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The Cure of Human Type 2 Diabetes via Systematic Transplantations of dgHPSCs Overexpressing Human ERRγ and Insulin Genes (II)

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ABSTRACT

We previously reported the cure of human type 2 diabetes (T2D) via transplantations of directly-generated human pluripotent stem-like cells (dgHPSCs) overexpressing human insulin (INS) and estrogen-related receptor γ (ERRγ) genes. Our strategy not only can completely replace the daily insulin injections of the patients, but also can potentially repair the complications of T2D patients. Here, we reported the cure of another patient case with similar treatments. This patient treated his T2D by daily taking Gliclazide Modified Release Tablets and Acarbose Tablets. After 19 times of transplantations of dgHPSCs, he stopped taking the medications completely, and his glucose levels were remained around normal levels during the past more than three years. In addition, the patient's liver function was also improved obviously. Therefore, this investigation is another vivid example for the cure of human T2D with our strategy.

Keywords

dgHPSCs, ERRγ, Insulin, Human type 2 diabetes.

Introduction

Since the discovery of insulin by Banting and his colleagues in 1922, daily injection of human insulin (INS) is gradually becoming a standard treatment for human type 1 (T1D) and type 2 diabetes (T2D) [1,2]. However, just as Banting stated in his Nobel Lecture that "Insulin is not a cure for diabetes, it is a treatment" [3], the sole administration of insulin cannot accurately control the blood glucose levels within the proper physiological range, and therefore, the diabetic complications will progressively develop inevitably [2]. Hence, it is an urgent need to develop more efficient strategies for diabetes treatment.

The success to obtain insulin-producing pancreatic β cells from human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) *in vitro* provides a great promising for the transplantation therapy to treat human diabetes [4]. After transplantations of these cells below the kidney capsule of mouse models, these cells can mimic the function of human islets *in vivo* to secrete human insulin into the serum of mice shortly after transplantation in a glucose-related manner [4]. This is a great achievement for the stem cell therapy to treat human diabetes. Another great achievement is to demonstrate that estrogen-related receptor γ (ERRγ) is a master regulator of β cell maturation *in vivo*. Forced expression of ERRγ in hiPSC-derived β-like cells enables glucose-responsive secretion of human insulin *in vitro*, and can further restore the glucose homeostasis in T1D mouse models after transplantations *in vivo* [5].

Up to now, many exciting investigations were reported in the field of the transplantation of human stem cells to treat diabetes, mainly in mouse models. These data indicated that the clinical

treatment of human diabetes via human stem cell transplantations might be achieved in the near future. Our inspirations are mainly obtained from the two aforementioned reports [4,5]. During the course of the development and progression of human diabetic complications, various tissues and organs will be damaged gradually. Therefore, compared with repairing the function of islet β cells and controlling the blood glucose levels, further repairing and restoring the complications are more important for diabetes patients. We reasoned that if we can overexpress human INS and ERRγ genes with human stem cells, then, transplant these stem cells into diabetic patient's body intravenously, the stem cells will move along with the blood everywhere in the human body, a small part of them may go to the pancreas and repair its functions, and the majority of them will eventually reside the other parts of the patient's body and repair or replace the damaged and aged cells wherever they are needed. Therefore, with this strategy, the insulin secreted by the transgenic human stem cells will control the blood glucose levels, whereas, the transplanted stem cells all over the body will repair the various damaged and aged tissues. Hence, we speculated that this strategy could not only effectively control the blood glucose levels, but also prevent from the development of complications and even repair the already existed complications. We optimistically hypothesized that, with this strategy, we could cure human diabetes completely, such as T2D.

Previously, we reported three cases of T2D patients treated with serial transplantations of directly-generated human pluripotent stem-like cells (dgHPSCs) overexpressing human insulin and ERRγ genes effectively [6-10]. More importantly, during the past more than five years, the correspondence author of this paper, G. Z., accepted 77 times human stem cell transplantations with or without overexpressing different human genes, and the total number of the human stem cells was up to approximately 6.36 X 10^9. After medical examinations, the results demonstrated that G Z's health conditions were basically normal. Therefore, this report preliminarily demonstrated that the intravenous transplantations of human stem cells were safe [11]. Here, we reported another patient case treated similarly. Our data revealed that, after dgHPSCs transplantations, the patient's diabetic symptoms were improved greatly, including but not limited, the controlling of his blood glucose and glycosylated haemoglobin levels around normal range without medications, the amelioration of liver functions and hypertension. In a word, our current investigation provided another vivid example for the cure of human T2D with our strategy.

Materials and Methods

Statement of Ethical Approval

The treatments for the patient and the use of human stem cells were approved by the Ethics Committee of Interventional Hospital of Shandong Red Cross Society (Shengjieyi 2003, No. 26) in compliance with Helsinki Declaration. The Ethics Committee of Interventional Hospital of Shandong Red Cross Society approved this clinical study and treatments. The participant provided his written confirmed consent to participate the clinical study and treatments. The Ethics Committee of Interventional Hospital of Shandong Red Cross Society approved this consent procedure. All the treatments for the patient and use of human stem cells were performed in accordance with the guidelines established in Interventional Hospital of Shandong Red Cross Society approved by the Ethics Committee. After traditional daily taking Gliclazide Modified Release Tablets and Acarbose Tablets for about ten years, the patient agreed to try the stem cell therapy with overexpression of human insulin and ERRγ genes in our hospital to control his blood glucose levels and wanted to improve his physical conditions and prevent from potential complications of T2D. The stem cells used in these clinical treatments included both autologous (Auto) and allogenic (Allo) stem cells, respectively, stored at our Stem Cell Bank. All these stem cells were isolated and proliferated with the written confirmed consent of the participants.

Patient Case

The patient (designated as patient #4, initials J. H., male, born at 1959) was diagnosed T2D and high blood pressure more than ten years ago (the patient did not remember the exact date). At present, the patient cannot remember the details of the early treatments. Currently, he takes Valsartan (80mg) and Amlodipine (5mg) Tablets (80mg/5mg/tablet, one tablet per day) to control his hypertension, and Gliclazide Modified Release Tablets (30mg/tablet, two tablets per day) and Acarbose Tablets (50mg/tablet, three tablets per day) to control his blood glucose levels. From April 14 of 2019 on, he stopped taking Gliclazide Modified Release Tablets and Acarbose Tablets to control his blood glucose levels and accepted stem cell therapy to treat his T2D.

Cell preparation, lentivirus vector construction, production and infection

The isolation, culture of human adipose-derived stem cells (hADSCs), and the induction of dgHPSCs without any genetic modifications were exactly the same as described previously [6-11,12]. The lentivirus vectors pWPI/INS and pWPI/ERRγ were constructed, produced and transduced according to the previous reports [13-17]. The detailed infection information was listed in Table 1.

dgHPSCs transplantations

He dgHPSCs overexpressing human ERRγ and INS genes were transplanted into the patient intravenously the same as the previous descriptions [6-11]. The detailed dates, cell types and cell numbers were shown in Table 1.

Clinical responses and treatment efficacy assessment

The fasting venous blood C-peptide (F-C-P), insulin (F-INS), glucose (F-GLU), glycosylated haemoglobin (HbA1c), Alanine aminotransferase (ALT) were tested by Community health service center of Zhuantang street, Xihu District and Hangzhou Dian Medical Laboratory Center Co., Ltd (Hangzhou, Zhejiang Province, China) (Table 2). The fasting fingertip capillary blood glucose levels (FFT-CBG) were monitored daily with some intervals (Table 3). The blood pressure was monitored sometimes at home (Table 4). The subjective symptoms were reported by the patient during the following-up visits.

Table 1: Transplantations of dgHPSCs Overexpressing Human INS and ERRγ Genes for the Patient.

Times	Dates	Cell types	Auto/Allo	Cell Numbers
#1	14/04/2019	dgHPSCs + 50 ml ERRγ	Allo	9.31 X 10^7
#2	21/04/2019	dgHPSCs + 50 ml ERRγ	Auto	1.14 X 10^8
#3	06/05/2019	dgHPSCs + 50 ml ERRγ + 50 ml INS	Auto	8.46 X 10^7
#4	12/05/2019	dgHPSCs + 50 ml ERRγ + 50 ml INS	Auto	8.69 X 10^7
#5	18/05/2019	dgHPSCs + 50 ml ERRγ + 50 ml INS	Auto	7.56 X 10^7
#6	26/05/2019	dgHPSCs + 50 ml ERRγ + 50 ml INS	Auto	8.1 X 10^7
#7	02/06/2019	dgHPSCs + 50 ml ERRγ + 50 ml INS	Auto	1.03 X 10^8
#8	21/09/2019	dgHPSCs + 50 ml ERRγ	Allo	6.21 X 10^7
#9	28/09/2019	dgHPSCs + 50 ml ERRγ	Allo	7.2 X 10^7
#10	12/10/2019	dgHPSCs + 50 ml ERRγ	Allo	7.5 X 10^7
#11	19/10/2019	dgHPSCs + 50 ml ERRγ	Allo	5.4 X 10^7
#12	26/10/2019	dgHPSCs + 50 ml ERRγ	Allo	6.3 X 10^7
#13	02/11/2019	dgHPSCs + 100 ml ERRγ	Allo	1.02 X 10^8
#14	09/11/2019	dgHPSCs + 100 ml ERRγ	Allo	1.36 X 10^8
#15	16/11/2019	dgHPSCs + 100 ml ERRγ	Allo	1.2 X 10^8
#16	18/09/2021	dgHPSCs + 100 ml ERRγ + 100ml INS	Allo	7.02 X 10^7
#17	27/09/2021	dgHPSCs + 150 ml ERRγ + 150ml INS	Allo	1.4 X 10^8
#18	09/10/2021	dgHPSCs + 150 ml ERRγ + 150ml INS	Allo	1.41 X 10^8
#19	30/10/2021	dgHPSCs + 150 ml ERRγ + 150ml INS	Allo	1.17 X 10^8

Table 2: Tests of F-INS, F-C-P, F-GLU, HbA1c and ALT before and after dgHPSCs Transplantations.

Test	Results (before) (27/03/2019)	Results (after) (24/06/2019)	Results (after) (17/09/2019)	Ref. ranges
F-INS	6.47	3.42	3.96	4.50-16.15 μU/ml
F-C-P	0.597	0.470	0.464	0.37-1.47 nmol/L
F-GLU	7.27	7.15	7.61	3.90-6.10 mmol/L
HbA1c	6.2	6.2	6.0	4.0-6.3%
ALT	25	18	13	0-40 IU/L

Table 3: Daily Monitoring of FFT-CBG levels (from 16/04/2019 to 29/09/2021).

Dates	Results (mmol/L)	Dates	Results (mmol/L)	Dates	Results (mmol/L)
16/04/2019	8.8	17/04/2019	8.9	18/04/2019	7.8
19/04/2019	8.0	20/04/2019	7.9	22/04/2019	9.8
23/04/2019	9.3	24/04/2019	9.0	25/04/2019	9.0
26/04/2019	7.8	27/04/2019	8.5	28/04/2019	7.7
29/04/2019	9.2	30/04/2019	9.2	01/05/2019	8.6
02/05/2019	7.9	03/05/2019	7.6	04/05/2019	7.8
05/05/2019	8.7	06/05/2019	7.9	07/05/2019	8.7
08/05/2019	7.8	09/05/2019	7.8	10/05/2019	8.2
11/05/2019	7.2	12/05/2019	7.6	13/05/2019	8.3
14/05/2019	7.4	15/05/2019	7.7	16/05/2019	7.3
17/05/2019	7.2	18/05/2019	6.8	19/05/2019	6.8
20/05/2019	7.2	21/05/2019	7.7	22/05/2019	7.6
23/05/2019	7.0	24/05/2019	7.3	25/05/2019	6.7
26/05/2019	7.8	27/05/2019	7.5	28/05/2019	6.2
29/05/2019	7.2	30/05/2019	8.2	31/05/2019	6.5
01/06/2019	6.2	02/06/2019	4.5	03/06/2019	6.8
04/06/2019	7.0	05/06/2019	6.3	06/06/2019	6.6
07/06/2019	6.9	08/06/2019	6.5	09/06/2019	6.8
10/06/2019	7.9	11/06/2019	7.8	12/06/2019	7.4
13/06/2019	7.9	14/06/2019	6.8	15/06/2019	6.7
16/06/2019	6.3	17/06/2019	8.0	18/06/2019	7.6
19/06/2019	6.9	20/06/2019	6.9	21/06/2019	6.9
22/06/2019	6.8	23/06/2019	6.8	25/06/2019	6.6
26/06/2019	6.6	27/06/2019	7.0	28/06/2019	7.6
29/06/2019	6.5	30/06/2019	7.3	01/07/2019	7.0
02/07/2019	7.4	03/07/2019	6.9	04/07/2019	7.4
05/07/2019	6.4	06/07/2019	6.6	07/07/2019	5.9

08/07/2019	7.0	09/07/2019	6.1	10/07/2019	6.3
11/07/2019	6.7	12/07/2019	5.9	13/07/2019	6.3
14/07/2019	7.1	15/07/2019	7.6	16/07/2019	6.7
17/07/2019	7.3	18/07/2019	6.1	19/07/2019	6.6
20/07/2019	6.5	21/07/2019	7.1	22/07/2019	6.8
23/07/2019	6.5	24/07/2019	6.7	25/07/2019	8.1
26/07/2019	6.9	27/07/2019	7.9	28/07/2019	6.7
29/07/2019	7.2	30/07/2019	6.7	31/07/2019	7.6
01/08/2019	6.9	02/08/2019	7.4	03/08/2019	6.6
04/08/2019	7.4	05/08/2019	6.9	06/08/2019	6.7
07/08/2019	6.6	08/08/2019	7.4	09/08/2019	7.1
10/08/2019	7.5	11/08/2019	7.7	12/08/2019	7.4
13/08/2019	7.9	14/08/2019	7.4	15/08/2019	7.2
16/08/2019	7.4	17/08/2019	6.4	18/08/2019	6.5
19/08/2019	6.0	20/08/2019	5.9	21/08/2019	6.4
22/08/2019	5.8	23/08/2019	5.9	24/08/2019	5.9
25/08/2019	6.0	26/08/2019	6.0	27/08/2019	6.1
28/08/2019	5.8	29/08/2019	6.0	30/08/2019	6.0
31/08/2019	6.0	01/09/2019	6.2	02/09/2019	5.6
03/09/2019	6.6	04/09/2019	6.3	05/09/2019	5.8
06/09/2019	6.5	07/09/2019	6.7	08/09/2019	6.4
09/09/2019	6.7	10/09/2019	7.4	11/09/2019	6.1
12/09/2019	6.3	13/09/2019	5.5	14/09/2019	6.3
15/09/2019	6.6	16/09/2019	6.3	17/09/2019	5.9
18/09/2019	6.6	19/09/2019	5.8	20/09/2019	7.2
21/09/2019	6.6	23/09/2019	5.9	24/09/2019	6.4
25/09/2019	6.2	26/09/2019	6.1	27/09/2019	6.8
28/09/2019	6.3	29/09/2019	6.4	30/09/2019	6.7
01/10/2019	6.6	02/10/2019	6.5	03/10/2019	7.4
04/10/2019	6.8	05/10/2019	7.4	06/10/2019	6.9
07/10/2019	6.6	08/10/2019	6.2	09/10/2019	7.0
10/10/2019	6.6	11/10/2019	6.2	12/10/2019	6.8
13/10/2019	6.8	14/10/2019	7.0	15/10/2019	7.8
16/10/2019	6.1	17/10/2019	6.6	18/10/2019	6.5
19/10/2019	6.8	20/10/2019	6.4	21/10/2019	6.8
22/10/2019	7.3	23/10/2019	7.6	24/10/2019	6.7
25/10/2019	7.2	26/10/2019	7.3	27/10/2019	7.8
28/10/2019	7.4	29/10/2019	7.1	30/10/2019	6.9
31/10/2019	7.6	01/11/2019	6.9	02/11/2019	6.3
03/11/2019	6.9	04/11/2019	7.4	05/11/2019	6.9
06/11/2019	6.8	07/11/2019	6.9	08/11/2019	6.4
09/11/2019	7.8	10/11/2019	7.2	11/11/2019	7.5
12/11/2019	7.4	13/11/2019	6.7	14/11/2019	7.1
15/11/2019	7.2	16/11/2019	6.1	17/11/2019	8.7
26/09/2021	5.9	27/09/2021	6.9	28/09/2021	7.6
29/09/2021	6.9	30/09/2021	7.5		

Table 4: The Decrease of Blood Pressure after dgHPSCs Transplantations without Taking Anti-hypertensive Drugs.

Date	Blood pressure	Date	Blood pressure	Date	Blood pressure
06/09/2019	111/68	07/09/2019	117/68	08/09/2019	118/70
09/09/2019	114/74	10/09/2019	118/74		

Table 5: The Diagnosis and Treatments before and after dgHPSCs Transplantations.

Diseases	Drugs and Dosages (Before)	After
T2D	Gliclazide Modified Release Tablets (30mg/tablet, 2 tablets per day) Acarbose Tablets (50mg/tablet, 3 tablets per day)	Completely stopped taking Gliclazide Modified Release Tablets and Acarbose Tablets
Hypertension	Valsartan and Amlodipine Tablets (5mg/tablet, 1 tablet per day)	Decreased the dosage of Valsartan and Amlodipine Tablets according to his feelings
Liver dysfunction	N/A	N/A

Results

Before the dgHPSCs transplantations, by and large, the patient could control his blood glucose and HbA1c levels around the normal ranges by taking Gliclazide Modified Release Tablets and Acarbose Tablets. At the same time, he needed to take Valsartan and Amlodipine Tablets to control his hypertension (Table 5).

On April 14 of 2019, the patient received the first dgHPSCs transplantation, and we suggested him to stop taking Gliclazide Modified Release Tablets and Acarbose Tablets. After the removal of the glucose controlling drugs, his daily blood glucose levels were increased and could reach to above 9 mmol/L, and then gradually decreased slowly (Table 3). Until June 2nd of 2019, after seven times of dgHPSCs transplantations (Table 1), his fasting glucose levels were decreased around 6-7 mmol/L, which is close to the normal range (Table 3). Importantly, the patient's HbA1c levels were 6.2% and 6.0%, respectively, as showed by the medical tests performed on June 24 of 2019 and September 17 of 2019, which were within the normal range (Table 2). Furthermore, his ALT levels were also decreased from 25 IU/L to 18 IU/L and further to 13 IU/L (Table 2), which showed the significant improvement of his liver functions. These data indicated that the patient's T2D was basically cured, because he did not need to take drugs, his glucose and HbA1c levels were remained around and within the normal physiological ranges, respectively, and his diabetic complications were ameliorated obviously.

According to the patient's description, after seven times transplantations, the patient could control his glucose levels around the normal range as long as he kept to be moderate in eating and exercise every day, such as running, swimming, jumping ropes, and playing basketball, etc. The patient wanted to eat more nutrient food to keep his health and satisfy his appetite, therefore, he wanted more dgHPSCs transplantations. From September 9 of 2019 on, he received eight times transplantations (Table 1). Afterwards, from September 18 to October 30 of 2021, the patient received the other four times of dgHPSCs transplantations (Table 1), and his blood glucose levels continued to be around the normal range (Table 3). Basically, up to date, the patient can eat as normal people.

The Follow-Up Visits of the Patient

During the follow-up visits, the patient reported that, after the first transplantation, he did not have a fever, but felt sleepy. After stopped taking the drugs, he felt thirsty at night. Two hours after the second transplantation, he had a fever, and took Ibuprofen Sustained-release Capsules (0.3g/capsule) at 6pm and 12pm, respectively, to reduce his fever. Afterwards, he got accustomed to the dgHPSCs transplantations gradually. He felt energetic every day, seldom got tired. He increased his daily diet moderately and accordingly, and exercised every day. His close friends said he looked like 10 years younger. Besides, his blood pressure was also decreased about four months after the transplantations as shown in Table 4. Sometimes, he stopped daily taking Valsartan and Amlodipine Tablets to control his blood pressure. But, because his job needs him to focus on his work intensely, he decreases the dosages of Valsartan and Amlodipine Tablets according to his feelings (Table 5).

Discussion

In 1922, Banting et al. proved that daily injection of insulin could effectively control the blood glucose levels in T1D patient [1]. This is a great achievement in the medicine history to triumph over human diseases. Banting and his colleague were awarded the Nobel Prize in Medicine and Physiology soon after [3]. Nowadays, T2D is an increasing threat to human health and life span, whereas, as Banting indicated that "Insulin is not a cure for diabetes, it is a treatment" [3]. Therefore, the sole daily injection of insulin cannot effectively prevent from the development of diabetic complications eventually [2].

During the past four years, with the best wish to cure human T2D, we systematically investigated the efficacy of transplantations of dgHPSCs overexpressing human INS and ERRγ genes for the treatment of T2D. Our data demonstrated that, with sufficient times of dgHPSCs transplantations, the patients not only could completely stop daily insulin administrations, but also their overall physical and mental conditions were improved greatly [6-10]. More importantly, up to date, the health conditions of all the recipients of dgHPSCs overexpressing different human genes are normal, which demonstrated that our strategies are safe, at least so far [6-11].

In our previous reports [6, 7, 8, 10], the patients were with severe T2D, and severe diabetic complications, such as coronary heart disease, were developed, and subsequently, cardiac stents were implanted and high dosages of insulin were administrated daily (24 IU and 36 IU daily, respectively). After different times of transplantations of dgHPSCs overexpressing human INS and ERRγ genes (14 times and 19 times, respectively) [6,7,10], the patients completely stopped daily injection of insulin, and their blood glucose and HbA1c levels were remained around normal ranges so far (four and three years after transplantations) [8,10]. Compared with the above reports, the patient in this clinical investigation was with moderate T2D, and he controlled his blood glucose levels by taking Gliclazide Modified Release Tablets and Acarbose Tablets daily. In addition, he was also diagnosed with diabetic complications, such as high blood pressure and high ALT levels (Table 2, Table 5). Altogether, after 19 times transplantations of dgHPSCs overexpressing human INS and ERRγ genes (Table 1), the patient not only completely stopped taking Gliclazide Modified Release Tablets and Acarbose Tablets to control his blood glucose levels, but also his hypertension and ALT levels were decreased significantly (Table 2, 4). The comparison before and after transplantations was listed in Table 5.

During the follow-up visits, the patient was very satisfied with the efficacy of transplantations. He felt his health conditions were improved greatly, physically and mentally, and he also felt he became younger obviously. Combined with the other patients reported, we can optimistically and preliminarily hope that the systematic transplantations of human stem cells not only can cure human T2D, but also may extend the human life span in the near future.

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.

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References

1. Banting FG, Best CH, Collip JB, et al. Pancreatic extracts in the treatment of diabetes mellitus preliminary report. Canadian Medical Association Journal. 1922; 12: 141-146.
2. Minami K, Seino S. Current status of regeneration of pancreatic β-cells. Journal of Diabetes Investigation. 2013; 4: 131-141.
3. Banting FG. Nobel Lecture. 1925.
4. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells *in vitro*. Cell. 2014; 159: 428-439.
5. Yoshihara E, Wei Z, Lin CS, et al. ERRγ is required for the metabolic maturation of therapeutically functional glucose-responsive β cells. Cell Metabolism. 2016; 23: 622-634.
6. Wang T, Wang X, Zhang B, et al. Transplantation of human pluripotent stem cells overexpressing ERRγ can efficiently improve the symptoms of type 2 diabetes patient. Adv Tissue Eng Regen Med Open Access. 2018; 4: 457-462.
7. Wang T, Wang X, Zhang B, et al. Transplantation of Human dgHPSCs Overexpressing Insulin and ERRγ can Efficiently Decrease the Glucose and HbA1c levels, Increase the Secretion of C-peptide and Repair the Complications of Coronary Heart Disease in T2D Patient (Case #1-A). Stem Cells Regen Med. 2018; 2: 1-9.
8. Wang T, Cui X, Yang Z, et al. Transplantation of Human dgHPSCs Over-expressing Human Insulin/ERRγ Genes Can Not Only Decrease the Glucose Levels but Also Decrease the Hypertension in T2D Patient (Case #1-B). Stem Cells Regen Med. 2019; 3: 1-5.
9. Wang T, Chen X, Cui X, et al. Transplantation of human pluripotent stem cells over expressing insulin/ERRγ can efficiently decrease the HbA1c levels of type 2 diabetes patient(Case #2-A). International Journal of Current Research. 2018; 10: 74690-74696.
10. Wang T, Cui X, Yang Z, et al. The Cure of Human Type 2 Diabetes via Systematic Transplantations of dgHPSCs Overexpressing Human ERRγ and/or Insulin Genes (I). Stem Cells Regen Med. 2021; 5: 1-4.
11. Wang T, Cui X, Yang Z, et al. The Transplantation of Human Pluripotent Stem Cells is Safe: A Personal Experience during the Past 5 Years (I). Stem Cells Regen Med. 2021; 5: 1-8.
12. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002; 13: 4279-4295.
13. Zhang G, Tandon A. Quantitative assessment on the cloning efficiencies of lentiviral transfer vectors with a unique clone site. Sci Rep. 2012; 2: 1-8.
14. Zhang G, Tandon A. "Combinatorial Strategy": A highly efficient method for cloning different vectors with various clone sites. American Journal of Biomedical Research. 2013; 1: 112-119.
15. Zhang G. A new overview on the old topic: The theoretical analysis of "Combinatorial Strategy" for DNA recombination. American Journal of Biomedical Research. 2013; 1: 108-111.
16. Zhang G, Zhang Y. On the "All or Half" law of recombinant DNA. American Journal of Biomedical Research. 2016; 4: 1-4.
17. Zhang G, Wang T. Efficient lentiviral transduction of different human and mouse cells. Int J Bioprocess Biotech: IJBBT-104. 2018; 1: 1-11.