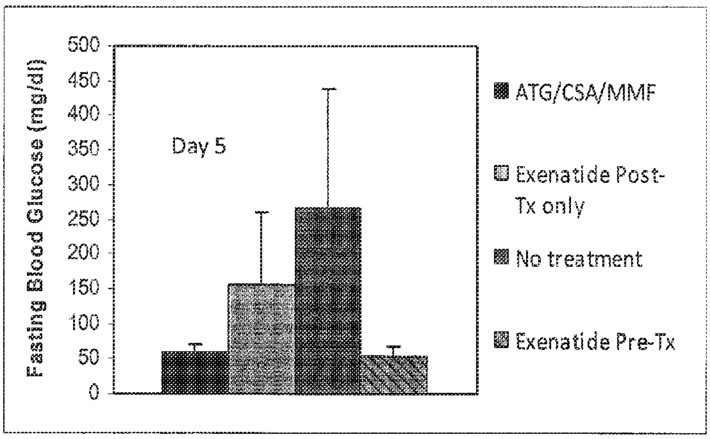
(54) **Title**: GLP-1 RECEPTOR AGONISTS FOR ISLET CELL TRANSPLANTATION

Figure 1



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(57) **Abstract**: The disclosure provides methods for treating diabetes by promoting graft survival and improved graft function in a patient receiving an islet transplant by treating the patient with a GLP-1 receptor agonist compound prior to the islet transplant. The methods may also comprise treating the islets with a GLP-1 receptor agonist compound prior to transplanting them in a patient. The methods may eliminate the need for immunosuppressive therapy in islet transplants. Any GLP-1 receptor agonist compound know in the art can be used in the methods described herein.

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GLP-1 Receptor Agonists for Islet Cell Transplantation

Field

This disclosure is related to the use of glucagon-like peptide-1 (GLP-1) receptor agonists to improve the health and quality of life for people living with diabetes.

Background

Type 1 diabetes has traditionally been treated by life-long insulin therapy or pancreas transplantation. However, frequent episodes of hypoglycemia are common in patients on life-long insulin therapy. And whole pancreas transplantation is an invasive surgical procedure with significant risks. Islet cell transplantation is an attractive alternative to the traditional treatments of type 1 diabetes. However, two of the major limiting factors in the widespread use of islet cell transplantation clinically are the availability of a sufficient number of islets and the inability of current immunosuppressive treatments to protect transplanted islets long-term.

As of 2005 an estimated 1.4 to 2.8 million people in the United States were diagnosed with insulin dependent diabetes (Collaborative Islet Transplant Registry, 5th Annual Report, Bethesda, MD: National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 2008). According to a 2007 report by the United Network for Organ Sharing (UNOS), only 1,931 pancreatic donors were reported (United Network of Organ Sharing; Donors Recovered in the U.S. by Donor Type. Washington, D.C.: United States Department of Health and Human Services, 2009). Of those, 1,363 were used for whole pancreas transplantation. Because islet transplantation is still an experimental procedure, priority of donor pancreata goes to whole organ transplant. Thus, only 568 pancreata would have been available in 2007 for islet cell transplantation. In addition to this already limited availability of pancreata for islet transplantation, most islet transplant recipients require more than one donor in order to acquire a sufficient number of islet cells to achieve insulin independence. This limits the number of people who could be helped by islet cell transplantation even more. Alternative sources of islet cells or development of a method for β-cell regeneration are essential to the widespread use of islet transplantation in treating type 1 diabetes.

Despite using 2-3 pancreata for each recipient, however, results reported by the Edmonton group have shown that the rate of success for functional islet grafts in the clinical setting is approximately 80% after 1 year, but only 10% after 5 years (Ryan et al, *Diabetes*, 54(7):2060-2069 (2005); Shapiro et al, *N Engl J Med*, 343(4):230-238 (2000)). Effects of both auto- and allogeneic immune responses severely limit the long-term success of islet grafts, even when an abundant number of islets have been transplanted. Thus, development of an immunosuppressive treatment strategy that protects islets long-term is necessary for the overall success of this procedure.

Many immunosuppressive protocols used in islet cell transplantation to date have relied on calcineurin inhibitors that have been shown to negatively affect pancreatic β-cell function and insulin sensitivity. Therefore, despite offering protection from host immune attack, these agents themselves can diminish graft function and contribute to failure of the transplanted islets. Additionally, recipients of islet grafts still demonstrate the auto-immune effects of diabetes development that led to their disease initially, thereby affecting function of transplanted islets long-term.

GLP-1 receptor agonists (such as exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, taspoglutide) bind to the GLP-1 receptor on beta cells and have been shown to improve insulin secretion in response to glucose in addition to protecting beta cells from apoptosis and promoting beta cell regeneration in animals. Shalev et al, *Horm Res*, 49(5):221-225 (1998); Chen et al, *Biochem Biophys Res Comm*, 346:1067-1074 (2006); Xu et al, *Diabetes*, 48:2270-2276 (1998); Tourrel et al, *Diabetes*, 50:1562-1570 (2001); Couto et al, *Metabolism Clinical and Experimental*, 56:915-918 (2007). Studies in NOD mice have also shown that pre-treatment of islet recipients with a DPPIV-inhibitor can alter T-cell migration to islets. Kim et al, *Diabetes*, 58:641-651 (2009).

Because of the drawbacks of conventional immunosuppressive therapy, there is a need in the art for an effective form of treatment to allow for long-term islet graft function. The disclosure is directed to the unexpected discovery that GLP-1 receptor agonists can meet this need.

Summary

It has not been previously shown whether treatment with GLP-1 receptor agonists will show protective properties in islet allotransplant recipients. We proposed and conducted studies that showed that pre-treatment of islet donors and/or recipients with GLP-1 receptor agonists promoted graft survival and improved graft function relative to post-transplant treatment alone. Moreover, this treatment method was successful without the use of immunosuppressive drugs.

In the example described herein, pancreatectomized cynomolgous monkeys underwent islet allotransplantation and were treated with the GLP-1 receptor agonist exenatide (5 mcg subcutaneous, twice daily) beginning on day 0 (n=3) or day -2 (n=3). A third group of animals (n=5) was treated with the immunosuppressive regimen of rabbit anti-thymocyte globulin, cyclosporine, and mycophenolate mofetil. A fourth group of animals remained untreated (n=4). Fasting blood glucose was measured daily and intravenous glucose tolerance tests were performed to evaluate graft function. The results showed that the average fasting blood glucose for pre-treated animals on day 5 post-transplant was 52.7 ± 14.8 mg/dl while the average fasting blood glucose for animals treated with exenatide post-transplant only was 154.3 ± 105.5 mg/dl. The day 5 average fasting blood glucose was 59.4 mg/dl ± 12.1 in animals treated with immunosuppression. Untreated animals had an average fasting blood glucose of 265.5 ± 172.3 mg/dl. Beta cell function as determined by homeostasis model assessment notably improved post-transplant in exenatide pre-treated animals (53.3% vs. 107%) and marginally improved in animals treated with immunosuppression (29.9% vs. 43.8%) while a marked decrease was noted in untreated animals (20.2% vs. 1.89%) as well as animals treated with exenatide post-transplant only (22.2% vs, 13.8%). intravenous glucose tolerance tests showed normal glucose and insulin curves in the pre-treated exenatide and immunosuppression groups only. These studies unexpectedly showed that the use of the GLP-1 receptor agonist exenatide, without immunosuppressive drugs, was able to maintain islet graft survival.

Brief Description of the Figures

Figures 1A-B. Fasting blood glucose monitoring of transplanted animals (A). Average fasting blood glucose levels measured at day 5 post-transplant (B). Untreated animals showed elevated blood glucose levels by day 1 post-transplant, animals treated with exenatide post-transplant only showed somewhat elevated blood glucose levels beginning at day 4 post-transplant, while animals treated with ATG/CSA/MMF or pre-treated with exenatide remained normoglycemic throughout the study period. In fact, two animals from the exenatide pre-treatment group remained normoglycemic up to 435 days post-transplant.

Figures 2A-B. Blood glucose levels measured following intravenous glucose administration (intravenous glucose tolerance test) with area under the curve measurements for glucose response (A). Serum insulin levels measured during intravenous glucose tolerance test as detected by ELISA (B). intravenous glucose tolerance tests were performed at baseline prior to pancreatectomy, at day 10 post-transplant for untreated and post-exenatide groups, and at day 90 post-transplant for ATG/CSA/MMF and exenatide pre-treatment groups. Animals pre-treated with exenatide or treated with ATG/CSA/MMF maintained glucose and insulin responses post-transplant that resembled that prior to pancreatectomy. Animals pre-treated with exenatide showed increased insulin production at both baseline and post-transplant compared to all other groups. Untreated recipients and animals receiving exenatide post-transplant only showed reduced insulin levels compared to baseline.

Figures 3A-B. Acute insulin response to glucose (μU/ml) as a measurement of first phase insulin secretion following i.v. glucose administration (A). Beta cell function as determined by homeostasis model assessment (HOMA-%B) (B). Untreated animals and animals treated with exenatide post-transplant only were tested at day 0 and at day 10. ATG/CSA/MMF and exenatide pre-treatment groups were tested at day 0 and day 90.

Figure 4. *In vitro* static glucose stimulation assays performed on freshly isolated islets showed a significant improvement in Stimulation Index of insulin release for islets that had been pre-treated with exenatide *in vivo* compared to untreated islets. * $p \leq 0.05$

Detailed Description

The disclosure provides methods for treating diabetes in patients by administering therapeutically effective amounts of GLP-1 receptor agonist compound to the patient prior to islet transplant, and transplanting islets into the patient; thereby treating diabetes. In one embodiment, in the patient is not administered an immunosuppressive drug or an immunosuppressive treatment regimen before, during, or after the islet transplant. In one embodiment, the diabetes is Type 1 diabetes. In one embodiment, the patient is a human.

The disclosure provides method for treating diabetes in patients by administering therapeutically effective amounts of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month; treating islets with a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month; transplanting the islets into the patient; and continuing administration of the therapeutically effective amounts of the GLP-1 receptor agonist compound to the patient after the islet transplant; thereby treating diabetes in the patient. In one embodiment, in the patient is not administered an immunosuppressive drug or an immunosuppressive treatment regimen before, during, or after the islet transplant. In one embodiment, the diabetes is Type 1 diabetes. In one embodiment, the patient is a human.

The disclosure provides methods for promoting graft survival and improved graft function in a patient receiving an islet transplant by administering therapeutically effective amounts of a GLP-1 receptor agonist compound to the patient prior to islet transplant; transplanting the islets into the patient; and continuing administration of the therapeutically effective amounts of the GLP-1 receptor agonist compound to the patient after the islet transplant; thereby promoting graft survival and improved graft function in the patient. In one embodiment, the methods include treating islets with therapeutically effective amounts of a GLP-1 receptor agonist compound prior to transplant into the patient. In one embodiment, in the patient is not administered an immunosuppressive drug or an immunosuppressive treatment regimen before, during, or after the islet transplant. In one embodiment, the diabetes is Type 1 diabetes. In one embodiment, the patient is a human.

The disclosure provides methods for promoting graft survival and improved graft function in a patient receiving an islet transplant by administering a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month; treating islets with a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month; transplanting the islets into the patient; and continuing administration of therapeutically effective amounts of the GLP-1 receptor agonist compound to the patient after the islet transplant; thereby promoting graft survival and improved graft function in the patient. In one embodiment, in the patient is not administered an immunosuppressive drug or an immunosuppressive treatment regimen before, during, or after the islet transplant. In one embodiment, the diabetes is Type 1 diabetes. In one embodiment, the patient is a human.

Any GLP-1 receptor agonist compound can be used in the methods described herein, as set forth in more detail below.

A "GLP-1 receptor agonist compound" refers to compounds having GLP-1 receptor activity. Such exemplary compounds include exendins, exendin analogs, exendin agonists, GLP-1(7-37), GLP-1(7-37) analogs, GLP-1(7-37) agonists, and the like.

The term "exendin" includes naturally occurring (or synthetic versions of naturally occurring) exendin peptides that are found in the salivary secretions of the Gila monster. Exendins of particular interest include exendin-3 and exendin-4. The exendins, exendin analogs, and exendin agonists for use in the methods described herein may optionally be amidated, and may also be in an acid form, pharmaceutically acceptable salt form, or any other physiologically active form of the molecule.

Exendin-4 (HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2 (SEQ ID NO:1)) is a peptide found in the saliva of the Gila monster, *Heloderma suspectum*; and exendin-3 (HSDGTFTSDLSKQMEEEAVRLFIEWLKNGG PSSGAPPPS-NH_2 (SEQ ID NO:2)) is a peptide found in the saliva of the beaded lizard, *Heloderma horridum*. Exendins have some amino acid sequence similarity to some members of the glucagon-like peptide (GLP) family. For example, exendin-4 has about 53% sequence identity with glucagon-like peptide-1(GLP-1)(7-37) (HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG (SEQ ID NO:22)). However, exendin-4 is transcribed from a distinct gene, not the Gila monster homolog of the mammalian proglucagon gene from which GLP-1 is expressed. Additionally, exendin-4 is not an analog of GLP-1(7-37) because the structure of synthetic exendin-4 peptide was not created by sequential modification of the structure of GLP-1. Nielsen et al, *Current Opinion in Investigational Drugs*, 4(4):401-405 (2003).

Synthetic exendin-4, also known as exenatide, is commercially available as BYETTA® (Amylin Pharmaceuticals, Inc. and Eli Lilly and Company). BYETTA® contains exenatide, a preservative (e.g., metacresol), a tonicity-adjusting agent (e.g., mannitol), and a buffer (e.g., an acetate buffer). A once weekly formulation of exenatide is currently awaiting FDA approval and is described in WO 2005/102293, the disclosure of which is incorporated by reference herein. This once weekly formulation comprises exenatide and biodegradable polymeric (e.g., poly(lactide-co-glycolide)) microspheres, and is referred to herein as EQW (BYDUREON™ by Amylin Pharmaceuticals, Inc., Eli Lilly and Company, Alkermes, Inc.).

"Exendin analog" refers to peptides or other compounds which elicit a biological activity of an exendin reference peptide, preferably having a potency equal to or better than the exendin reference peptide (e.g., exendin-4), or within five orders of magnitude (plus or minus) of potency compared to the exendin reference peptide, when evaluated by art-known measures such as receptor binding and/or competition studies as described, e.g., by Hargrove et al, *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. Preferably, the exendin analogs will bind in such assays with an affinity of less than 1 μM, and more preferably with an affinity of less than 3 nM, or less than 1 nM. The term "exendin analog" may also be referred to as "exendin agonist".

Exendin analogs also include the peptides described herein which have been chemically derivatized or altered, for example, peptides with non-natural amino acid residues (e.g., taurine, β-amino acid residues, γ-amino acid residues, and D-amino acid residues), C-terminal functional group modifications, such as amides, esters, and C-terminal ketone modifications and N-terminal functional group modifications, such as acylated amines, Schiff bases, or cyclization, as found, for example, in the amino acid pyroglutamic acid. Exendin analogs may also contain other chemical moieties, such as peptide mimetics.

Exemplary exendins and exendin analogs include exendin-4 (SEQ ID NO:1); exendin-3 (SEQ ID NO:2); Leu^{14}-exendin-4 (SEQ ID NO:3); Leu^{14},Phe^{25}-exendin-4 (SEQ ID NO:4); Leu^{14},Ala^{19},Phe^{25}-exendin-4 (SEQ ID NO:5); exendin-4(1-30) (SEQ ID NO:6); Leu^{14}-exendin-4(1-30) (SEQ ID NO:7); Leu^{14},Phe^{25}-exendin-4(1-30) (SEQ ID NO:8); Leu^{14},Ala^{19},Phe^{25}-exendin-4(1-30) (SEQ ID NO:9); exendin-4(1-28) (SEQ ID NO:10); Leu^{14}-exendin-4(1-28) (SEQ ID NO:11); Leu^{14},Phe^{25}-exendin-4(1-28) (SEQ ID NO:12); Leu^{14},Ala^{19},Phe^{25}-exendin-4 (1-28) (SEQ ID NO:13); Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Phe^{25},Gln^{28}-exendin-4 (SEQ ID NO:14); Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Gln^{28}-exendin-4 (SEQ ID NO:15); octylGly^{14},Gln^{28}-exendin-4 (SEQ ID NO:16); Leu^{14},Gln^{28},octylGly^{34}-exendin-4 (SEQ ID NO:17); Phe^{4},Leu^{14},Gln^{28},Lys^{33},Glu^{34}, $Ile^{35,36}$,Ser^{37}-exendin-4(1-37) (SEQ ID NO:18); Phe^{4},Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Gln^{28}-exendin-4 (SEQ ID NO:19); Val^{11},Ile^{13},Leu^{14},Ala^{16},Lys^{21},Phe^{25}-exendin-4 (SEQ ID NO:20); exendin-4-Lys^{40} (SEQ ID NO:21); lixisenatide (Sanofi-Aventis/Zealand Pharma); CJC-1134 (ConjuChem, Inc.); [N^{ε}-(17-carboxyheptadecanoic acid)Lys^{20}]exendin-4-NH_2; [N^{ε}-(17-carboxyhepta-decanoyl)Lys^{32}]exendin-4-NH_2; [desamino-His^{1},N^{ε}-(17-carboxyheptadecanoyl)Lys^{20}]exendin-4-NH_2; [$Arg^{12,27}$,NLe^{14},N^{ε}-(17-carboxy-heptadecanoyl)Lys^{32}]exendin-4-NH_2; [N^{ε}-(19-carboxy-nonadecanoylamino)Lys^{20}]-exendin-4-NH_2; [N -(15-carboxypentadecanoylamino)Lys^{20}]-exendin-4-NH_2; [N^{ε}-(13-carboxytridecanoylamino)Lys^{20}]exendin-4-NH_2; [N^{ε}-(11-carboxy-undecanoyl-amino)Lys^{20}]exendin-4-NH_2; exendin-4-Lys^{40}(ε-MPA)-NH_2; exendin-4-Lys^{40}(ε -AEEA-AEEA-MPA)-NH_2; exendin-4-Lys^{40}(ε -AEEA-MPA)-NH_2; exendin-4-Lys^{40}(ε -MPA)-albumin; exendin-4-Lys^{40}(ε -AEEA-AEEA-MPA)-albumin; exendin-4-Lys^{40}(ε -AEEA-MPA)-albumin; and the like. AEEA refers to [2-(2-amino)ethoxy)]ethoxy acetic acid. EDA refers to ethylenediamine. MPA refers to maleimidopropionic acid. The exendins and exendin analogs may optionally be amidated.

Other exendins and exendin analogs useful in the methods described herein include those described in WO 98/05351; WO 99/07404; WO 99/25727; WO 99/25728; WO 99/40788; WO 00/41546; WO 00/41548; WO 00/73331; WO 01/51078; WO 03/099314; US Patent No. 6,956,026; US Patent No. 6,506,724; US Patent No. 6,703,359; US Patent No. 6,858,576; US Patent No. 6,872,700; US Patent No. 6,902,744; US Patent No. 7,157,555; US Patent No. 7,223,725; US Patent No. 7,220,721; US Publication No. 2003/0036504; and US Publication No. 2006/0094652, the disclosures of which are incorporated by reference herein in their entirety.

"GLP-1(7-37) analogs" refers to peptides or other compounds which elicit a biological activity similar to that of GLP-1(7-37), when evaluated by art-known measures such as receptor binding assays or in vivo blood glucose assays as described, e.g., by Hargrove et al, *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. In one embodiment, the term "GLP-1(7-37) analog" refers to a peptide that has an amino acid sequence with 1, 2, 3, 4, 5, 6, 7 or 8 amino acid substitutions, insertions, deletions, or a combination of two or more thereof, when compared to the amino acid sequence of GLP-1(7-37). In one embodiment, the GLP-1(7-37) analog is GLP-1(7-36)-NH_2. GLP-1(7-37) analogs include the amidated forms, the acid form, the pharmaceutically acceptable salt form, and any other physiologically active form of the molecule.

Exemplary GLP-1(7-37) and GLP-1(7-37) analogs include GLP-1(7-37) (SEQ ID NO:22); GLP-1(7-36))-NH_2 (SEQ ID NO:23); liraglutide (VICTOZA® from Novo Nordisk); dulaglutide (LY2189265, a GLP-1 analog linked to an immunoglobulin G4 by Eli Lilly and Company); albiglutide (SYNCRIA® from GlaxoSmithKline); taspoglutide (Hoffman La-Roche); dulaglutide (LY2189265, a GLP-1 analog linked to an immunoglobulin G4 by Eli Lilly and Company); LY2428757 (a GLP-1 analog linked to a polyethylene glycol by Eli Lilly and Company); desamino-His^{7},Arg^{26},Lys^{34}(N^{ε}-(γ-Glu(N-α- hexadecanoyl)))-GLP-l(7-37); desamino-His^{7},Arg^{26},Lys^{34}(N^{ε}-octanoyl)-GLP-l(7-37); $Arg^{26,34}$,Lys^{38}(N^{ε}-(ω-carboxypentadecanoyl))-GLP-l(7-38); $Arg^{26,34}$,Lys^{36}(N^{ε}-(γ-Glu(N-α- hexadecanoyl)))-GLP-l(7-36); $Aib^{8,35}$,$Arg^{26,34}$,Phe^{31}-GLP-1(7-36)) (SEQ ID NO:24); $HXaa_8EGTFTSDVSSYLEXaa_{22}Xaa_{23}AAKEFIXaa_{30}WLXaa_{33}Xaa_{34}G\ Xaa_{36}Xaa_{37}$; wherein Xaa_8 is A, V, or G; Xaa_{22} is G, K, or E; Xaa_{23} is Q or K; Xaa_{30} is A or E; Xaa_{33} is V or K; Xaa_{34} is K, N, or R; Xaa_{36} is R or G; and Xaa_{37} is G, H, P, or absent (SEQ ID NO:25); Arg^{34}-GLP-1(7-37) (SEQ ID NO:26); Glu^{30}-GLP-1(7-37) (SEQ ID NO:27); Lys^{22}-GLP-1(7-37) (SEQ ID NO:28);

$Gly^{8,36}$,Glu^{22}-GLP-1(7-37) (SEQ ID NO:29); Val^{8},Glu^{22},Gly^{36}-GLP-1(7-37) (SEQ ID NO:30); $Gly^{8,36}$,Glu^{22},Lys^{33},Asn^{34}-GLP-1(7-37) (SEQ ID NO:31); Val^{8},Glu^{22},Lys^{33},Asn^{34},Gly^{36}-GLP-1(7-37) (SEQ ID NO:32); $Gly^{8,36}$,Glu^{22},Pro^{37}-GLP-1(7-37) (SEQ ID NO:33); Val^{8},Glu^{22},$Gly^{36}Pro^{37}$-GLP-1(7-37) (SEQ ID NO:34); $Gly^{8,36}$,Glu^{22},Lys^{33}, Asn^{34},Pro^{37}-GLP-1(7-37) (SEQ ID NO:35); Val^{8},Glu^{22},Lys^{33},Asn^{34},Gly^{36},Pro^{37}-GLP-1(7-37) (SEQ ID NO:36); $Gly^{8,36}$,Glu^{22}-GLP-1(7-36) (SEQ ID NO:37); Val^{8},Glu^{22},Gly^{36}-GLP-1(7-36) (SEQ ID NO:38); Val^{8},Glu^{22},Asn^{34},Gly^{36}-GLP-1(7-36) (SEQ ID NO:39); $Gly^{8,36}$,Glu^{22},Asn^{34}-GLP-1(7-36) (SEQ ID NO:40). Each of the GLP-1(7-37) and GLP-1(7-37) analogs may optionally be amidated.

In one embodiment, the GLP-1(7-37) or GLP-1(7-37) analogs are covalently linked (directly or by a linking group) to an Fc portion of an immunoglobulin (e.g., IgG, IgE, IgG, and the like). For example, any one of SEQ ID NOs:25-40 may be covalently linked to the Fc portion of an immunoglobulin comprising the sequence of: AESKYGPPCPPCPAPXaa_{16} $Xaa_{17}$$Xaa_{18}$GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFXaa_{80}STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGXaa_{230}; wherein Xaa_{16} is P or E; Xaa_{17} is F, V or A; Xaa_{18} is L, E or A; Xaa_{80} is N or A; and Xaa_{230} is K or absent (SEQ ID NO:41). The linking group may be any chemical moiety (e.g., amino acids and/or chemical groups). In one embodiment, the linking group is $(\text{-GGGGS-})_x$ (SEQ ID NO:42) where x is 1, 2, 3, 4, 5 or 6; preferably 2, 3 or 4; more preferably 3. In one embodiment, the GLP-1(7-37) analog covalently linked to the Fc portion of an immunoglobulin comprises the amino acid sequence: HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGGGGGGSGGGGSGGGGSA ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLG (SEQ ID NO:43).

In another embodiment, the GLP-1(7-37) or GLP-1(7-37) analog may be covalently linked (directly or through a linking group) to one or two polyethylene glycol molecules. For example, a GLP-1(7-37) analog may comprise the amino acid sequence: HXaa_{8}EGTFTSDVS SYLEXaa_{22}QAAKEFIAWLXaa_{33}KGGPSSGAPPP$C_{45}$$C_{46}$-Z, wherein Xaa_{8} is: D-Ala, G, V, L, I, S or T; Xaa_{22} is G, E, D or K; Xaa_{33} is: V or I; and Z is OH or NH_2, (SEQ ID NO:44), and, optionally, wherein (i) one polyethylene glycol moiety is covalently attached to C_{45}, (ii) one polyethylene glycol moiety is covalently attached to C_{46}, or (iii) one polyethylene glycol moiety is attached to C_{45} and one polyethylene glycol moiety is attached to C_{46}. In one embodiment, the GLP-1(7-37) analog is HVEGTFTSDVSSYLEEQAAKEFIAWLIKGGPSSGAPPP$C_{45}C_{46}$-NH_2 (SEQ ID NO:45) and, optionally, wherein (i) one polyethylene glycol moiety is covalently attached to C_{45}, (ii) one polyethylene glycol moiety is covalently attached to C_{46}, or (iii) one polyethylene glycol moiety is attached to C_{45} and one polyethylene glycol moiety is attached to C_{46}.

GLP-1 receptor agonist compounds may be prepared by processes well known in the art, e.g., peptide purification as described in Eng et al, *J. Biol. Chem.,* 265:20259-62 (1990); standard solid-phase peptide synthesis techniques as described in Raufman et al, *J. Biol. Chem.*, 267:21432-37 (1992); recombinant DNA techniques as described in Sambrook et al, Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989); and the like.

The disclosure also provides pharmaceutical compositions comprising the GLP-1 receptor agonist compounds described herein and a pharmaceutically acceptable carrier. The GLP-1 receptor agonist compounds can be present in the pharmaceutical composition in a therapeutically effective amount and can be present in an amount to provide a minimum blood plasma level of the GLP-1 receptor agonist compound necessary for therapeutic efficacy. Such pharmaceutical compositions are known in the art and described, e.g., in US Patent No. 7,521,423; US Patent No. 7,456,254; WO 2000/037098; WO 2005/021022; WO 2005/102293; WO 2006/068910; WO 2006/125763; WO 2009/068910; US Publication No 2004/0106547; and the like, the disclosures of which are incorporated herein by reference.

Pharmaceutical compositions containing the GLP-1 receptor agonist compounds described herein may be provided for peripheral administration, such as parenteral (e.g., subcutaneous, intravenous, intramuscular), a continuous infusion (e.g., intravenous drip, intravenous bolus, intravenous infusion), topical, nasal, or oral administration. Suitable pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, such as Remington's Pharmaceutical Sciences by Martin; and Wang et al, Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

The GLP-1 receptor agonist compounds described herein can be provided in parenteral compositions for injection or infusion. They can, for example, be suspended in water; an inert oil, such as a vegetable oil (e.g., sesame, peanut, olive oil, and the like); or other pharmaceutically acceptable carrier. In one embodiment, the compounds are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to 8.0, or about 3.0 to 5.0. The compositions may be sterilized by conventional sterilization techniques or may be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following subcutaneous injection, transdermal injection or other delivery method. The desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes. In one embodiment for intravenous infusion, the formulation may comprise (i) the GLP-1 receptor agonist compound, (2) sterile water, and, optionally (3) sodium chloride, dextrose, or a combination thereof.

Carriers or excipients can also be used to facilitate administration of the GLP-1 receptor agonist compounds. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents.

The GLP-1 receptor agonist compounds can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Exemplary pharmaceutical formulations of GLP-1 receptor agonist compounds are described in US Patent No. 7,521,423, US Patent No. 7,456,254; US Publication No 2004/0106547, WO 2006/068910, WO 2006/125763, and the like, the disclosures of which are incorporated by reference herein.

The therapeutically effective amount of the GLP-1 receptor agonist compounds described herein for use in the methods described herein will typically be from about 0.01 μg to about 5 mg; about 0.1 μg to about 2.5 mg; about 1 μg to about 1 mg; about 1 μg to about 50 μg; or about 1 μg to about 25 μg. Alternatively, the therapeutically effective amount of the GLP-1 receptor agonist compounds may be from about 0.001 μg to about 100 μg based on the weight of a 70 kg patient; or from about 0.01 μg to about 50 μg based on the weight of a 70 kg patient. These therapeutically effective doses may be administered once/day, twice/day, thrice/day, once/week, biweekly, or once/month, depending on the formulation. The exact dose to be administered is determined, for example, by the formulation, such as an immediate release formulation or an extended release formulation. For transdermal, nasal or oral dosage forms, the dosage may be increased from about 5-fold to about 10-fold.

Example

Materials and Methods:

Animals: Cynomolgous monkeys (*Macaca fascicularis*), aged 2-4 years, were obtained from Charles River Laboratories (Houston, TX) or Covance Research (Alice, TX). Animals had a starting weight of 4.35 kg ± 1.00 (range 2.5-6.1). Animals were housed in individual cages (28x30x24 in) and given a continuous water supply. Animals were fasted for 12 hours prior to surgery and intravenous glucose tolerance tests, but were otherwise fed with a regular primate diet supplemented with fresh produce. The procedures described in this study were conducted according to the guidelines set forth in the "Guide for the Care and Use of Laboratory Animals" and by the Institutional Animal Care and Use Committee (IACUC) and University Laboratory Animal Resources (ULAR) (Guide for the Care and Use of Laboratory Animals, 7^{th} Ed. Washington D.C.: National Academy Press (1996)). The studies were conducted at Ohio State

University, where the animal care program is accredited by AAALAC, Int.

Study Design: All animals underwent total pancreatectomies to induce diabetes and were transplanted with islet allografts. The average dose of islets transplanted was 12,110 IEq/kg ± 7442.8. (IEq is Islet equivalent.) Group 1 (n=3) was treated with 5 µg exenatide twice daily (Amylin Pharmaceuticals, Inc., San Diego, CA) subcutaneously two days before (i.e., days -2) to the study endpoint, where day 0 was the day of transplant. Group 2 (n=3) was also treated with exenatide (5 µg twice daily subcutaneous) to study endpoint, but beginning on the day of transplant (i.e., day 0). Group 3 (n=5) was treated with an immunosuppression regimen: induction therapy consisted of rabbit antithymocyte globulin (ATG) (Thymoglobulin®, Genzyme, Cambridge, MA) at a dose of 1.5 mg/kg intravenously on days 0-3 and prednisone (Solu-medrol®, Pfizer, New York, NY) tapered from 25-5 mg over days 0-3. Immunosuppression maintenance consisted of 25 mg cyclosporine (CSA) (Neoral®, Novartis, East Hanover, NJ) and 250 mg mycophenolate mofetil (MMF) (CellCept®, Roche, Nutley, NJ) given orally from day 0 to the study endpoint. Group 4 (n=4) was untreated and served as the control group.

Surgical Procedures: Mismatched pairs of animals were placed under general anesthesia with isoflurane. A midline laparotomy was made in order to perform a total pancreatectomy. The pancreas was dissected from the splenic artery and vein, the portal vein and the duodenum with preservation of the spleen and common bile duct. Blood supply between the spleen and duodenum was double ligated, and the pancreas removed for islet isolation. Animals were maintained under anesthesia during the islet isolation with blood glucose monitoring completed every 15 minutes to ensure normoglycemia. Isolated islets from a mismatched allogeneic donor were immediately transplanted into the recipient pancreaectomized animal. For Group 1, both donor and recipient animals were pretreated with exenatide for 2 days prior to pancreatectomy and transplantation. Recipients from Groups 2, 3 and 4 received islets that had not been pretreated. The mesenteric vein was located and cannulated with an 18 gauge angiocatheter toward the portal vein. Islets suspended in 50 mL CMRL-1066 transplant media (Mediatech, Herndon, VA) without heparin were slowly injected over 10 minutes. The catheter was removed and the vein ligated. The incision was closed, and animals recovered under close observation until conscious. Buprenex® (0.05 mg/kg, Reckitt Benckiser, Berkshire, UK) was given as a post-operative analgesic.

Islet Isolation: Islet isolation was performed according to the modified human islet isolation protocol described by Rajab et al, *Cell Transplantation*, 17(9):1015-1023 (2008). Islet number was determined by dithizone staining and conversion to islet equivalents (IEq).

Post-Transplant Follow-up: For the first 48 hours post-transplant, blood glucose was measured twice daily using the tail prick method. A 10 µl drop of blood was drawn from the animal's tail for measurement on a standard glucometer (Ascensia Elite®, Bayer Healthcare, Mishawaka, IN). Fasting blood glucose was then measured once daily through day 7 post-transplant and weekly thereafter (for animals that were normoglycemic). Fasting blood glucose was measured prior to feeding the animals in the morning. Animals with a fasting blood glucose measuring 300 mg/dl or greater were monitored daily and given 2 units of NPH insulin (Eli Lilly, Indianapolis, IN). Intravenous glucose tolerance tests were performed prior to pancreatectomy on day 0 and post-transplant on days 10 and 90. The study endpoint was considered 90 days post-transplant for Groups 1-3 and 10 days post-transplant for the untreated Group 4 (due to the poor health noted by day 10 of animals in Group 4). However, two animals in group 1 (exenatide pre-treatment) were monitored beyond 90 days and an additional intravenous glucose tolerance test was performed on day 220. Body weights for animals were monitored throughout the study.

Intravenous Glucose Tolerance Test: Animals were fasted 12 hours prior to each intravenous glucose tolerance test. Baseline glucose and insulin were measured at times -5 and 0. A 50% solution of glucose was administered i.v. at time 0. Blood was drawn at times 1, 3, 5, 10, 15, 20, 25 and 30 minutes after glucose administration for measurement of blood glucose and serum insulin levels.

In vitro Glucose Stimulation Assay: Freshly isolated islets were handpicked (n=5 islets per replicate x 3 replicates) and incubated at 37°C in either "high" (16.7mM) glucose or "low" (1.67mM) glucose for 1 hour. Supernatants were collected by centrifugation and measured for insulin content using an ELISA kit for human insulin (Dako, Carpinteria, CA). An insulin stimulation index (S.I. = high/low glucose insulin release) was determined for each sample.

Data Analysis: Area under the curve (AUC) was determined for all intravenous glucose tolerance test glucose curves. Glucose disappearance rate constants (k_G) were used as a measure of glucose tolerance and insulin sensitivity for intravenous glucose tolerance tests. k_G was calculated as the negative slope of the linear regression for the natural logarithm of glucose from

10-30 minutes. Acute insulin response to glucose (AIRg) was used as a measure of first phase insulin secretion during intravenous glucose tolerance tests. AIRg was calculated as the mean of insulin at time 3-5 minutes minus the mean at time 0. Beta cell function was measured by the mathematical assessment of glucose regulation called the homeostasis model assessment (HOMA-%B). HOMA-%B was calculated as the average basal insulin (μIU/mL) multiplied by 20 and divided by the average basal glucose (mmol/mL) minus 3.5.

Statistical analysis: All results are expressed as mean ± SEM unless otherwise stated. Student t-test and two-way analysis of variants (ANOVA) were used for parametric analysis. A probability value (p) of less than 0.05 is considered statistically significant.

Results

Fasting Blood Glucose: Animals in the untreated control group showed elevated blood glucose levels by day 1 post-transplant (Figure 1A), with the average fasting blood glucose at day 5 post-transplant being 265 mg/dl ± 172 (Figure 1B). Comparatively, animals treated with the immunosuppression regimen of ATG, CSA and MMF maintained normoglycemia throughout their 90 day follow-up period and had an average fasting blood glucose of 59.4 mg/dl ± 12.1 at day 5 post-transplant (Figure 1). Animals that were pre-treated with exenatide also maintained normoglycemia. In fact, two animals in this group were followed for 435 days post-transplant and continued to maintain normoglycemia throughout this period (Figure 1A). On day 5 post-transplant, the average fasting blood glucose for this group was 52.7 mg/dl ± 14.8 (Figure 1B). Finally, animals treated with exenatide post-transplant only showed moderately elevated fasting blood glucose from day 4 post-transplant on (Figure 1A), with an average fasting blood glucose on day 5 of 154 mg/dl ± 105 (Figure 1B).

Intravenous Glucose Tolerance Tests: intravenous glucose tolerance test results post-transplant were impaired in both untreated animals as well as animals treated with exenatide post-transplant only (Figure 2). Blood glucose levels were significantly elevated in untreated animals with the AUC being significantly increased post-transplant. Animals treated with exenatide post-transplant only had an abnormal glucose curve although the AUC was not significantly different (Figure 2A). Insulin curves post-transplant for both groups were abnormal compared to baseline with no noticeable 2^{nd} phase insulin production and severely reduced insulin levels (Figure 2B). On the other hand, intravenous glucose tolerance tests for animals treated with ATG/CSA/MMF as well as animals pre-treated with exenatide were indicative of functional islet grafts, with blood glucose responses resembling that prior to pancreatectomy (Figure 2A). There was no significant change post-transplant in the AUC for animals in these groups. Insulin levels actually increased post-transplant in the ATG/CSA/MMF group. For animals pre-treated with exenatide, there was some reduction in insulin over time post-transplant, however, insulin levels were still higher than that of any other treatment group. First and second phase insulin responses also continued to be noted post-transplant for both of these groups (Figure 2B).

First phase insulin secretion (AIRg) in untreated recipients was severely reduced at 10 days post-transplant compared to baseline (9.53 μU/ml ± 19.2 vs. 61.0 μU/ml ± 40.0) (Figure 3A). Beta cell function as determined by homeostasis model assessment (HOMA-%B) was also significantly reduced post-transplant in untreated animals (1.89% ± 9.14 vs. 20.2% ± 8.3 at baseline; p=0.01) (Figure 3B). Islet recipients treated with exenatide post-transplant only had a mean AIRg at day 0 pre-pancreatectomy of 23.7 μU/ml ± 35.9. At 10 days post-transplant, this was reduced to 16.6 μU/ml ± 18.1 (Figure 3A). Similarly, beta cell function also dropped post-transplant from 22.2 % ± 46.4 at baseline to 13.8% ± 26.1 (Figure 3B). On the other hand, recipients treated with ATG/CSA/MMF maintained a comparable first phase insulin secretion post-transplant. AIRg was 35.5 μU/ml ± 14.1 at baseline and continued at 39.7 μU/ml ± 26.6 ninety days post-transplant (Figure 3A). Beta cell function increased slightly in this group although the difference was not significant. HOMA-%B in ATG/CSA/MMF-treated animals was 29.9% ± 24.3 at baseline and 43.8% ± 29.5 at day 90 (Figure 3B). Animals that were pre-treated with exenatide showed notably higher first phase insulin secretion at baseline compared to all other groups (211 μU/ml ± 150). This did drop post-transplant to 105 μU/ml ± 19.0 at 90-days but continued to remain significantly higher than other treatment groups (Figure 3A). Baseline beta cell function was also increased in the exenatide pre-treatment group compared to other groups (53.3% ± 5.55), and this actually showed a significant increase post-transplant to 107% ± 28.6 at 90 days (Figure 3B).

In Vitro Glucose Stimulation: The average stimulation index for islets isolated from animals receiving *in vivo* exenatide pre-treatment was 2.98 ± 1.85. For islets isolated from untreated donor animals (not previously treated with exenatide), the average stimulation index was 0.52 ± 0.32. This was significantly lower than that of exenatide-treated animals (p=0.04).

Discussion

Fasting blood glucose levels were used as a determinant for islet graft function post-transplant. Untreated recipients had an average fasting blood glucose on day 5 post-transplant of 265 mg/dl ± 172. Rejection was expected in these animals, and this hyperglycemia was indicative of graft failure. Animals receiving exenatide beginning on the day of transplant had an average fasting blood glucose at day 5 of 154 mg/dl ± 105. Animals in this group showed variable fasting blood glucose levels that remained somewhat elevated from day 4 post-transplant to endpoint. While fasting blood glucose levels were less severely elevated than those of untreated animals and did not consistently meet the criteria for diabetes determination (fasting blood glucose ≥ 250 mg/dl), they remained elevated throughout the study. Comparatively, ATG/CSA/MMF-treated animals as well as animals pre-treated with exenatide maintained normoglycemia following islet cell transplant, indicating functional islet grafts for the duration of the study. In fact, overall fasting blood glucose was significantly lower in animals pre-treated with exenatide compared to animals treated with ATG/CSA/MMF. The immunosuppression strategy employed in this study included the calcineurin inhibitor, cyclosporine, which has been shown to have diabetogenic properties. The use of exenatide in place of this immunosuppression regimen may have reduced the damaging effects of cyclosporine on islet cell function. In addition, these results suggest that exenatide alone is sufficient for the prevention of graft rejection.

Results from intravenous glucose tolerance tests also indicate functioning islet allografts in animals pre-treated with exenatide or treated with ATG/CSA/MMF, whereas untreated animals had elevated glucose levels and reduced insulin production. Animals receiving exenatide treatment post-transplant only also showed impaired insulin production and abnormal glucose curves. Second phase insulin responses were not noticeable in either untreated or exenatide post-only treatment groups. Islet cell transplant recipients treated with exenatide prior to transplant showed increased insulin production in response to glucose compared to recipients treated only with the immunosuppression regimen of ATG, CSA and MMF. First phase insulin secretion was also significantly higher in the exenatide pre-treatment group at 90 days post-transplant relative to the ATG/CSA/MMF group. Also, at 90 days post-transplant, animals treated with exenatide alone showed significantly improved beta cell function compared to ATG/CSA/MMF-treated animals. Thus, in addition to protecting islets from rejection, exenatide was actually able to improve graft function relative to regular immunosuppression.

Due to our experimental set-up, both donors and recipients in the exenatide pre-treatment group began treatment 2 days prior to transplant. *In vitro* glucose stimulation assays performed on freshly isolated islets in this study indicated a significant improvement in islet function for islets pre-treated with exenatide compared to those that did not receive exenatide treatment. This suggests that exenatide pre-treated islets were of a higher quality upon transplantation. Improved glucose tolerance, insulin secretion and beta cell function in animals pre-treated with exenatide supports this. Additionally, even at day 0 prior to transplantation, insulin secretion and glucose tolerance were better in exenatide pre-treated animals compared to other groups. Serum insulin levels produced in response to i.v. glucose administration were also significantly higher in animals pre-treated with exenatide. Because this improvement was noted even at day 0, this suggests that pre-treatment with exenatide may be key in improved graft function and protection over time. Animals treated with exenatide post-transplant only did not show the same improvements and/or maintenance of graft function compared to those receiving pre-treatment.

In summary, we have shown in this study that exenatide can improve graft function relative to treatment with immunosuppression and that, in fact, exenatide treatment alone is sufficient in itself in protecting islet allografts from rejection. However, pre-treatment of donors and/or recipients appears to be necessary to achieve this level of graft function. When exenatide treatment of the recipient is not initiated until day 0 and transplanted islets are also untreated, graft function becomes impaired and more closely resembles that of grafts in untreated animals. This, along with its potential to protect islets from auto-immune attack, makes exenatide a useful treatment for long-term success in islet transplantation in type 1 diabetic patients.

Claims

What is claimed is:

1. A method for treating diabetes in a patient in need thereof comprising:
   (i) administering a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient prior to islet transplant;
   (ii) transplanting islets into the patient;

   thereby treating diabetes in the patient.

2. A method for treating Type 1 diabetes in a patient in need thereof comprising:
   (iii) administering a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month;
   (iv) treating islets with a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month;
   (v) transplanting the islets into the patient;
   (vi) administering a therapeutically effective amount of the GLP-1 receptor agonist compound to the patient after the islet transplant;

   thereby treating Type 1 diabetes in the patient.

3. A method for promoting graft survival and improved graft function in a patient receiving an islet transplant comprising the steps of:
   (i) administering a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient prior to islet transplant;
   (ii) treating islets with a therapeutically effective amount of a GLP-1 receptor agonist compound prior to transplant;
   (iii) transplanting the islets into the patient;
   (iv) administering a therapeutically effective amount of the GLP-1 receptor agonist compound to the patient after the islet transplant;

   thereby promoting graft survival and improved graft function in the patient.

4. A method for promoting graft survival and improved graft function in a patient receiving an islet transplant comprising the steps of:
   (v) administering a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month;

(vi) treating islets with a therapeutically effective amount of a GLP-1 receptor agonist compound to the patient for a period of time of 1 day to 1 month;

(vii) transplanting the islets into the patient;

(viii) administering a therapeutically effective amount of the GLP-1 receptor agonist compound to the patient after the islet transplant;

thereby promoting graft survival and improved graft function in the patient.

5. The method of any one of Claims 1-4. wherein the patient is not administered an immunosuppressive drug or an immunosuppressive treatment regimen before, during, or after any step in the method.

6. The method of any one of Claims 1-5, wherein the patient is a human.

7. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is exenatide.

8. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound comprises the amino acid sequence of exendin-4.

9. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is a peptide having at least 90% sequence identity to exenatide.

10. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound comprises the amino acid sequence of Leu^{14}-exendin-4.

11. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is lixisenatide.

12. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is liraglutide.

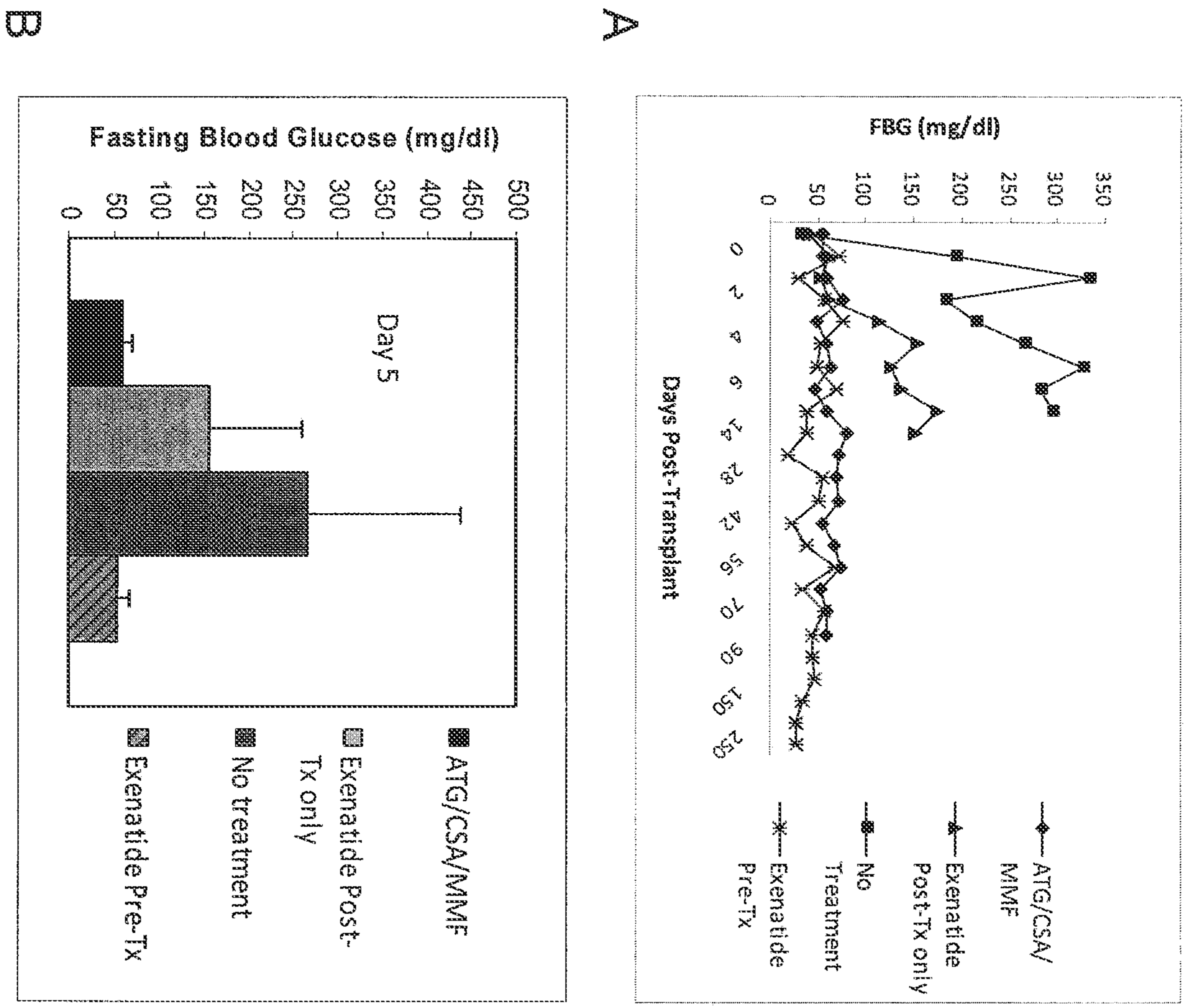
13. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is dulaglutide.

14. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is albiglutide.

15. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist compound is taspoglutide.

16. The method of any one of Claims 1-6, wherein the GLP-1 receptor agonist is a peptide having at least 90% sequence identity to GLP-1(7-36)NH_2.

Figure 1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100
150
200
250
300
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2
4
6
14
28
42
56
70
90
150
250
Days Post-Transplant
ATG/CSA/MMF
Exenatide Post-Tx only
No Treatment
Exenatide Pre-Tx
B
Fasting Blood Glucose (mg/dl)
0
50
100
150
200
250
300
350
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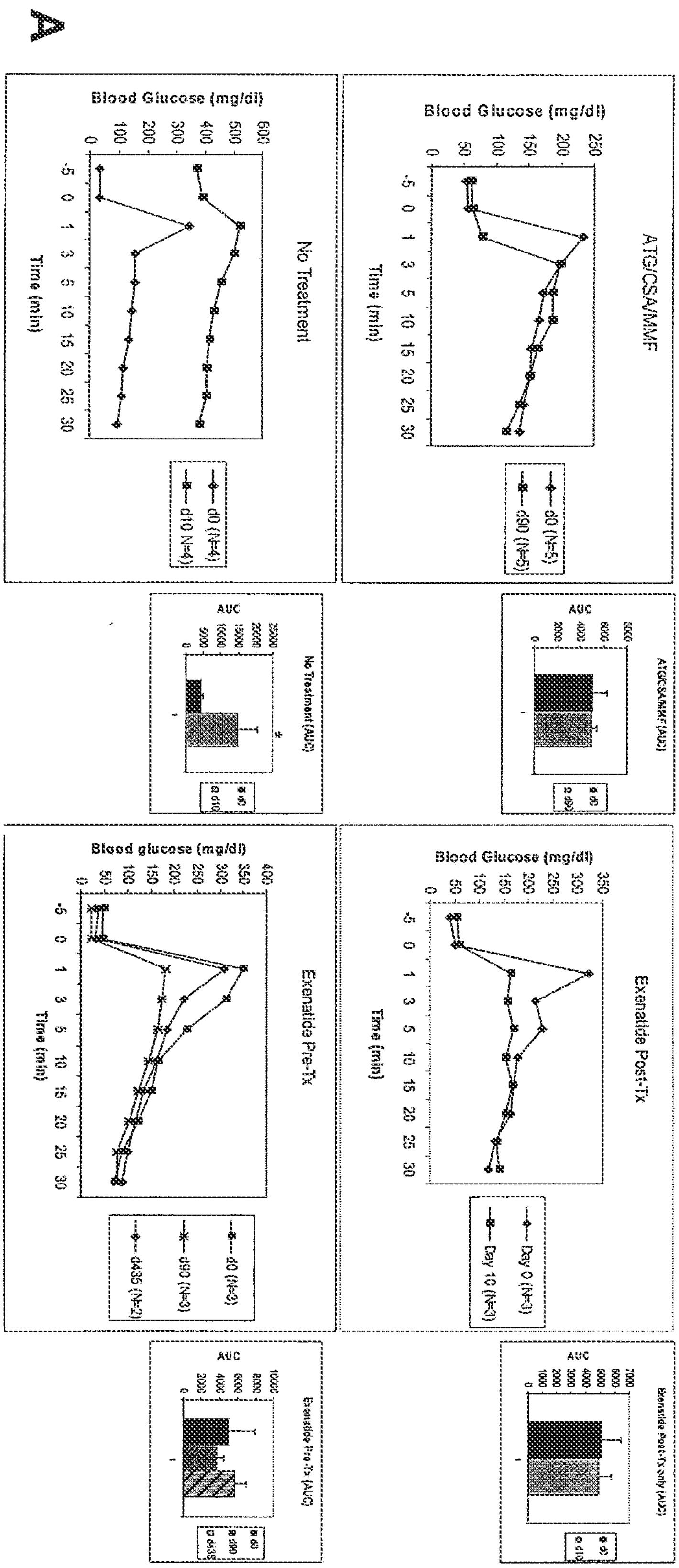
450
500
Day 5
ATG/CSA/MMF
Exenatide Post-Tx only
No treatment
Exenatide Pre-Tx

Figure 2


A
ATG/CSA/MMF
Blood Glucose (mg/dl)
Time (min)
d0 (N=5)
d90 (N=5)
AUC
No Treatment
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Time (min)
d0 (N=4)
d10 N=4)
AUC
No Treatment (AUC)
Exenatide Post-Tx
Blood Glucose (mg/dl)
Time (min)
Day 0 (N=3)
Day 10 (N=3)
AUC
Exenatide Pre-Tx
Blood glucose (mg/dl)
Time (min)
d0 (N=3)
d90 (N=3)
d435 (N=2)
AUC
Exenatide Pre-Tx (AUC)

Figure 2

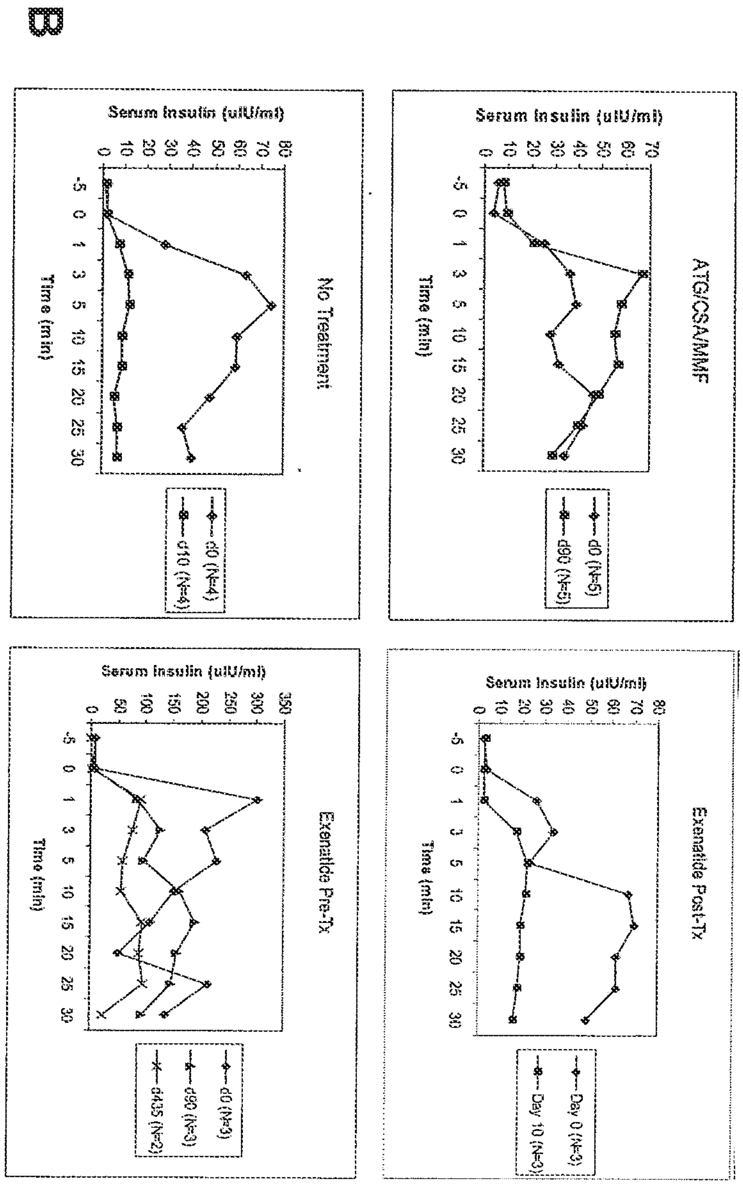
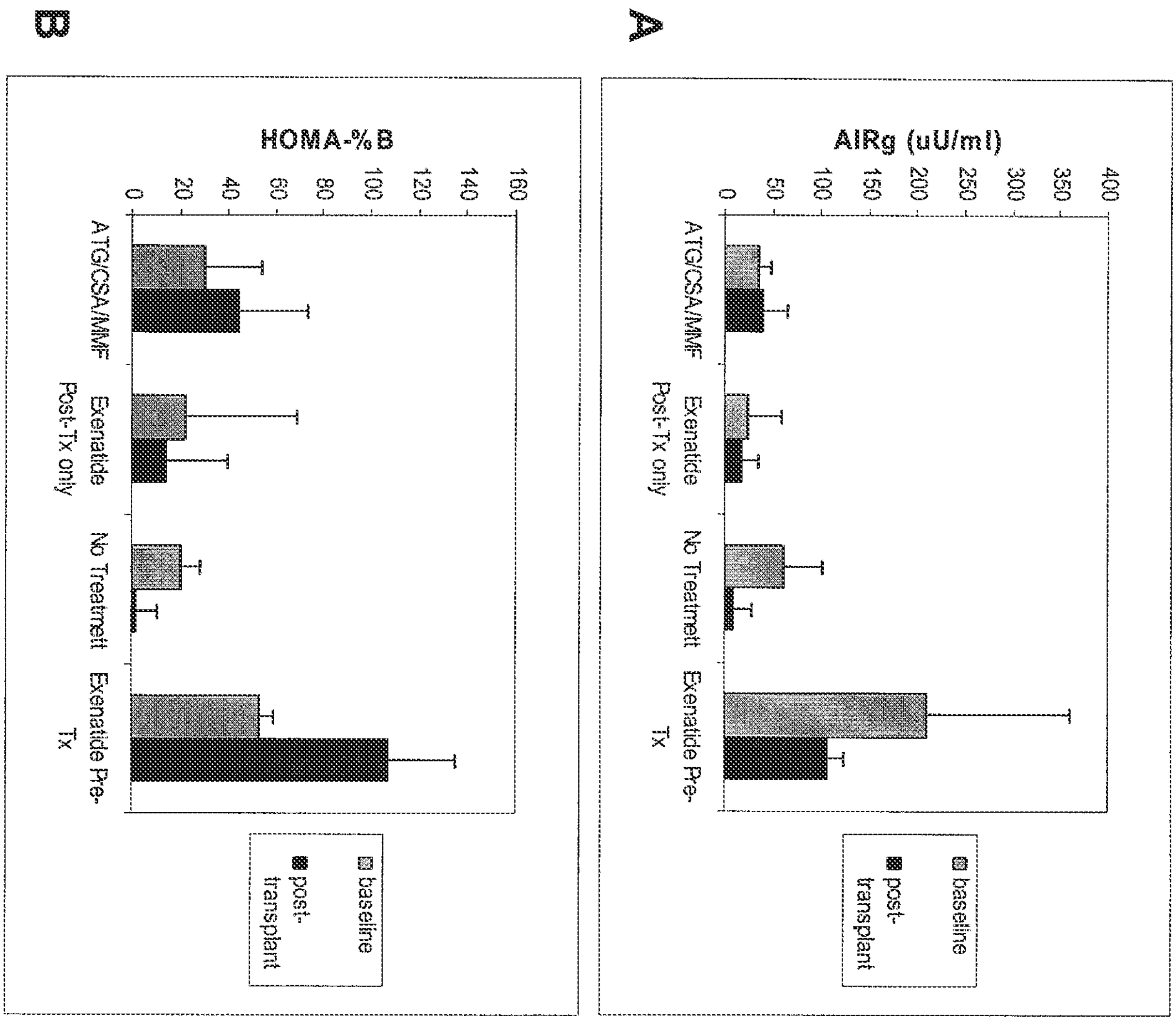

B
ATG/CSA/MMF
Serum Insulin (uIU/ml)
Time (min)
d0 (N=5)
d90 (N=5)
No Treatment
Serum Insulin (uIU/ml)
Time (min)
d0 (N=4)
d10 (N=4)
Exenatide Post-Tx
Serum Insulin (uIU/ml)
Time (min)
Day 0 (N=3)
Day 10 (N=3)
Exenatide Pre-Tx
Serum Insulin (uIU/ml)
Time (min)
d0 (N=3)
d90 (N=3)
d435 (N=2)

Figure 3


A
AIRg (uU/ml)
0
50
100
150
200
250
300
350
400
ATG/CSA/MMF
Exenatide Post-Tx only
No Treatmett
Exenatide Pre-Tx
baseline
post-transplant
B
HOMA-%B
0
20
40
60
80
100
120
140
160
ATG/CSA/MMF
Exenatide Post-Tx only
No Treatmett
Exenatide Pre-Tx
baseline
post-transplant

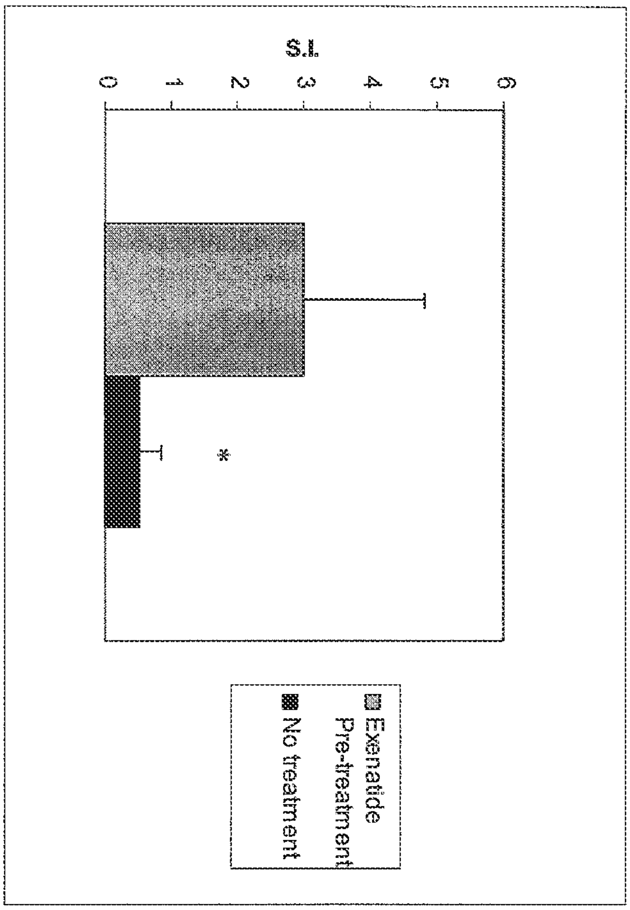


Figure 4