Transgene and islet cell delivery systems using nano-sized carriers for the treatment of diabetes mellitus

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\section*{ABSTRACT}
Gene therapy that targets the pancreas and intestines with delivery systems using nano-sized carriers such as viral and non-viral vectors could improve the control of blood glucose levels, resulting in an improved prognosis for patients with diabetes mellitus. Allogenic pancreatic islet cell transplants using such delivery systems have been developed as therapeutic options for diabetes mellitus. This review focuses on transgenes and islet cell delivery systems using nano-sized carriers for the treatment of diabetes mellitus.

\section*{1. Introduction}
Diabetes mellitus is a group of metabolic diseases characterized by continuing high blood glucose levels over a prolonged period resulting from defective insulin secretion from pancreatic β cells and/or insulin action \cite{1}. The prevalence of diabetes mellitus is increasing globally, with the number of adults with diabetes mellitus having increased from 108 million in 1980 to 422 million in 2014 \cite{1}. Diabetes mellitus increases the risk for the development of various diseases, including cardiovascular diseases, stroke, neuropathy, retinopathy, and nephropathy \cite{2,3}. It is important that blood glucose levels are maintained so patients do not develop complications associated with diabetes mellitus \cite{2,3}. Various small molecules and peptides that can decrease blood glucose levels have been developed and used in clinical settings for patients with diabetes mellitus. Recent therapeutic strategies including gene therapies and pancreatic islet cell transplantation have been developed. Nano-sized carriers such as viral and non-viral vectors have been shown to enhance the delivery and treatment effects of gene therapies \cite{4,5}. These technologies may be potential new options for the treatment of diabetes mellitus. This review focuses on transgenes and islet cell delivery systems using nano-sized carriers, and several other transfection methods such as ultrasound and electroporation, for the treatment of diabetes mellitus.

\section*{2. Gene therapy delivery systems for the treatment of diabetes mellitus}
The pancreas plays a central role in modulating blood glucose levels \cite{6-9}. Pancreatic β cells produce insulin, which decreases blood glucose levels, and pancreatic α cells produce glucagon, which increases blood glucose levels \cite{6-9}. Many gene therapies with delivery systems using nano-sized carriers have targeted the pancreas in attempts to modulate blood glucose levels for the treatment of diabetes mellitus.

Another target organ of gene therapies using delivery systems for the treatment of diabetes mellitus is the intestines. Intestinal L cells secrete glucagon-like peptide-1 (GLP-1), which enhances insulin secretion from β cells and decreases glucagon secretion from α cells in the pancreas \cite{6-9}.

Details of gene therapies with delivery systems targeting the pancreas and intestines using nano-sized carriers including viral vectors and non-viral vectors for the treatment of diabetes mellitus are summarized in Table 1 and Figure 1.

\subsection*{2.1. Viral vectors}
Among various viral vectors, adenoviral vectors have been most widely used for the delivery of transgenes to both the pancreas and intestines. The expression efficiency of the delivered transgenes using adenovirus vectors to the targeted cells tends to be of short...
Table 1. Gene therapies with viral and non-viral vectors for the treatment of diabetes mellitus.

| Vectors                  | Transgene               | Target organ         | Administration route | Effects                                                                 | Authors (year published) | Reference No. |
|--------------------------|-------------------------|----------------------|----------------------|--------------------------------------------------------------------------|--------------------------|--------------|
| Adenovirus               | PDX-1-DNA               | Pancreas             | Common bile duct     | Neogenesis and ductal proliferation of pancreatic β cells                | Taniguchi et al. (2003)  | [10]         |
| Adenovirus               | ISL-1-DNA               | Pancreas             | Tail vein injection  | Promoted regenerative potential of pancreatic cells                      | Miyazaki et al. (2012)  | [11]         |
| Adenovirus               | GLP-17–37-DNA           | Intestines           | Tail vein injection  | Increased plasma GLP-1 level. Normoglycemia                               | Phillips and Kay (2014)  | [12]         |
| Adenovirus               | GLP-17–37-DNA           | Intestines           | Tail vein injection  | Increased plasma GLP-1 level. Decreased blood glucose level               | Lee et al. (2008)        | [13]         |
| Adenovirus               | GLP-1-DNA               | Intestines           | Tail vein injection  | Increased plasma GLP-1 level. Increased insulin secretion, sensitivity, and tolerance | Parsons et al. (2007)    | [14]         |
| Recombinant adenovirus   | GLP-1-DNA               | Intestines           | Tail vein injection  | Increased insulin-stimulated glucose uptake in adipocytes. Decreased blood glucose level | Lee et al. (2007)        | [15]         |
| Adenovirus               | GLP-1-DNA               | Intestines           | Tail vein injection  | Increased plasma GLP-1 level. Decreased blood glucose level               | Choi and Lee (2011)      | [16]         |
| Adenovirus               | GLP-1-DNA               | Intestines           | Tail vein injection  | Increased plasma GLP-1 level. Improved glucose tolerance                 | Liu et al. (2007)        | [17]         |
| Recombinant adenovirus   | GLP-1 and HGF/NK1-DNA   | Intestines           | Intra-intestinal injection | Increased plasma insulin and GLP-1 levels. Decreased blood glucose level | Lee et al. (2007)        | [15]         |
| AAV-8                    | GLP-1-DNA               | Intestines           | Intraperitoneal injection | Increased serum GLP-1 expression. Protected against the development of diabetes mellitus | Riedel et al. (2010)     | [19]         |
| AAV-9                    | GLP-1 and REG3 protein  | Intestines           | Intraperitoneal injection | Prevented hyperglycemia. Increased insulin-positive cell mass            | Tonne et al. (2013)      | [21]         |
| AAV-8                    | GLP-1-DNA               | Pancreas             | Intraperitoneal injection | Prevented onset of diabetes                                               | Flores et al. (2014)     | [22]         |
| AAV-2                    | Klotho                  | Pancreas             | Intraperitoneal injection | Increased glucose tolerance and attenuated β cell apoptosis.             | Lin and Sun (2015)       | [23]         |
| Double-stranded AAV-8    | GLP-1-DNA               | Intestines           | Intraperitoneal injection | Increased β cell mass and prevented β cell apoptosis. Decreased blood glucose level | Gaddy et al. (2012)      | [20]         |
| AAV-9                    | GLP-1-DNA               | Intestines           | Intraperitoneal injection | Increased insulin secretion. Decreased blood glucose level                | Kim et al. (2013)        | [24]         |
| AAV-8                    | GLP-1-DNA               | Pancreas             | Tail vein injection  | Delayed the development of diabetes mellitus                             | Jeong et al. (2010)      | [25]         |
| Double-stranded AAV-8    | GLP-1-DNA               | Intestines           | Tail vein injection  | Increased insulin secretion. Decreased blood glucose level                | Choi et al. (2005)       | [26]         |
| Cationic nanomicelles    | GLP-1-DNA               | Intestines           | Subcutaneous injection in dorsal or intramuscular injection in hind legs | Enhanced insulin secretion. Improved glucose tolerance                   | Jean et al. (2011)       | [28]         |
| Cationic nanomicelles    | GLP-1-DNA               | Intestines           | Subcutaneous injection in dorsal or intramuscular injection in hind legs | Enhanced insulin secretion. Improved glucose tolerance                   | Jean et al. (2011)       | [28]         |
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| Cationic nanomicelles    | GLP-1-DNA               | Intestines           | Subcutaneous injection in dorsal or intramuscular injection in hind legs | Enhanced insulin secretion. Improved glucose tolerance                   | Jean et al. (2011)       | [28]         |

**Abbreviations:** PDX-1: pancreas/duodenum homeobox protein 1; ISL-1: insulin gene enhancer protein-1; GLP-1: glucagon-like peptide-1; DNA: deoxyribonucleic acid; AAV: adeno-associated viral vector; HGF/NK1: N and K1 domains of hepatocyte growth factor; REG3: regenerating islet-derived protein 3; IL-2: interleukin-2; PEI: polyethylenimine; ATR3: activating transcription factor 3; ER: endoplasmic reticulum; IL-4: interleukin-4; IL-10: interleukin-10; ABP: arginine-grafted bioreducible polymer; ANGPTL8: angiopoietin-like protein 8.
duration, mostly being 1 month after the delivery of transgenes [31–34]. Recombinant adeno-associated viral vectors (AAV) have been developed for transgene delivery to the pancreas for the treatment of diabetes mellitus using animal models to try to increase the expression efficiency [34]. AAV are transfected into cells by receptor-mediated endocytosis [35–38]. Heparan sulfate is one receptor for AAV [35]. Fibroblast growth factor receptor, αvβ5 integrin, and hepatocyte growth factor receptor have been reported to work as co-factors [36–38]. Among the many types of AAV, single-stranded AAV, such as serotypes 8 (AAV-8) and 9 (AAV-9), and double-stranded AAV have been reported to have effective transduction of transgenes into the pancreas [39–44].

Recently, helper-dependent adenoviral vectors (HDAd) have been developed as carriers of transgenes. HDAd are constructed by removing viral sequences from the adenoviral vector genome, except for the packaging sequence. HDAd eliminate the problem of viral gene expression in transfected cells, which accompanies AAV [45]. HDAd have been reported to show long-term expression of transgenes in the pancreas [46].

Lentiviral vectors and herpes simplex virus type 1 vectors are reported to show the potential to deliver transgenes to the pancreas [47–50]. In terms of administration routes of viral vectors for the delivery of transgenes to the pancreas in vivo, although intravenous administration has been used most often, intrapancreatic ductal injections might be more efficient because transgenes with viral vectors can more easily escape from phagocytes in the liver via this administration route [51]. The transduction efficiency of transgenes with viral vectors in the pancreas via intravenous administration was reported to improve under conditions of reduced blood flow to the liver, such as with a liver bypass or transient blockade of liver circulation [44, 52]. However, other studies have reported that intravenous administration of AAV-8 or AAV-9 substantially delivered transgenes to the pancreas [40, 53]. There is, therefore, room for debate on suitable administration routes of transgenes with viral vectors to the pancreas.

For the intestines, many previous studies have demonstrated that intraperitoneal and intravenous administration of viral vectors can deliver transgenes to the intestines, and have reported the treatment effects on diabetes mellitus by lowering blood glucose levels in vivo.

### 2.2. Non-viral vectors

There are several non-viral vectors that can deliver transgenes to the pancreas and intestines [24–29, 54]. For example, polyethylenimine (PEI), cationic nanomicelles comprising chitosan, which is a linear polysaccharide, and arginine-grafted bioreducible polymer have been shown to deliver transgenes effectively to the pancreas and intestines in animal models of diabetes mellitus, and their treatment effects on diabetes mellitus have also been
demonstrated [24–29,54]. The internalization of PEI and chitosan cationic nanomicelles into target cells can be performed by making use of the positive surface charge of PEI or cationic nanomicelles and the negative charge of the cell membrane [55,56]. The internalization of arginine-grafted bioreducible polymer is possible because the arginine peptide is reported to possess a cell-penetrating ability [24,54,57].

2.3. Other transgene delivery systems

Transgene delivery to the pancreas using an ultrasound device has been reported [30,58]. In that method, lipid-stabilized microbubbles containing plasmid DNA were injected into a catheter that was inserted into the internal jugular vein. Ultrasound was directed at the pancreas to destroy the microbubbles within the pancreatic microcirculation. This transgene delivery system was reported to provide substantial transgene expression in the pancreas in vivo [30,58]. An electroporation method was also shown to be effective at transfecting transgenes into the pancreas. In that method, naked plasmid DNA was injected into one compartment of the pancreatic parenchyma. The injection site of the pancreas was then sandwiched with a pair of tweezer-type electrodes, and electroporation was carried out using a square-pulse generator [24]. Magnetic nanoparticles comprising super-paramagnetic iron oxide and bearing short interfering RNA (siRNA) have been reported to transfect successfully siRNA into cultured pancreatic islet cells [59]. The internalization of magnetic nanoparticles into target cells is possible via manipulation of energy-dependent endocytosis [60,61].

3. Transgenes for the treatment of diabetes mellitus

Several transgenes have been reported to show effects for the treatment of diabetes mellitus when delivered with nano-sized carriers in vivo.

3.1. Pancreas/duodenum homeobox protein 1

Pancreas/duodenum homeobox protein 1 (PDX-1) is a transcription factor necessary for pancreatic regeneration [62,63]. Administration of adenoviral vectors designed for expression of PDX-1 via the common bile duct was reported to induce neogenesis of pancreatic β cells in vivo [10]. Delivery of adenoviral vectors designed for expression of insulin gene enhancer protein-1, which is a transcription factor in addition to PDX-1, has been reported to promote the regenerative potential of pancreatic cells [11]. These findings suggest that PDX-1 may be one of the key transgenes for the treatment of diabetes mellitus by promoting pancreatic regeneration.

3.2. NEUROG3

NEUROG3 can initiate pancreatic islet cells to differentiate and maintain their functions [64,65]. Prophylactic administration of adenoviral vectors designed for expression of NEUROG3 via the tail vein was shown to inhibit the development of diabetes mellitus in a mouse model of diabetes mellitus [12]. Interestingly, delivery of multiple plasmid DNA expressing different transcription factors including NEUROG3 to the liver was shown to induce transdifferentiation of liver cells to pancreatic β cells [66]. These results suggest that delivery of exogenous NEUROG3 to not only the pancreas but also the liver in vivo has promising potential for the treatment of diabetes mellitus.

3.3. GLP-1

GLP-1 is an incretin hormone that contributes to insulin secretion from β cells and decreases glucagon secretion from α cells of the pancreas [6–9]. GLP-1 is secreted from intestinal L cells in response to glucose and fatty acids [6–9]. Numerous studies have reported on the efficacy of GLP-1 transgene delivery to the intestines with viral vectors in animal models of diabetes mellitus in vivo. Intravenous or intraportal systemic administration of GLP-1 transgene with viral vectors to the intestines was shown to increase plasma GLP-1 levels, resulting in increased insulin secretion, decreased blood glucose levels, and promotion of the regeneration of insulin-producing cells in the pancreas in streptozotocin-induced animal models of diabetes mellitus [13–17,19]. Another study reported that intra-intestinal injection of adenovirus vectors designed for expression of GLP-1 increased serum GLP-1 levels in the intestines, resulting in increased insulin secretion and decreased blood glucose levels after 2 weeks of administration [67].

Several studies have reported the treatment effects of GLP-1 transgene delivery to the intestines using non-viral vectors in animal models of diabetes mellitus in vivo [24,28,54]. Delivery of GLP-1 transgene with cationic nanomicelles comprising chitosan or arginine-grafted bioreducible polymer to the intestines was reported to have insulinotropic effects in animal models of diabetes mellitus [24,28,54]. It was reported that co-delivery of GLP-1 transgene to the intestines with other molecules could enhance the treatment effects for diabetes mellitus [18,20,21,26]. Co-delivery of GLP-1 transgene with N and K1 domains of hepatocyte growth factor (NK1/HGF) with double-stranded AAV vectors to the intestines was shown to delay the onset of diabetes mellitus, increase the mass of pancreatic β cells, and increase insulin secretion in an animal model of diabetes mellitus [18]. Other studies have demonstrated that co-delivery of GLP-1
transgene with interleukin (IL)-4 or NK1/HGF with double-stranded AAV-8 vectors to the intestines promoted pancreatic β cell proliferation and prevented pancreatic β cell apoptosis in an animal model of diabetes mellitus [20]. Co-delivery of GLP-1 transgene with regenerating islet-derived protein 3, which contributes to pancreatic islet neogenesis, with AAV vectors to the intestines was shown to decrease fasting blood glucose levels and increase the number of insulin-positive cells in the pancreas of a mouse model of diabetes mellitus [21]. Intravenous systemic administration of plasmid DNA expressing GLP-1 together with plasmid DNA expressing nuclear factor-kappa B with PEI was shown to improve insulin secretion and decrease body weight in a mouse model of diabetes mellitus [26].

4. Other transgenes

Knockdown of activating transcription factor 3 (ATF3) expression in pancreatic β cells by siRNA targeted to ATF3 delivery with a cationic polymer was shown to attenuate endoplasmic reticulum stress-mediated pancreatic β cell dysfunction in a mouse model of diabetes mellitus [24]. Knockdown of Fas (also known as cluster of differentiation 95) expression in the pancreas by Fas-siRNA delivery with PEI via intravenous administration was shown to delay the progression of pancreatic insulitis in a mouse model of non-obese diabetes [25]. Over-expression of IL-2 in β cells by plasmid DNA expressing IL-2 via delivery with AAV-8 could prevent the onset of diabetes [22]. Over-expression of serum IL-4 and IL-10 by plasmid DNA expressing IL-4 and IL-10 via delivery with cationic nanomicelles comprising chitosan administered by intramuscular injection was shown to decrease blood glucose levels and have protective effects against insulitis in a mouse model of diabetes mellitus [26]. Over-expression of Klotho in β cells by plasmid DNA expressing Klotho via delivery with AAV-2 could protect against β cell apoptosis and improve glucose tolerance in a mouse model of diabetes mellitus [23].

4.1. MicroRNA

Several studies have reported that inhibitors or mimics of microRNA (miRNA) delivery with viral and non-viral vectors are effective for the treatment of diabetes mellitus. Over-expression of miRNA-375 with miR-375 mimic expression adenoviral vector and AAV was shown to suppress glucose-induced insulin secretion and partially inhibited the expression of a target gene, myotrophin, which contributes to insulin secretion in cultured pancreatic β cells in vitro [68,69]. miRNA-375 is reported to be involved in the maintenance of β cell mass, and over-expression of miRNA-375 may contribute to the generation of insulin-producing cells in vitro [70–72]. These findings suggest that over-expression of miRNA-375 mimic delivery with viral and non-viral vectors to the pancreas may be a potentially good therapeutic option for the treatment of diabetes mellitus in vivo.

Several other miRNAs, including miR-9, miR-124a, miR-126, miR-34a, and miR21, have been studied for their roles in glucose regulation or pancreatic β cell function; however, there are few studies on their therapeutic effects for diabetes mellitus [1,73–77]. Further studies on the effects of gene therapies using targeted miRNA for the treatment of diabetes mellitus in vivo are required.

Gene therapies using viral and non-viral nano-sized carriers for the treatment of diabetes mellitus in vivo have been developed; however, their long-term efficacy, phagocytic uptake, side effects including toxicity, immunogenicity, and unexpected host genome alternations, and their effects on non-targeted organs have not been fully investigated and require further study before these technologies are applied in clinical studies.

5. Islet cell transplantation

Islet cell transplantation is a treatment option that it is hoped will improve blood glucose levels, resulting in an improved prognosis for patients with diabetes mellitus [78,79]. Technologies for pancreatic islet cell transplantation using delivery vectors have been developed. Details of the development of islet cell transplantation are summarized in Table 2.

Islet cells have been mainly transplanted into the liver via portal vein injection because this method is relatively non-invasive and requires fewer islet cells compared with other organs [90,91]. However, a non-specific inflammatory and thrombotic reaction called instant blood-mediated inflammatory reaction (IBMIR), which leads to massive destruction of transplanted islet cells, may possibly occur when islet cells are exposed to the recipient blood [92]. IBMIR leads to the activation of complement systems and coagulation [92]. To overcome these problems, technologies for delivery systems for islet cell transplantation have been developed. Surface-modulated islet cells coated with PEG-phospholipid conjugated with urokinase or heparin were shown to improve survival rates when transplanted into the liver by preventing IBMIR or biological reactions such as complement activation [80,81].

With regard to islet cell transplantation sites, intramuscular and subcutaneous spaces are considered to be clinically better because they are highly accessible and less invasive [91,93]. However, hypoxic conditions in intramuscular and subcutaneous spaces have been reported to reduce the survival of transplanted islet cells [94–96]. To overcome this problem, artificially modified islet cells transplanted into intramuscular and subcutaneous spaces have been studied. Islet
| Vectors          | Moderated substance | Administration route       | Transplanted site            | Effects                                                                 | Authors (year published)               | Reference No. |
|------------------|---------------------|---------------------------|-----------------------------|-------------------------------------------------------------------------|----------------------------------------|---------------|
| Viral vectors    |                     |                           |                             |                                                                         |                                        |               |
| Adenovirus       | GLP-1               | Direct transplantation    | Left kidney capsule         | Enhanced islet cell survival. Preserved islet mass. Achieved normoglycemia | Chae et al. (2012)                      | [54]          |
| PEG              | Urokinase           | Portal vein injection     | Liver                       | Increased plasma insulin level. Inhibited IBMIR                         | Teramura and Iwata (2011)              | [80]          |
| PEG              | sCR1, heparin       | Portal vein injection     | Liver                       | Increased plasma insulin level. Normalized glucose level. Reduced islet cell damage by IBMIR | Teramura et al. (2013)                 | [81]          |
| PGA              | None (only polymer layer) | Direct transplantation | Abdominal subcutaneous tissue | Normalized blood glucose level. Revascularized transplanted islet cells | Juang et al. (1996)                    | [82]          |
| PET mesh bag     | bFGF                | Direct transplantation    | Intermuscular space         | Normalized blood glucose level                                          | Balamurugan et al. (1996)             | [83]          |
| PET mesh bag     | Agarose             | Unknown                   | Peritoneal cavities         | Induced blood vessels around transplanted islets                         | Gu et al. (2000)                      | [84]          |
| PET mesh bag     | Agarose             | Unknown                   | Peritoneal cavities         | Induced prevascularization. Maintained normoglycemia over the long term   | Gu et al. (2000)                      | [85]          |
| PET mesh bag     | bFGF in agarose and hyaluronic acid | Direct transplantation | Subcutaneous tissue of dorsum | Induced angiogenesis. Normalized blood glucose levels in the long term                         | Kawakami et al. (2001)                | [86]          |
| Cationic lipid reagent | VEGF              | Direct transplantation    | Left kidney capsule         | Normalized blood glucose level. Preserved transplanted islet cells with increasing vascularization | Chae et al. (2005)                     | [43]          |
| RSV6 peptide micelles | siRNA-INES, 17β-estradiol | Direct transplantation | Left kidney capsule         | Improved glycemic control. Reduced apoptosis of transplanted islet cells | Hwang et al. (2015)                   | [87]          |
| Magnetic iron oxide nanoparticles | siRNA-human caspase-3 | Direct transplantation | Left kidney capsule         | Decreased apoptosis in transplanted islet cells                           | Wang et al. (2011)                    | [88]          |
| Magnetic iron oxide nanoparticles | siRNA-β2 microglobulin | Direct transplantation | Left kidney capsule         | Delayed onset of diabetes mellitus caused by immune rejection           | Wang et al. (2012)                    | [89]          |

**Abbreviations:** GLP-1: glucagon-like peptide-1; IBMIR: instant blood-mediated inflammatory reactions; PEG: polyethylene glycol; PGA: polyglycolic acid; PET: polyethylene terephthalate; bFGF: basic fibroblast growth factor; CR1: soluble complement receptor 1; PVA: polyvinyl alcohol hydrogel; VEGF: vascular endothelial growth factor; RSV6: three arginine and six valine; siRNA: short interfering RNA; INOS: inducible nitric oxide synthase.
cells coated with polyglycolic acid polymer have been shown to provide better glucose tolerance with more revascularization compared with naked islet cells when transplanted into the subcutaneous space of a mouse model of diabetes mellitus [82]. Other studies have reported that bio-artificial materials improved transplanted islet cell survival [83–86]. In these studies, a polyethylene terephthalate (PET) mesh bag that enclosed a collagen sponge and biodegradable gelatin microsphere containing basic fibroblast growth factor was transplanted into the subcutaneous space. Islet cells were then transplanted into the PET mesh bag. This transplantation method was shown to improve islet cell survival and function by promoting neo-vascularization in a rat model of diabetes mellitus [83–86].

Genetically modified islet cells have also been studied in efforts to improve the outcome of islet cell transplantation. Islet cells over-expressing GLP-1 or vascular endothelial growth factor were shown to preserve mass and function better compared with control islet cells when transplanted into the kidney capsule of a mouse model of diabetes mellitus [43,54]. Another study reported that inducible nitric oxide synthase-siRNA and 17b-estradiol-siRNA using the R3V6 peptide vector, which comprises three arginine and six valine and which forms self-assembled micelles in aqueous solution, transplanted into islet cells and delivered into the renal subcapsular space of a mouse model of diabetes mellitus suppressed cytokine-induced transplanted islet cell destruction, resulting in better control of blood glucose levels [87]. Human islet cells treated with magnetic iron oxide nanoparticles that entrapped caspase 3-siRNA or β2 microglobulin-siRNA were shown to inhibit apoptosis and immune rejection, respectively, when transplanted into the renal subcapsular space of a mouse model of diabetes mellitus [88,89]. Additionally, the transplanted islet cells pre-treated with magnetic iron oxide nanoparticles were found to be detectable using magnetic resonance imaging in vivo [88,89].

6. Conclusion

Transgene technologies using nano-sized carriers such as viral and non-viral vectors for delivery to the pancreas and intestines and islet cell transplantation technologies using genetic modification and bio-artificial material have been developed for the treatment of diabetes mellitus.

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Authors’ contributions

Kiyonori Ito drafted the manuscript. Susumu Ookawara and Kenichi Ishibashi supervised the writing of the manuscript. Yoshiyuki Morishita conceived the study and supervised the writing of the manuscript. All authors contributed to preparing the manuscript and agree to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the authors.

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