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Functional Cure of an Elderly Type 2 Diabetes Patient via 40 Times Intravenous Transplantations of Human UC-MSCs Overexpressing Human Insulin and ERRγ Genes

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ABSTRACT

We report the functional cure of an elderly type 2 diabetes (T2D) patient by intravenous transplantations of mesenchymal stem cells derived from Wharton's jelly portion of human umbilical cord (UCWJ-MSCs) double overexpressing human estrogen-related receptor γ (ERRγ) and insulin genes. After 40 times of systemic infusions, the patient's antidiabetic drugs (3 tablets of Acarbose and 3 tablets of Metformin daily) and exogenous insulin injections (47 IU daily) were completely replaced. More importantly, the patient's T2D-derived microvascular and macrovascular complications were repaired and improved significantly during and after transplantations. Our data provides a proof of principle for human stem cell-gene therapy to treat human diabetes. As we invented and applied this protocol to treat human diabetes in China, we designated this method as "China Protocol".

Keywords

UCWJ-MSCs, T2D, ERRγ, Insulin, Intravenous transplantations, China protocol.

Introduction

In 1922, Banting et al. first discovered that a type 1 diabetes (T1D) patient could be successfully treated with a pancreatic extract (known subsequently as insulin) [1,2]. From then on, insulin (INS) is widely used for the treatment of both type 1 and type 2 diabetes (T2D). However, even with careful administration of exogenous insulin, blood glucose levels cannot be effectively controlled within the narrow physiological range, it fails to prevent progression of microvascular and macrovascular complications in many subjects, and imprecision delivery of insulin often results in hypoglycaemia and glycemic lability [3,4]. Therefore, more efficient strategies for diabetes treatment are urgently needed to develop.

In 2000, a great scientific breakthrough took place in Edmonton, Canada. Shapiro et al. isolated human pancreatic islets from brain-dead donors and transplanted these freshly prepared islets immediately by means of a percutaneous transhepatic portal embolization procedure, accompanied with a glucocorticoid-free immunosuppressive regimen to treat seven T1D patients [5]. This method was designated as "Edmonton Protocol" [6]. In 2022, Marfil-Garza et al. reported the 20-year outcomes of intraportal islet transplantation with the Edmonton Protocol [7]. Of 255 patients followed up, insulin independence was ever achieved in 79% of recipients, which decreased to 61% by 1 year, 32% by 5

years, 20% by 10 years and 8% by 20 years after transplantations [2,7]. In addition, during the 20-year duration, 70% of the recipients had sustained islet graft function with positive serum C-peptide, stabilized glycaemic control and correction of glycated haemoglobin (HbA1c) concentrations [2,7]. From then on, more than 1,500 islet transplantations have been performed worldwide. However, the paucity of islets from deceased donors and the need for life-long systemic immunosuppressive therapy are two major limitations to impede the widespread adoption of this procedure [8,9].

To address the limited supply of donor pancreas, in 2021, two groups reported open-label, first-in-human phase 1/2 studies to evaluate the safety and efficacy of pluoripotent stem cell-derived pancreatic endoderm cells (PEC-01) implanted subcutaneously in T1D patients [4,8]. After implantation, the recipients had increased fasting and mixed meal-stimulated C-peptide levels. In addition, the explanted grafts contained matured β cells. More importantly, the implanted PEC-01-VC-02 macroencapsulation devices were well tolerated, and no teratoma formation and severe graft-related adverse events occurred. However, there was no significant clinical relevance on glycemic control and insulin use in these studies [4,8]. Surprisingly, funded by Vertex Pharmaceuticals, in 2025, Reichman et al. infused zimislecel (stem cell-derived, fully differentiated islets) into the patient's portal vein, accompanied with glucocorticoid-free immunosuppressive therapy, to treat human T1D. Their results showed that 83% of the participants had insulin independence and were not using exogenous insulin at day 365. This method provides an inexhaustible supply of replacement islets for human T1D [10].

To provide unlimited autologous human islets for treating T1D, in 2024, Wang et al. generated chemically induced pluripotent stem cells (CiPSCs) from the patient's adipose-derived mesenchymal stromal cells, and differentiated the CiPSCs into islets, and then transplanted these CiPSC-islets into the patient beneath the addominal anterior rectus sheath [11]. For convenience, this procedure can be designated as "CiPSC-islet protocol". The transplanted CiPSC-islets functioned well in the patient, and the patient's endogenous, glucose-responsive insulin secretion recovered. In addition, the authors found that, 75 days post-transplantation, the patient achieved consistent insulin independence up to 1 year, and from the 4th month on, the patient's time-in-target glycemic range was at >98%, and the HbA1c was at around 5%, which is an indicator of long-term systemic glucose levels at a non-diabetic level. More importantly, no evidence of teratoma formation was found in the graft site during the 1-year follow-up. However, due to T1D is an autoimmune disease, immunosuppressants would be necessitated for this autologous islet transplantation therapy [11].

Compared with T1D, T2D accounts for nearly 90% of the approximately 537 million cases of diabetes worldwide [12]. T2D could lead to microvascular and macrovascular complications that would cause profound physical and psychological distress to the patients [13]. Previously, we reported that intravenous transplantations of human adipose-derived mesenchymal stem cells overexpressing human insulin (INS) and/or estrogen-related receptor γ (ERRγ) genes [14] can effectively decrease the blood glucose and HbA1c levels of T2D patients. In addition, sufficient times of transplantations of these stem cells overexpressing INS + ERRγ can not only replace the exogeneous insulin injection and antidiabetic drugs but also can effectively repair and improve the T2D-derived complications of the patients [15-20]. More importantly, to evaluate the safety and efficacy of intravenous transplantations of different kinds of human stem cells overexpressing different human genes, the correspondence author of these investigations, G Z, voluntarily accepted human stem cell transplantations. During the past five years (from October of 2016 to January of 2021), G Z accepted totally 77 times different kinds of human stem cell transplantations with/without overexpressing different human genes, and the whole number of human stem cells transplanted was up to approximately 6.36 x 10^9. The medical examination results showed that G Z's health conditions were basically normal [21]. These data demonstrated that intravenous transplantations of human stem cells overexpressing different human genes are safe for the treatment of different human diseases.

The isolation, culture and characterization of fibroblast-like cells derived from the Wharton's jelly portion of human umbilical cord (UC) were first reported by McElreavey et al. in 1991 [22]. UC-derived mesenchymal stem cells (UC-MSC) have the capability to differentiate into three germ layer cells, such as osteocytes, chondrocytes, adipocytes, cardiomyocytes, neurons and glia, oligodentrocytes, hepatocytes, and so on [23]. In addition, UC-MSCs can accumulate in damaged tissue or inflamed regions, promote tissue repair, and modulate immune responses [23]. Therefore, UC-MSCs are believed to be a promising and versatile tool for regenerative medicine and immunotherapy.

Here, we report, for the first time, allogeneic transplantations of human UC-MSCs overexpressing human INS and ERRγ (UC-MSC-INS-ERRγ) genes intravenously into a patient with T2D as a phase 1 clinical study, which resulted in the total replacement of insulin and antidiabetic drug administrations. As we invented and applied this protocol to treat diabetes patients in China, for convenience, we designated this procedure as "China protocol". More importantly, the patient not only maintained consistent almost normal blood glucose levels but also the patient's diabetes-derived complications were repaired and improved significantly. Therefore, this study provides a proof of principle for the clinical treatment of T2D with human stem cells overexpressing human INS and ERRγ genes.

Materials and Methods

Statement of Ethical Approval

The treatments for the participant and the use of human UC-MSC-INS-ERRγ cells were approved by the Ethics Committee of Interventional Hospital of Shandong Red Cross Society (Ethical Review Approval Number: 2021-003) in compliance with Helsinki Declaration. The participant provided written confirmed consent to participate the clinical study and treatments. All the treatments

for the participant and use of human stem cells were performed in accordance with the guidelines established in the Interventional Hospital of Shandong Red Cross Society approved by the Ethics Committee. The participant agreed to try the UC-MSC-INS-ERRγ cell therapy in our hospital to treat the participiant's T2D. The stem cells used in this clinical treatment are allogeneic UC-MSCs, stored at our Stem Cell Bank.

Study participant medical history

This participant is the first patient enrolled in the ongoing trial conducted in the International Hospital of Shandong Red Cross Society (Ethical Review Approval Number: 2021-003). An age range of 75-80-year-old woman was diagnosed with T2D for more than 20 years (as of the time of transplantations in 2023). As the patient described, probably, the patient already had had T2D for a long time before the diagnosis of T2D. But the patient was unaware of her health conditions until she was diagnosed with T2D in 2003. Before the transplantation therapy, the patient's body weight was 91.5 kilograms, her body height was 1.54 meters, and her body mass index [BMI=body weight (kilogram)/body height (meter)^2] was approximately 38.6.

The patient developed microvascular and macrovascular diabetes-related complications, including hypertension, cerebral infarction, and retinopathy, etc. Her left eye was ablepsia. And her legs were numb and weak, and she used a wheelchair. Before the transplantations of human UC-MSC-INS-ERRγ, the patient needed to inject 47 IU insulin daily (25 IU in the morning and 22 IU at night), and orally take 3 tablets of Acarbose (50mg/tablet, 1 tablet in the morning, 1 tablet at noon, and 1 tablet at night, respectively) and 3 tablets of Metformin Hydrochloride Sustained Release Tablets (0.5g/tablet, 3 tablets at noon) to control her blood glucose levels. The patient was informed of the risks and benefits of this clinical experimental therapy. Informed consent was signed, which stated potential risks and other treatment options. From April of 2023 on, the patient began to accept human UC-MSC-INS-ERRγ transplantation therapy to treat her T2D disease.

UC-MSC preparation

The research protocol was approved by the Ethics Committee of Interventional Hospital of Shandong Red Cross Society (Ethical Review Approval Number: 2021-003). Informed consent was signed and obtained from the mother before delivery. The MSCs were isolated and cultured from the Wharton's jelly portion of human UC (UCWJ-MSCs) by the explant method according to the reported descriptions [22,24]. Briefly, Wharton's jelly was removed, minced into 1-2 mm^3 fragments. The fragments were aligned and attached at regular intervals to 10 cm dishes and cultured in basal medium. The basal medium consisted of MEM Alpha basic (gibco, made in China) supplemented with 10% UltraGRO™-Advanced (GMP Grade) (AventaCell HELIOS, USA). Cultures were incubated in a humidified atmosphere with 5% CO_2 at 37°C. The growth medium consisted of basal medium supplemented with 5ng/ml Human FGF-basic (154aa) (fibroblast growth factor, bFGF, PEPROTECH, USA). After expansion, the UC-MSCs were cryopreserved in liquid nitrogen.

Lentivirus vector construction, production and infection

The third generation lentiviral Gateway destination expression vector pLenti CMV Blast DEST (addgene Plasmid #17451) [25] was modified by removing the sequence fragments between attR1 and attR2, and EM7 promoter and Blasticidin fragments, and inserting several appropriate clone sites, such as BamH I, Pme I, etc (Data not shown). Human ERRγ and INS genes were inserted, respectively, into the modified pLenti vector with a unique BamH I site to construct pLenti-ERRγ and pLenti-INS vectors according to the "Combinatorial strategy" previously described [26-28]. The pLenti-ERRγ and pLenti-INS lentiviral vectors were produced and infected into UC-MSC cells according to the previous report [29].

Briefly, the UC-MSC cells were thawed from liquid nitrogen and cultured for 1 to 2 weeks and then were ready for the infection with pLenti-ERRγ and pLenti-INS lentiviral vectors. This period of culture can recover the UC-MSCs from frozen state to normal growing state and thus increase the infection efficiency, and simultaneously, can reduce the "cryo stun effect" during the subsequent infusion procedure [30]. The format of infection was that 12.5 ml pLenti-ERRγ and 12.5 ml pLenti-INS were added into one 15-cm dish of UC-MSCs, respectively, and mixed gently, but thoroughly, to infect the UC-MSCs with ERRγ and INS genes (UC-MSCs-ERRγ+INS) (Table 1). Consequently, the UC-MSCs-ERRγ+INS cells could double express ERRγ and INS genes constitutively. After addition of pLenti-ERRγ and pLenti-INS lentiviral vectors, the UC-MSC cells were incubated overnight.

UC-MSCs-ERRγ+INS transplantations

The UC-MSCs-ERRγ+INS cells were trypsinized and harvested, and then, washed with Compound Sodium Chloride Injection (State Food and Drug Administration approval number: H34020046, China) 5 times. The cell numbers were counted, and then the cells were diluted in 100 ml Compound Sodium Chloride Injection containing 0.5% human albumin (Albutein, GRIFOLS, USA). Before infusion of the UC-MSCs-ERRγ+INS cells intravenously, the patient was infused with Compound Sodium Chloride Injection for 10-15 minutes at approximately 50-60 drops per minute to mitigate the instant blood-mediated inflammatory reaction (IBMIR) [5,31]. After the UC-MSCs-ERRγ+INS cells were completely infused into the patient, the patient was infused with Compound Sodium Chloride Injection for 10-15 minutes to further the cells into the blood circulation. Because UC-MSC cells have the advantage of low immunogenicity with good immunosuppressive ability, no immunosuppressants were used for the patient in this clinical study [23]. In the first 11 times of transplantations, less UC-MSCs-ERRγ+INS cells were infused. After the patient adapted the transplantations, more cells were infused gradually. Approximately 2.0 x 10^7 to 8.0 x 10^7 cells were transplanted into the patient, and the intervals between transplantations were around 5 to 7 days, respectively. The total transplantation times were 40, and approximately 1.98 x 10^9 UC-MSC-ERRγ+INS cells were transplanted into the patient (Table 1).

Clinical responses and treatment efficacy assessment

During the transplantation period, the fasting fingertip capillary

Table 1: Intravenous transplantations of UC-MSCs- ERRγ + INS cells for the patient.

Times	Cell type	Cell numbers	Antidiabetic drug and insulin administrations
#1	UC-MSCs + 25ml pLenti-ERRγ + 25ml pLenti-INS	3.0 x 10^7	Morning: 25 IU; Night: 22 IU; Morning: 1; Noon: 1; Night: 1 tablet of Acarbose respectively; Noon: 3 tablets of metformin
#2	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	2.0 x 10^7	Morning: 25 IU; Night: 22 IU; Morning: 1; Night: 1 tablet of Acarbose respectively; Noon: 3 tablets of metformin
#3	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	3.5 x 10^7	Noon: 1 tablet of metformin Morning: 25 IU; Night: 22 IU
#4	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	3.3 x 10^7	Morning: 25 IU; Night: 19 IU
#5	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	2.6 x 10^7	Morning: 23 IU; Night: 19 IU
#6	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	2.3 x 10^7	Morning: 20 IU; Night: 19 IU
#7	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	2.8 x 10^7	Morning: 16 IU; Night: 19 IU
#8	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	3.5 x 10^7	Morning: 14 IU; Night: 17 IU
#9	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	5.7 x 10^7	Morning: 14 IU; Night: 14 IU
#10	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	5.3 x 10^7	Morning: 12 IU; Night: 12 IU
#11	UC-MSCs +25ml pLenti-ERRγ+25ml pLenti- INS	3.8 x 10^7	Morning: 12 IU; Night: 12 IU
#12	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.6 x 10^7	Morning: 10 IU; Night: 10 IU
#13	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	2.5 x 10^7	Morning: 8 IU; Night: 8 IU
#14	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	2.7 x 10^7	Morning: 8 IU; Night: 8 IU
#15	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	3.6 x 10^7	Morning: 6 IU; Night: 8 IU
#16	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.0 x 10^7	Morning: 6 IU; Night: 5 IU
#17	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	5.5 x 10^7	Morning: 3 IU; Night: 5 IU
#18	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.9 x 10^7	Morning: 3 IU; Night: 5 IU
#19	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	7.5 x 10^7	Night: 5 IU
#20	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.0 x 10^7	Night: 5 IU
#21	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.3 x 10^7	Night: 5 IU
#22	UC-MSCs +50 ml pLenti-ERRγ+50 ml pLenti- INS	4.9 x 10^7	Night: 5 IU
#23	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	7.8 x 10^7	Night: 3 IU
#24	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	7.9 x 10^7	Stopped
#25	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	7.0 x 10^7	Stopped
#26	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	6.5 x 10^7	Stopped
#27	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	6.3 x 10^7	Stopped
#28	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	6.2 x 10^7	Stopped
#29	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	6.1 x 10^7	Stopped
#30	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	7.6 x 10^7	Stopped
#31	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	5.7 x 10^7	Stopped
#32	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	4.8 x 10^7	Stopped
#33	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	5.2 x 10^7	Stopped
#34	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	7.5 x 10^7	Stopped
#35	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	5.4 x 10^7	Stopped
#36	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	8.0 x 10^7	Stopped
#37	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	6.2 x 10^7	Stopped
#38	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	5.3 x 10^7	Stopped
#39	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	4.0 x 10^7	Stopped
#40	UC-MSCs +75 ml pLenti-ERRγ+75 ml pLenti- INS	4.2 x 10^7	Stopped
total		1.98 x 10^9	

Table 2: Daily monitoring of the patient's FFCBG levels.

Dates	FFCBG (mmol/L)	Dates	FFCBG (mmol/L)	Dates	FFCBG (mmol/L)	Dates	FFCBG (mmol/L)
Day 1	6.5	Day 2	6.4	Day 3	6.2	Day 4	8.9
Day 5	6.6	Day 6	6.2	Day 7	6.3	Day 8	6.0
Day 9	6.0	Day 10	5.9	Day 11	6.8	Day 12	5.8
Day 13	10.3	Day 14	6.0	Day 15	6.0	Day 16	6.2
Day 17	6.9	Day 18	6.4	Day 19	7.2	Day 20	7.0
Day 21	8.7	Day 22	6.8	Day 23	8.5	Day 24	6.9
Day 25	6.5	Day 26	5.8	Day 27	5.8	Day 28	7.1
Day 29	6.2	Day 30	6.0	Day 31	6.6	Day 32	7.1
Day 33	7.4	Day 34	6.0	Day 35	5.9	Day 36	5.7
Day 37	5.8	Day 38	5.6	Day 39	5.8	Day 40	5.8
Day 42	5.7	Day 43	5.6	Day 44	5.9	Day 45	7.6
Day 46	5.7	Day 47	5.5	Day 48	6.6	Day 49	6.2
Day 50	7.2	Day 51	6.6	Day 52	7.0	Day 53	8.3
Day 54	7.1	Day 55	6.8	Day 56	6.4	Day 57	6.7
Day 58	7.3	Day 59	7.6	Day 60	7.6	Day 61	6.8
Day 62	7.5	Day 63	8.2	Day 64	9.7	Day 65	7.9
Day 66	7.8	Day 67	7.9	Day 68	10	Day 69	7.5
Day 70	7.2	Day 71	8.4	Day 72	7.6	Day 73	7.6
Day 74	6.7	Day 75	7.0	Day 76	7.2	Day 77	7.6
Day 78	7.4	Day 79	7.6	Day 80	7.7	Day 81	7.8
Day 82	7.6	Day 83	9.4	Day 84	8.6	Day 85	9.4
Day 86	9.8	Day 87	9.5	Day 88	8.8	Day 89	10.3
Day 90	8.7	Day 91	10.3	Day 92	9.9	Day 93	9.5
Day 94	9.0	Day 95	9.3	Day 96	8.0	Day 97	8.1
Day 98	8.1	Day 99	6.7	Day 100	7.5	Day 101	7.0
Day 102	7.5	Day 103	7.7	Day 104	8.2	Day 105	8.3
Day 106	8.0	Day 107	8.1	Day 108	8.5	Day 109	8.6
Day 110	8.4	Day 111	9.1	Day 112	8.7	Day 113	10
Day 114	9.5	Day 115	9.5	Day 116	9.7	Day 118	8.5
Day 119	9.3	Day 120	8.2	Day 121	8.1	Day 122	9.1
Day 123	9.6	Day 124	9.1	Day 125	9.3	Day 126	9.1
Day 127	9.3	Day 128	9.2	Day 129	8.3	Day 130	9.4
Day 131	9.1	Day 132	9.8	Day 133	8.9	Day 134	8.8
Day 135	9.5	Day 136	9.0	Day 137	9.6	Day 138	10.4
Day 139	10.9	Day 140	12.5	Day 141	10.1	Day 142	9.6
Day 143	10.6	Day 144	9.6	Day 145	10.3	Day 146	8.0
Day 147	8.8	Day 148	9.0	Day 149	8.0	Day 150	8.2
Day 151	8.0	Day 152	8.2	Day 153	8.8	Day 154	8.9
Day 155	8.5	Day 156	8.2	Day 157	8.6	Day 158	8.5
Day 159	8.9	Day 160	8.8	Day 161	10.0	Day 162	8.5
Day 163	9.2	Day 164	10.0	Day 165	11.0	Day 166	9.5
Day 167	9.3	Day 168	10.3	Day 169	9.8	Day 170	10.1
Day 171	9.9	Day 172	10.2	Day 173	9.3	Day 174	9.6
Day 175	9.1	Day 176	9.8	Day 177	10.2	Day 178	10.1
Day 179	9.5	Day 180	9.4	Day 181	9.6	Day 182	9.5
Day 183	9.7	Day 184	9.8	Day 185	9.5	Day 186	9.2
Day 187	9.3	Day 188	9.5	Day 189	9.0	Day 190	9.2
Day 191	8.8	Day 192	8.6	Day 193	8.6	Day 194	9.2
Day 195	8.9	Day 196	9.2	Day 197	9.0	Day 198	9.3
Day 199	9.3	Day 200	9.0	Day 201	9.3	Day 202	9.2
Day 203	9.3	Day 204	9.2	Day 205	8.9	Day 206	9.0
Day 207	9.2	Day 208	9.0	Day 209	9.0	Day 210	9.2
Day 211	9.2	Day 212	9.3	Day 213	9.2	Day 214	8.9

Day 215	9.1	Day 216	8.9	Day 217	8.7	Day 218	8.6
Day 219	9.0	Day 220	9.2	Day 221	8.7	Day 222	8.9
Day 223	9.2	Day 224	9.2	Day 225	9.1	Day 226	9.0
Day 227	9.3	Day 228	9.1	Day 237	9.2	Day 238	9.0
Day 239	9.1	Day 240	9.2	Day 241	8.9	Day 242	8.7
Day 243	9.0	Day 244	9.1	Day 245	9.1	Day 246	8.7
Day 247	9.1	Day 248	8.8	Day 249	9.1	Day 250	9.2
Day 251	9.0	Day 252	9.2	Day 253	9.0	Day 254	9.1
Day 255	9.1	Day 256	9.3	Day 257	9.1	Day 258	9.0
Day 259	9.1	Day 260	9.0	Day 261	9.1	Day 262	9.3
Day 263	9.1	Day 265	8.9	Day 266	9.0	Day 267	9.0
Day 268	9.1	Day 269	9.1	Day 270	8.9	Day 271	9.0
Day 272	9.1	Day 273	9.0	Day 274	8.9	Day 275	9.2
Day 276	9.3	Day 277	9.0	Day 278	9.1	Day 279	8.9
Day 280	9.1	Day 281	9.0	Day 282	9.2	Day 283	9.0
Day 284	9.1	Day 285	9.0	Day 286	9.2	Day 287	8.8

Table 3: Comparisons of Edmonton protocol and CiPSC-islet protocol with China protocol.

Comparisons	**Edmonton protocol [5, 10]**	**CiPSC-islet protocol [11]**	**China protocol**
Methods	Percutaneous transhepatic portal embolization	Beneath the abdominal anterior rectus sheath	Intravenous transplantation
Supply	Limited by the deceased donors [5]; inexhaustible supply with zimislecel [**10**]	Unlimited and sufficient	Unlimited and sufficient
Duration of functions	Long-term duration up to more than 20 years	Long-term duration, up to at least 1 year	Long-term duration up to at least 8 years [15, 17-19]
Insulin independence	Initially 79%, 61% by 1 year, down to 8% by 20 years	100% by 1 year (one patient)	100% with sufficient times of transplantations up to at least 8 years
Allogeneic/autologous	Allogeneic	Autologous	Allogeneic
Immunosuppression	Need	Need	Not need
Glucose responsive secretion of insulin	Yes	Yes	No
Glycemic and HbA1c control	Effectively	Effectively	Effectively
Prevent and repair microvascular and macrovascular complications	Can prevent	Can prevent	Effectively prevent, repair, and improve
Side effects	Moderate bleeding at the site of the transhepatic puncture; minor superficial ulceration of the buccal mucosa [5]; diarrhea, headache, nausea, mouth ulceration, neutropenia [10].	Pain at the puncture area and nausea and vomiting due to general anesthesia	Sometimes, transient fever
Potential risks of infection and cancer	Yes, due to life-long immunosuppression [2, 9]	Yes, due to life-long immunosuppression [2, 9]	No, due to not need immunosuppression

blood glucose (FFCBG) values were monitored by the patient daily (Table 2). The subjective symptoms were reported by the patient during the following-up visits.

Data statistical analysis

The patient's FFCBG values were analyzed with Mean ± Standard derivation (2 tails type 3 tests).

Results

The antidiabetic drugs and exogenous insulin administrations were completely replaced by the intravenous transplantations of UC-MSCs-ERRγ+INS cells

In 2016, Yoshihara et al. demonstrated that ERRγ is a master regulator of β cell maturation both *in vitro* and *in vivo* [14]. Inspired by this great discovery, previously, we constructed the second generation of lentiviral vectors pWPI-INS and pWPI-ERRγ from original vector pWPI-hPLK-WT-Neo (Addgene plasmid #35385) [32], which harbour an EF-1α ubiquitous expressing promoter to drive the constitutive expression of inserted genes, ERRγ and INS, respectively, in the infected target cells. After lentiviral transduction, we found that dgHPSC cells (directly-generated human pluripotent-like stem cells derived from human adipose-derived stem cells) overexpressng ERRγ (dgHPSCs-ERRγ) could produce and secrete insulin into the cell culture supernatant, and the concentration of insulin in the supernatant was up to 30.84μIU/ml. Whereas, the concentration of secreted insulin in the supernatant was only 11.61μIU/ml produced and secreted by dgHPSC cells overexpressing human INS gene (dgHPSCs-INS) [15,16]. This is the first time to find that overexpression of ERRγ gene alone can directly produce and secrete insulin in

the stem cell state, and the stem cells do not need to differentiate into matured pancreatic islet β cells. More importantly, we found that dgHPSC cells double overexpressing ERRγ and INS genes (dgHPSCs-INS+ERRγ), constitutively and simultaneously, could synergistically potentiate the production and secretion of insulin into the cell culture supernatant, and the concentration of INS in the supernatant was up to 84.47μIU/ml [17]. More importantly, due to the constitutive ubiquitous expressing cassettes, EF-1α-ERRγ and EF-1α-INS, after the transplantations of stem cells infected with pWPI-ERRγ and pWPI-INS vectors into the recipients intravenously, no matter what kinds of tissue cell types that the transplanted stem cells could differentiate, these cells would continue to keep long-term overexpression of ERRγ and INS genes, respectively, and thus, would continue to secrete insulin into the blood in the recipients. Consequently, we treated three T2D patients with multiple intravenous infusions of dgHPSCs overexpressing ERRγ, and INS+ERRγ genes, respectively. After the transplantations, these patient's antidiabetic drugs and insulin administrations were replaced, and their blood glucose and HbA1c values were around the normal ranges. Moreover, after transplantations, their T2D-derived complications were improved and partially repaired, and they felt much healthier than before the transplantations mentally and physically [15,17-20]. One patient, before stem cell transplantations, he needed to inject 24 IU insulin daily. After accepted 5 times dgHPSCs-ERRγ and 9 times dgHPSCs-ERRγ+INS, this patient's insulin injections were completely replaced [15,17]. In addition, From November to December of 2021, this patient accepted 4 times of dgHPSCs-ERRγ+INS infusions, and during April of 2023, he accepted 2 times of UC-MSCs-ERRγ+INS infusions (data not shown). From October of 2023 to September of 2024, the patient began to take one tablet of Metformin Hydrochloride Sustained Release Tablets (0.5g/tablet) daily. And from October of 2024 until now (As of the time of the writing of this article), the patient changed to take one tablet of Metformin Hydrochloride and Empagliflozin Tablets (I) (500mg: 5mg) daily to replace Metformin Hydrochloride Sustained Release Tablets. To date (as the time of this writing), the patient sustained his HbA1c values approximately 7%, and his FFCBG levels were approximately a little bit more than 6 mmol/L [15,17]. In brief, to date (the time of this writing), this patient has almost achieved insulin and antidiabetic drug independence for 8 years. This data demonstrated that the transplanted dgHPSCs + ERRγ and dgHPSCs + ERRγ + INS cells have effectively maintained their functionality for at least 8 years [15,17]. Another patient needed 36 IU exogenous insulin administrations daily before the transplantations of dgHPSCs + ERRγ and dgHPSCs + ERRγ + INS cells. After 19 times of transplantations (4 times of dgHPSCs + ERRγ and 15 times of dgHPSCs + ERRγ + INS, respectively), the patient completely replaced his insulin injections [19]. Up to the time of this writing, this patient maintained his HbA1c values around 6.6-6.8%. Therefore, this patient has achieved insulin independence for about 7.5 years with the infused dgHPSCs + ERRγ and dgHPSCs + ERRγ + INS cells sustaining their functionality [19].

In this clinical study, we constructed the third generation lentiviral vectors pLenti-ERRγ and pLenti-INS, which harbour a CMV ubiquitous expressing promoter to drive the constitutive expression of the genes of interest, ERRγ and INS, in the infected target cells, respectively. Before the transplantations of UC-MSCs-ERRγ+INS cells, the patient necessitated to orally take 3 tablets of Acarbose and 3 tablets of Metformin Hydrochloride Sustained Release Tablets. In addition, the patient needed to inject 47 IU insulin daily to maintain her blood glucose levels. From April to January 2023, the patient accepted 40 times UC-MSCs-ERRγ+INS cell transplantations totally. After the patient accepted the first transplantation, she maintained the same number of drugs and insulin administrations (Table 1). After the patient accepted the second transplantation, the patient stopped to take 1 tablet of Acarbose at noon. And then, after the patient accepted the third transplantation, she stopped to take 1 tablet of Acarbose in the morning and 1 tablet of Acarbose at night, and she took 1 tablet of Metformin Hydrochloride Sustained Release Tablets at noon (Table 1). On April 30, the patient stopped to take 1 tablet of Metformin Hydrochloride Sustained Release Tablets at noon, and on May 1, the patient took 1 tablet of Acarbose at noon. During the abovementioned period, the patient injected the same dosage of insulin daily (Table 1). Since then, the patient did not take Acarbose and Metformin completely. After the patient accepted the 4th transplantation, the insulin administration dosage was reduced 3 IU daily (Table 1). Since then, when the patient accepted one more transplantation, the insulin injection dosages were reduced approximately 2-4 IU daily, gradually and sequentially. The interval between two sequential transplantations was around 1 week (Table 1). After 24 times of infusion, the patient's antidiabetic drugs and insulin administrations were completely replaced. From Day 1 to Day 159, the patient's average FFCBG value was approximately 7.92 mmol/L, and the standard derivation was ±1.41 mmol/L (7.92 ± 1.41 mmol/L, n=157) (Table 1, Table 2).

Because the patient appreciated the therapeutic effects of the UC-MSCs-ERRγ+INS cell transplantations, she requested to accept more times of transplantations. To consolidate the therapeutic effects, we consented to administer more times of transplantations with the hope to further recover and improve the patient's diabetes-derived complications. The patient continued to accept 16 times of transplantations totally (Table 1). To our surprise, from Day 160 to Day 287, the patient's average FFCBG value was approximately 9.19 ± 0.38 mmol/L (n=119), which was higher than the average value of the former period (7.92 mmol/L± 1.41). Whereas, when the standard derivations were compared, they were ± 1.41 versus ± 0.38 (7.92 ± 1.41 mmol/L versus 9.19 ± 0.38 mmol/L, p=1.63607E-21) (Table 1, Table 2). This result indicated that, after further 16 times of transplantations, the patient's blood glucose levels were more stable, and the fluctuations were significantly decreased. In addition, probably, with more times of transplantations, the patient's whole health conditions gradually improved, and the patient's appetite and metabolism were ameliorated obviously. Consequently, the patient's FFCBG values elevated evidently. Therefore, from September of 2023, when the patient achieved independence of insulin injection, to the time of this writing, the patient has maintained insulin and antidiabetic

drug independence for more than 2 years.

The patient's subjective symptoms were improved significantly

During the follow-up visits, the patient reported that he had a slight transient fever after the second transplantation. After the third transplantation, in the afternoon, the patient had another slight transient fever, and her body temperature was 37.5℃. The patient did not take any medications to treat her transient fevers. After the 8th transplantation, the patient had a transient fever again, and her body temperature was 37.5℃. The patient took 1 capsule of Ibuprofen Sustained Release Capsules (0.3g/capsule) to treat her fever (Table 1). The fever faded away subsequently.

Before the transplantation therapy, the patient's body weight was approximately 91.5 kilograms, and her BMI was approximately 38.6. After the transplantations, the patient's body weight was approximately 79.5 kilograms, and her BMI was approximately 33.5. According to the recommended BMI standards of the World Health Organization (WHO), the patient's BMI decreased from obesity grade 2 to obesity grade 1. The patient developed diabetes-derived retinopathy for a long time, and her left eye could not feel any light. After the transplantations, the patient's left eye can feel some light, but still cannot see clearly. Before the transplantations, the patient's legs were numb and weak, and she needed to use a wheelchair. But, after about 18 times of transplantations, the patient can walk with the help of a walking stick. The patient's health conditions improved gradually and effectively. Before the finishing of the 40 times of transplantations, the patient can walk by herself without the help of walking stick. Before the transplantations, the patient got bad cold several times each year and needed hospitalization each time. After the transplantations, the patient did not get any cold until now (the writing of this paper). Most importantly, before the transplantations, the patient had a lot of psychological pressure, and she almost lost heart for her health, and always stayed at home, and lay in bed for most of the time. After the transplantations, the patient was encouraged by the therapeutic effects, and every day, she would like to walk outside accompanied by her husband for as much time as she could, at the same time, she began to keep on a diet according to our instructions. In a word, the patient's overall physical and psychological health conditions were improved significantly.

Discussion

Comparison of China Protocol with Edmonton Protocol and CiPSC-islet Protocol

Until 2022, approximate 537 million people live with T1D and T2D diseases worldwide. Among them, T2D accounts for more than 90% of the patients. T2D leads to microvascular and macrovascular complications, which cause profound psychological and physical distress to the patients [12,13]. Careful administration of exogenous insulin alone cannot maintain blood glucose levels within the narrow physiological range, consequently, fails to prevent progression of diabetes-derived complications, and results in hypoglycemia and glycemic lability [3,4].

To improve treatment effect and to mitigate diabetes-derived complications, scientists endeavoured to pioneer new protocols for diabetes treatment. "Edmonton Protocol" is a great scientific breakthrough for T1D treatment (Table 3) [5,6]. On the one hand, the advantages of "Edmonton Protocol" include the following aspects. Firstly, this intraportal vein islet transplantation protocol can partially achieve insulin independence, and in some cases, the insulin independence can last up to 20 years [2,7]. Secondly, most of the recipients can sustain their long-term islet graft functions and achieve effectively stabilized glycemic and HbA1c controls [2,7]. Thirdly, the transplanted donor islets can be tolerated well and function quickly, and no episodes of acute cellular rejection were observed [5]. And finally, all the patients did not need long-term hospitalization, and most adverse events were mild or moderate in severity [5,10]. On the other hand, the disadvantages of "Edmonton Protocol" contain the following aspects. Firstly, only a small fraction of the recipients can achieve insulin independence [2,7]. Secondly, the lack of sufficient supply of islets limits the widespread adoption of this protocol [9]. And finally, the need of life-long systemic immunosuppressants causes potential side effects of infections and cancer [8,9]. Recently, stem cell-derived, fully differentiated islets (zimislecel) were used for the treatment of T1D. Although zimislecel can provide an inexhaustible supply for T1D treatment, immunosuppressive therapy is still needed, thus, the potential side effects of infections and cancer remain [10].

To address the limited supply of donor pancreas, Wang et al. reported autologous human CiPSC-derived islets transplantation protocol beneath the abdominal anterior rectus sheath of T1D disease patient (CiPSC-islet protocol) [11]. Compared with "Edmonton Protocol" (Table 3) [5], the greatest advantage of this protocol is the sufficient supply of CiPSC-derived islets for the treatment of T1D patients. The other advantages of this transplant site include, as the authors reported, the benefit in supporting the engraftment, vascularisation, and functional maturation of the CiPSC-derived islets, consequently resulting in markedly increased C-peptide secretion, and the circumvention of graft loss from IBMIR [11]. However, as T1D is an autoimmune disease, this autologous CiPSC-islet transplant protocol still necessitates the use of immunosuppressants [11]. In summary, both protocols can mimic authentic pancreatic β cells and secrete insulin efficiently into the blood responsively to glucose changes. Consequently, both methods can significantly improve diabetes symptoms, and in some cases, even can achieve insulin independence for up to 20 years [5,11]. Unfortunately, both protocols cannot effectively repair and improve preexisting diabetes-derived complications, such as retinopathy, neuropathy, nephropathy, and ischemic heart disease, etc. [12].

Previously, we reported that intravenous infusion of human adipose-derived mesenchymal stem cells overexpressing human INS and/or ERRγ genes [14] with the second generation of lentiviral vector pWPI to treat T2D patients. We demonstrate that sufficient times of transplantations of these stem cells can not only completely replace the exogeneous insulin injection and antidiabetic drugs but also can effectively repair and improve T2D-derived complications of the patients [15-20]. More importantly,

to evaluate the safety and efficacy of intravenous transplantations of different kinds of human stem cells overexpressing different human genes, the correspondence author of these investigations, G Z, voluntarily accepted human stem cell transplantations. During the five-year period, G Z accepted totally 77 times different kinds of human stem cell transplantations with/without overexpressing different human genes, and the total number of human stem cells was up to approximately 6.36 X 10^9. The medical examination results showed that G Z's health conditions were basically normal [21]. Thus, our intravenous transplantation of human stem cells overexpressing different human genes protocol is a safe procedure.

In this clinical study, we treated an elderly T2D patient with intravenous infusions of UC-MSCs-ERRγ+INS cells. Compared with bone marrow-derived MSCs (BM-MSCs) and embryonic stem cells (ESCs), the gene expression profile of UC-MSCs is more like that of ESCs [23]. And in addition, the self-renewal rate of UC-MSCs is faster than that of BM-MSCs [23]. UCWJ-MSCs can differentiate into three germ layers, which include adipogenic, chondrogenic and osteogenic lineages, cardiomyocytes, neurons, glia cells, oligodentrocytes, and hepatocytes, etc. [23]. We reasoned that the intravenously infused UC-MSCs-ERRγ+INS cells would reach any tissues within the patient's body along with circulation, and eventually differentiate into different types of tissue cells according to their residing niches, and efficiently produce insulin and secrete into the blood, and subsequently, the patient gradually reduces her dosages of antidiabetic drugs and insulin injection until achieve antidiabetic and insulin independence after sufficient times of transplantations. In addition, the lentiviral vectors pLenti-ERRγ and pLenti-INS, which harbour a CMV ubiquitous expressing promoter, can drive the constitutive expression of ERRγ and INS genes, respectively, in the targeted cells. Thus, as long as the infused UC-MSCs-ERRγ+INS cells and their progenies keep alive, no matter what types of tissue cells differentiated, these cells will continue to produce insulin and secrete into the blood, and consequently, decrease the patient's glucose levels. We hypothesized that a small proportion of the infused UC-MSCs-ERRγ+INS cells can reach the pancreas and differentiate into β cells due to the microenvironment of pancreatic niche and the forced overexpression of ERRγ gene [14]. Whereas most of the infused UC-MSCs-ERRγ+INS cells will migrate and localize at almost all the other different tissues of the recipients and give rise to different cell types according to their inhabited specific niches. At present, according to our point of view, we do not know whether these UC-MSCs-ERRγ+INS cells inhabited at different parts of the body, which are affected by different microenvironments, can differentiate into pancreatic β-like cells driven by forced overexpression of ERRγ gene [14]. Based on the above analysis, we supposed that most of the UC-MSCs-ERRγ+INS cells would differentiate into different cell types according to their different niches. Therefore, the insulin production and secretion of these cells cannot be regulated responsively to the blood glucose levels in a β-cell-like manner. Rather, these cells will consistently produce and secrete insulin into the blood in a constitutive manner at approximately the same rate until these cells die. From 2017 to 2025, we have already treated 10 T2D patients using our protocol. Almost all the patients achieved independence of insulin and antidiabetic drugs with sufficient times of transplantations [15-17,19,20]. (The treatment data of some other T2D patients were not shown). Therefore, we expect that all the T2D patients can achieve insulin and antidiabetic drug independence provided that sufficient times of UC-MSCs-ERRγ+INS cells were intravenously infused. Furthermore, our protocol is safer, more convenient, and time saving, and without the need of immunosuppressive drugs compared with Edmonton and CiPSC-islet protocols (Table 3) [5,11]. In addition, we had previously treated two T1D patients with our protocol as well, their insulin dosages administered reduced evidently. But, these two patients did not continue this transplantation therapy with sufficient times of infusion, until their insulin administrations were completely replaced (Data not shown).

Intravenous transplantation of UC-MSCs-ERRγ+INS cell protocol can improve and repair type 2 diabetes-derived complications

What does functionally cure of diabetes mean? On the one hand, it can refer to completely or partially achieving insulin and antidiabetic drug independence. On the other hand, based on a more stringent criterion, it can refer to completely or almost achieving insulin and antidiabetic drug independence, and partially repair and improve the preexisting diabetes-derived microvascular and macrovascular complications. As most of the diabetes patients, particularly for T2D patients, are usually of old ages, it is very difficult to completely repair their diabetes-derived complications, but partially repaired their diabetes-derived complications are achieved with our protocol, including but not limited, decreasing hypertension [18,20], improving coronary heart disease [15,17], ameliorating early cataract [16], ameliorating liver dysfunction (reducing the alanine aminotransferase values) [20], improving angina pectoris (data not shown), improving kidney function (data not shown), ameliorating cerebral infarction and retinopathy, physically becoming stronger, and psychologically feeling happier [15-18,20], etc. In summary, intravenous transplantations of UC-MSCs-ERRγ+INS cells can not only replace the antidiabetic drug and insulin administrations, but also effectively improve and repair preexisting various diabetes-derived complications.

Functionality of infused UC-MSCs-ERRγ+INS cells and duration of their efficacy

When the UC-MSCs-ERRγ+INS cells were infused intravenously, some of the cells would die due to IBMIR [5,31]. A large fraction of the live UC-MSCs-ERRγ+INS cells would be entrapped within the lungs of the recipient and be arrested during the first pass through the precapillary [33]. Afterwards, the UC-MSCs-ERRγ+INS cells might integrate with the endothelial layer as embedded pericytes of the capillaries or microvessels, such as arterioles and postcapillary venules [34]. These UC-MSCs-ERRγ+INS cells possess extensive migratory capabilities within a tissue, and can preferentially localize within injured, inflamed, cancerous tissues and the bone marrow, and simultaneously, can also non-specifically distribute throughout various tissues and organs, including the lung, liver, kidney, spleen, skeletal muscle and brain, etc [34]. In

addition, these UC-MSCs-ERRγ+INS cells can also redistribute after their initial localization in tissues, for example, gradually moving from the lung to the liver, spleen, kidney, bone marrow, etc [34]. Furthermore, infused UC-MSCs-ERRγ+INS cells and their progenies can differentiate to replenish the parenchymal and stromal cells in their specific niches, as evidenced that they can differentiate to express some unique markers of mature cell types, such as dystrophin, cytokeratin, and osteocalcin, etc [34].

Besides the abovementioned, the other benefits of systemically infused UC-MSCs-ERRγ+INS cells to the patients include, but not limited, the following. Firstly, the lack of significant immunogenicity of UC-MSCs-ERRγ+INS cells permits allogeneic transplantations without the need of immunosuppressive drugs. Secondly, the infused UC-MSCs-ERRγ+INS cells and their progenies have trophic activity, to promote tissue repair, to promote vascularisation and to modulate immune response. Finally, UC-MSCs-ERRγ+INS cells within the patients can secrete cytokines, which may serve as paracrine and endocrine factors to reduce inflammation, apoptosis and fibrosis [23,33,34].

As reported, many infused UC-MSCs-ERRγ+INS cells will die within the patient mainly due to IBMIR [5,31], only a small percentage of infused UC-MSCs-ERRγ+INS cells can reach the target tissues [33]. But, how long the infused UC-MSCs-ERRγ+INS cells will keep alive and sustain their functionalities in the patients has not yet been confirmed. After many times of transplantations intravenously, such as 40 times in this study, the live cells infused will accumulate up to a large amount. These live UC-MSCs-ERRγ+INS cells overexpressing ERRγ and INS genes will persistently produce and secrete sufficient insulin, which can completely replace antidiabetic drugs and exogenous insulin administrations. As our investigations demonstrated that, after 7 to 8 years, the patients still maintained almost insulin and antidiabetic drug independence. These data verified that, except the initial death of the infused cells shortly after the infusion procedure, most of the left live cells could sustain their functionalities up to at least 7 to 8 years [15,17,19]. These findings strongly suggest that certain amount of intravenously transplanted UC-MSCs-ERRγ+INS cells can keep long-term alive within the patient's body.

Conclusions

In this clinical investigation, we demonstrated that multiple intravenous transplantations of human UCWJ-MSCs double overexpressing human ERRγ and INS genes, constitutively and simultaneously, can completely replace antidiabetic drugs and exogenous insulin administrations and achieve functional cure of human T2D. This novel paradigm provides a proof of principle for human stem cell-gene therapy. More importantly, with this protocol, T2D-derived microvascular and macrovascular complications can also be effectively repaired and improved. In addition, this protocol is feasible to treat human T1D with sufficient times of transplantations to produce sufficient insulin to achieve insulin independence and to repair and improve T1D-derived microvascular and macrovascular complications as well. In summary, compared with "Edmonton Protocol" and "CiPSC-islet protocol", our protocol is safer, easier, more efficient, and with no adverse events. More importantly, our protocol can not only replace exogenous insulin and antidiabetic drug therapies but also can repair and improve preexisting diabetes-derived complications. Therefore, our protocol provides a brand-new paradigm for the treatment of human diabetes. Because we innovated and applied this protocol to treat human diabetes in China, we designated this protocol as "China Protocol".

Availability of supporting data

The datasets generated and/or analysed during the current study are not publicly available due to the protection of the confidential information of the participated patient but are available from the corresponding author on reasonable request.

Authors Contributions

G. Z. instructed and supervised the whole scientific research work. T. W. instructed and supervised the whole clinical work. X. C. and X. W. performed the vector construction. M. W. charged the lentiviral production and transduction. C. Z. and X. S. did the stem cell culture. W. L., S. D. and X. W. worked on the clinical treatments of the cells. All the authors discussed, read and approved the final manuscript.

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