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# Molecular imaging of β-cells: diabetes and beyond☆

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ABSTRACT

Since diabetes is becoming a global epidemic, there is a great need to develop early β-cell specific diagnostic techniques for this disorder. There are two types of diabetes (*i.e.*, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)). In T1DM, the destruction of pancreatic β-cells leads to reduced insulin production or even absolute insulin deficiency, which consequently results in hyperglycemia. Actually, a central issue in the pathophysiology of all types of diabetes is the relative reduction of β-cell mass (BCM) and/or impairment of the function of individual β-cells. In the past two decades, scientists have been trying to develop imaging techniques for noninvasive measurement of the viability and mass of pancreatic β-cells. Despite intense scientific efforts, only two tracers for positron emission tomography (PET) and one contrast agent for magnetic resonance (MR) imaging are currently under clinical evaluation. β-cell specific imaging probes may also allow us to precisely and specifically visualize transplanted β-cells and to improve transplantation outcomes, as transplantation of pancreatic islets has shown promise in treating T1DM. In addition, some of these probes can be applied to the preoperative detection of hidden insulinomas as well. In the present review, we primarily summarize potential tracers under development for imaging β-cells with a focus on tracers for PET, SPECT, MRI, and optical imaging. We will discuss the advantages and limitations of the various imaging probes and extend an outlook on future developments in the field.



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## 1. Introduction

Diabetes mellitus (DM) has laid tremendous pressures on healthcare systems worldwide [1]. In 2001, the prevalence of youth with type 1 diabetes mellitus (T1DM) in the U.S. was 1.48 per 1000, increasing to 1.93 per 1000 in 2009, a 21% increase between 2001 and 2009 after adjustment [2]. The World Health Organization estimated that there were 422 million adults over 18 years of age living with all types of diabetes in 2014, which was four times higher than that in 1980 (the number at that time was 108 million) [3]. It is expected that over 550 million people will be diagnosed with diabetes by 2030 [4].

Diabetic disorders can be broadly divided into four groups: type 1, type 2, gestational, or a group of other specific syndromes [5]. T1DM, as an autoimmune disorder, results from immune-mediated destruction of insulin-producing β-cells, while type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with insulin desensitization or resistance, which occurs at multiple levels of the insulin receptors on different cell types [6–8]. There is growing evidence indicating a significant overlap across these two different types of diabetes, as both T1DM and T2DM have been associated with a functional loss of beta cell mass (β-cell mass, BCM) [9]. Specifically, BCM was reported to be reduced in patients with T2DM [10]. Hyperglycemia may trigger a stress response which plays a role in the induction of β-cell apoptosis in both T1DM and T2DM [11]. Hyperglycemia seems to be associated with changes in β-cell phenotype, such as dedifferentiation of β-cells, which is important to the development of diabetes [12]. Therefore, an insufficient number and/or functional decline of β-cells have been determined to be central components in the development and progression of hyperglycemia and diabetes.

Currently only circulating C-peptide and insulin levels are relatively reliable approaches to measure BCM. However, these two methods still lack sensitivity and reproducibility, as these indexes only indirectly reflect BCM and are not able to determine the changes in BCM amounts [5,13]. From a clinical perspective, early detection of β-cell changes is key to timely diagnosis and intervention of diabetes, such as in initial stages of the disease or in the β-cell compensation phase (when glucose levels are not elevated). Therefore, sensitive new tools that can noninvasively map BCM are urgently needed. β-cell imaging is one of the most optimal candidates [14]. While in people affected by T1DM the value of β-cell specific imaging may lie in detecting almost complete loss of BCM, in people with T2DM, β-cell imaging techniques can be applied to monitor the subtle changes of BCM over longer time periods [15–18].

$^{18}$F-FDG, the most commonly-used positron emission tomography (PET) tracer, has been employed to delineate transplanted islets and to assess the mass of β-cells in streptozotocin (STZ)-induced diabetic rats [19]. Although $^{18}$F-FDG-labeled islets allowed qualitative and quantitative analysis of transplanted islets [20], the role of $^{18}$F-FDG in monitoring BCM was controversial as it failed to accumulate less in the diabetic pancreas compared to the control [21]. Therefore, $^{18}$F-FDG PET/CT may hold potential in monitoring islet transplantation; however, this technique faces a number of challenges, including the need for pretreatment of islets, minimal sensitivity for small islet losses, and the relatively short half-life of $^{18}$F [22]. The need for noninvasive and quantitative assessment of BCM has prompted the development of many β-cell-specific imaging agents targeting the vesicular monoamine transporter 2 (VMAT2), sulphonylurea receptors (SUR-1), glucagon-like peptide 1 (GLP-1), free fatty acid receptor 1 (FFAR1), and β-cell-specific antigens [16,17,23]. Of them, Mn-DPDP [24], $^{11}$C-DTBZ [25], $^{18}$F-AV-133 [26], $^{18}$F-FDOPA [27], and $^{68}$Ga-NOTA-exendin-4 [28] are representative probes which have been tested in clinical settings and have shown great promise for evaluating BCM. Several imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), PET, single-photon emission computed tomography (SPECT), and optical imaging have been explored for noninvasive detection and measurement of BCM and β-cell function. In the past, Wu and others elaborately prepared reviews of radionuclide-based molecular imaging probes for β-cells [15,17,22]; since then, substantial molecular imaging probes for various targets have been developed and investigated for diabetes or other β-cell related conditions (*i.e.*, insulinomas and islet transplantation). By reviewing the most recent reports and highlighting remaining research gaps, we herein systematically summarize potential molecular probes for imaging β-cells (Fig. 1), and we believe that β-cell imaging will lead to tailored diagnostic tools and development of personalized medicine for patients with diabetes and insulinomas in the near future.

## 2. Manganese-based imaging probes

### 2.1. Manganese-based MRI contrast agents

Manganese ($Mn^{2+}$) is a $Ca^{2+}$ analogue and can enter β-cells through the voltage-dependent $Ca^{2+}$ channel [29], resulting in a robust, glucose-dependent signal in β-cell lines and in islets [30–34]. A proof-of-concept study reported that manganese-enhanced magnetic resonance imaging could noninvasively distinguish normoglycemic and type 2 diabetic patients through enhanced pancreatic signals on the MRI images [24]. More importantly, manganese-enhanced magnetic resonance imaging was able to identify early changes of functional BCM during β-cell compensation in C57Bl/6J mice following a high-fat/high-sucrose diet. Additionally, this imaging modality detected rapidly decreased MRI signals in the pancreas of STZ-induced diabetic mouse models [35], indicating that manganese-enhanced magnetic resonance imaging is a reliable tool for monitoring functional BCM adaptation and reduction throughout diabetes progression. However, as individual islets vary in size from 40 to 300 μm and are non-uniformly distributed throughout the pancreas [36], quantification of their mass and function is challenging through traditional MRI or CT. In addition, the toxicity of larger doses of $Mn^{2+}$ has to be considered when used as a contrast agent. Long-

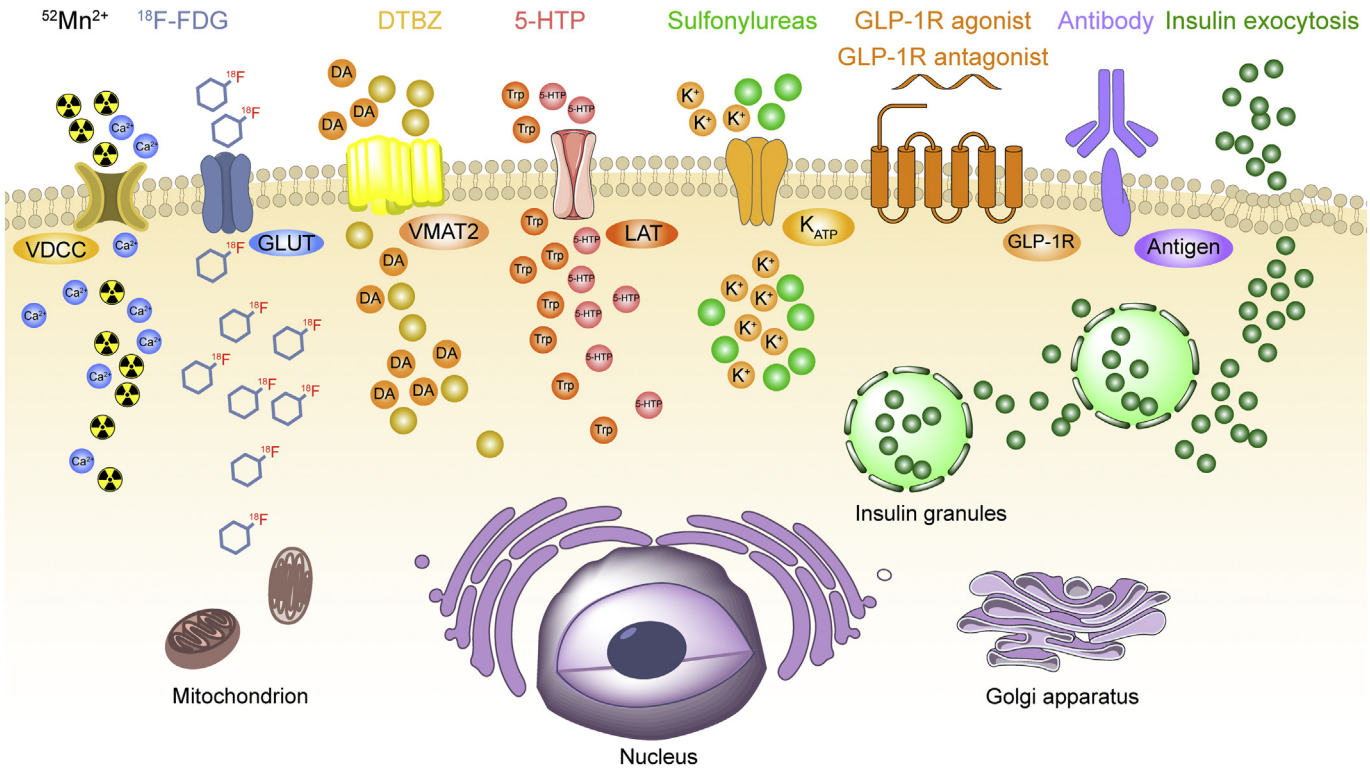


**Fig. 1.** Noninvasive molecular imaging of β-cells. Abbreviations: VDCC, voltage-dependent $Ca^{2+}$ channel; GLUT, glucose transporter; $^{18}$F-FDG, $^{18}$F-fluorodeoxyglucose; DA, dopamine; VMAT2, vesicular monoamine transporter-2; DTBZ, dihydrotetrabenazine; Trp, tryptophan; 5-HTP, 5-hydroxytryptophan; LAT, L-type amino acid transporter; GLP-1R, glucagon-like peptide 1 receptor.

term exposure to elevated concentrations of $Mn^{2+}$ ($LD_{50}$ 38 mg/kg) may lead to extrapyramidal dysfunction and also systemic toxicity, such as temperature regulation malfunctions [37–39].

### 2.2. Manganese-based PET probe

PET is a technique that detects two coincident gamma rays resulting from the annihilation of a positron with a nearby electron [40,41]. It thus has significantly greater imaging sensitivity than MRI, inherently probing physiology rather than anatomy since the tracers can be targeted to specific tissues [42,43], which may prove useful in the clinical quantification of functional BCM. We recently reported that radiomanganese ($^{52}Mn^{2+}$, $t_{1/2}$: 5.6 d) is a tracer of choice for studying β-cell physiology noninvasively [44,45]. Uptake of $^{52}Mn^{2+}$ was successfully manipulated pharmacologically *in vitro* and *in vivo*. By using an STZ-induced type 1 diabetes mouse model, we revealed that $^{52}Mn^{2+}$ uptake in the diabetic pancreas was distinguished from healthy controls as further confirmed by histological quantification of β-cell mass (Fig. 2A). $^{52}Mn^{2+}$-PET also reported the expected increase in functional β-cell mass in the *ob/ob* model of pre-type 2 diabetes (Fig. 2B), which was corroborated by histological β-cell mass measurements and live-cell imaging of β-cell $Ca^{2+}$ oscillations. These results demonstrated that $^{52}Mn^{2+}$-PET is a sensitive new tool for noninvasive assessment of functional BCM and future studies are warranted to confirm and broaden the applications of this new imaging probe.

## 3. Imaging of vesicular monoamine transporter 2 (VMAT2)

### 3.1. Radiolabeled VMAT2 targeting probes

VMAT2 is expressed in chromaffin cells, the peripheral and central nervous systems, as well as in the hematopoietic system, and is responsible for the storage and release of a variety of monoamines (*i.e.* dopamine, norepinephrine, and serotonin) in the synaptic terminals. In the pancreas, gene-expression studies have revealed higher VMAT2 expression in islets than in exocrine tissue, and immunohistochemical studies in humans have found coexpression of VMAT2 and β-cells, and further costaining of VMAT2 and insulin [46–48]. It has been proven that VMAT2 contains a high-affinity binding site for DTBZ, which is an active metabolite of tetrabenazine (TBZ). In 1993, DaSilva et al. first synthesized and reported $^{11}$C-DTBZ, suggesting that this imaging agent would be a potential tracer for studying neurodegenerative disorders [49]; later, the same team reported that $^{11}$C-DTBZ bound to VMAT2 with high specificity in normal rats *in vivo* [50]. In human studies, $^{11}$C-DTBZ has initially been used as a highly VMAT2-specific radioligand in clinical brain imaging, being able to noninvasively measure VMAT2 density in human brains [51]. Subsequently, $^{11}$C-DTBZ has been extensively used to evaluate BCM in both rodents and humans [25,52–56]. However, the larger-scale implementation of this tracer is limited due to the short half-life of $^{11}$C ($t_{1/2}$: 20 min).

A way to overcome this aforementioned drawback is to label the compound with longer-lived positron emitters; therefore, $^{18}$F-labeled ($t_{1/2}$ = 110 min) analogs of DTBZ, such as [$^{18}$F] fluoropropyl [FP]-DTBZ, [$^{18}$F] fluoroethyl [FE]-DTBZ, and [$^{18}$F]-FE-DTBZ-d4, have been explored in preclinical or clinical studies [57–62]. Of note, a study from Lin et al. showed that $^{18}$F-FP-(+)-DTBZ (also known as $^{18}$F-AV-133) is safe for imaging VMAT2 sites and expression levels in humans [62]. Normandin et al. then evaluated $^{18}$F-FP-(+)-DTBZ for quantitative assessment of BCM in healthy control subjects and patients with T1DM, and they found that $^{18}$F-FP-(+)-DTBZ could evaluate islet β-cell density and aggregate BCM as evidenced by the correlation between radiotracer binding parameters and insulin secretion capacity. Representative PET images from this study showed a striking uptake difference of $^{18}$F-FP-(+)-DTBZ between control and diabetic subjects (Fig. 2C) [26]. Freeby et al. further confirmed these results in a relatively larger cohort [63]. These findings provided encouraging evidence that DTBZ-based tracers could be applied to visualize and quantify BCM clinically.

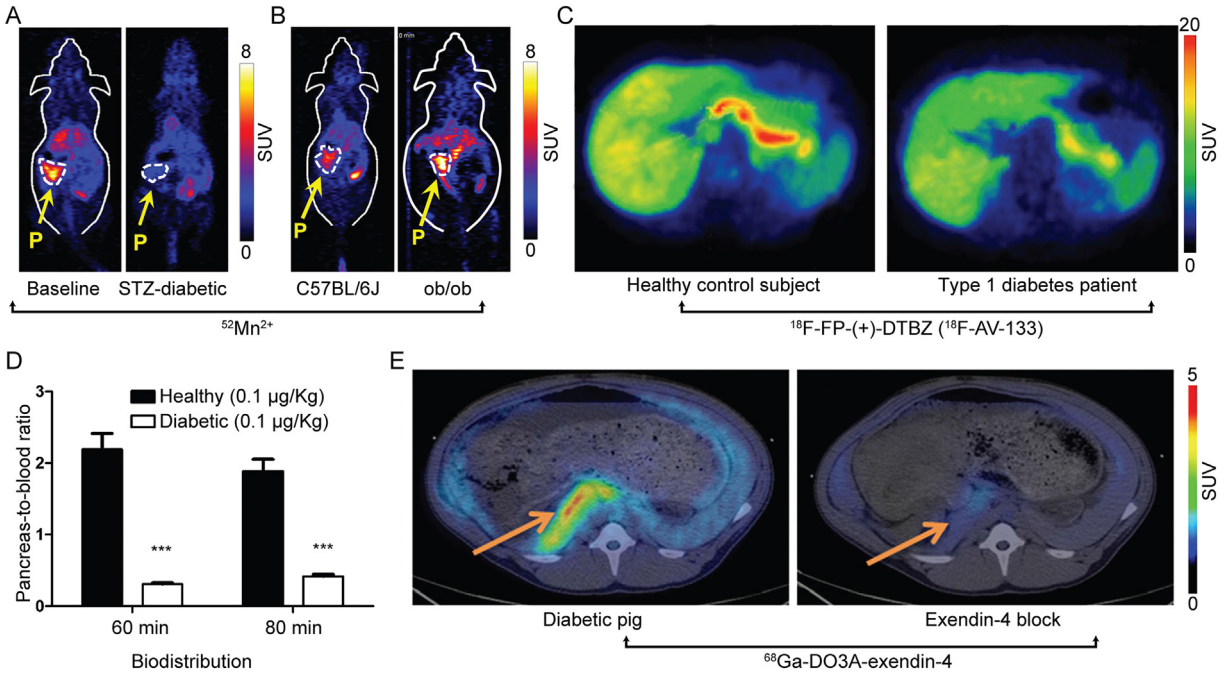


**Fig. 2.** Representative manganese-, VMAT2- and GLP-1R-based PET tracers and corresponding *in vivo* imaging results. (A) $^{52}Mn^{2+}$-PET imaging in healthy ICR mice (left) and STZ-induced type 1 diabetic mice (right). Note that STZ-diabetic ICR mice showed clearly reduced $^{52}Mn^{2+}$ uptake in the pancreas (B) Coronal PET images acquired at 1 h after $^{52}Mn^{2+}$ administration in C57BL/6J control mice (left) and ob/ob prediabetic mice (right). $^{52}Mn^{2+}$ accumulation in the pancreas of ob/ob mice was significantly higher than that in the wild-type C57BL/6J mice, indicating that application of $^{52}Mn^{2+}$-PET imaging may precisely detect diabetes even in the early compensation phase. The pancreas (P) is demarcated by white dashed contours. (C) While $^{18}$F-FP-(+)-DTBZ PET imaging acquired for healthy control subject showed high uptake of the tracer in the pancreas (left), the corresponding pancreas uptake was reduced in patients with type 1 diabetes (right). Concentration of radioactivity normalized by standardized uptake value (SUV) was significantly lower in the pancreas of patients with T1DM ($10.7 \pm 2.6$, n = 7) than that in the control subjects ($17.2 \pm 4.0$, n = 9). (D) Biodistribution performed 60 and 80 min after intravenous administration of $^{68}$Ga-DO3A-exendin-4. Results showed that uptake in rats with STZ-induced diabetes decreased by more than 80% at both time points compared with that in healthy controls. Asterisks indicate statistical significance. (E) $^{68}$Ga-DO3A-exendin-4 scanning showed pancreatic uptake in diabetic pigs. Competition with unmodified exendin-4 in excess abolished the pancreatic tracer uptake (right), indicating that the tracer uptake is GLP-1R mediated. Although GLP-1R specific, $^{68}$Ga-DO3A-exendin-4 may not be the most optimal β-cell imaging probe. The pancreas was indicated by an arrow.
Adapted with permission from [26,45,105,108].

### *3.2. Drawbacks of VMAT2 targeting probes*

In spite of the above-mentioned promising results, other studies demonstrated that $^{11}$C-DTBZ and $^{18}$F-labeled analogs of DTBZ may not suitable for imaging BCM because of their high nonspecific binding to the exocrine pancreas [59,64,65]. Therefore, the validity of VMAT2 targeting probes for β-cell imaging has been debated for some time [66,67]. Despite the controversies, nonspecific uptake of the tracer can be corrected by using an appropriate reference region. Singhal et al. set out to compare diagnostic efficacy of $^{11}$C-DTBZ and $^{18}$F-FP-(+)-DTBZ in targeting VMAT2 and found that the latter tracer could provide a noninvasive method to quantify BCM. In addition, in this study the authors also suggested that the high-flow kidney cortex, rather than the liver, is an appropriate reference region for quantitative imaging of BCM in animal models of diabetes [59], because uptake variability of these tracers in the kidney cortex was less than that in liver [53]. Contrary to this, Naganawa et al. found that uptake of $^{18}$F-FP-(+)-DTBZ was lowest in the spleen and was less affected by partial volume effects and radiometabolites, and therefore proposed the spleen as a more practical scaled-reference region when quantifying BCM using $^{18}$F-FP-(+)-DTBZ PET [68]. More recently, the same team extended their work and assessed $^{18}$F-FP-(+)-DTBZ and $^{18}$F-FP-(−)-DTBZ in healthy controls and T1DM patients. The authors confirmed that use of the spleen as the scaled-reference resulted in the highest non-displaceable uptake and the largest differences for the healthy controls *vs.* the T1DM group [69].

Also of note, the pancreas volumes tend to be smaller in T1DM patients than in non-diabetic subjects [70,71], and the partial-volume effect is a potential limitation of PET when imaging such small structures like individual islets [72,73]. Respiration-induced pancreatic movement artifacts further degrade spatial resolution and intensify partial-volume effects [74]. These reasons may synergistically result in an underestimation of the radioactivity measured in an individual islet. While 90% of β-cells express VMAT2, approximately 40% of PP cells (also known as gamma cells) express VMAT2 [75]. Consequently, the nonspecific binding of $^{18}$F-FP-(+)-DTBZ to PP cells may lead to an overestimation of the measured BCM. In addition, BCM in patients with T1DM is considered to be nearly depleted, so the uptake of $^{18}$F-FP-(+)-DTBZ might be lower than that observed in currently-reported studies. Therefore, further studies are needed with these tracers to establish reference regions and to thoroughly assess pancreatic non-displaceable binding of $^{18}$F-FP-(+)-DTBZ in humans, especially in patients with T1DM [76].

## 4. Imaging of sulfonylurea receptor 1 (SUR1)

In mammals, insulin secretion is mediated by the membrane potential of pancreatic β-cells. Increases in glucose levels lead to blocking of ATP-sensitive potassium channels ($K_{ATP}$ channels) in the plasma membrane, which lead to membrane depolarization, increases in calcium influx, and subsequent insulin granule exocytosis. Hetero-octameric $K_{ATP}$ channels are composed of four inward-rectifier $K^+$ channel subunits and four sulphonylurea receptor subunits (SUR1, SUR2A, or SUR2B) [22,77,78]. By binding to SUR1 [79], sulfonylureas are used in patients with T2DM to mitigate T2DM symptoms by stimulating insulin secretion even in the absence of glucose [80]. Although SURs are also expressed by other endocrine pancreatic cells [81], sulfonylureas, especially glibenclamide (glyburide) and tolbutamide, have emerged as attractive candidates for BCM imaging [82–85].

Since the original glibenclamide molecule underwent hepatic clearance and radiolabeled glibenclamide therefore had high liver uptake, it was unsuitable for islet imaging [86]. Therefore, novel glibenclamide derivatives targeting pancreatic β-cells with optimized pharmacokinetics and biodistributions have been developed. In 2007, Schneider et al. synthesized a high affinity glibenclamide-glucose conjugate by adding new moieties to the glibenclamide structure, and found that this new conjugate had enhanced hydrophilicity (a 12-fold increase) and preserved its high binding affinity to SUR1 *in vitro*. Furthermore, *in vivo* studies verified that this compound was cleared much faster from circulation, mainly because of its lower plasma protein binding [87]. Therefore, this glucose conjugate could serve as a potential lead compound for designing other glibenclamide derivatives and for β-cell imaging by targeting SURs. Repaglinide, an oral medication for T2DM, induces insulin secretion by closing ATP-dependent potassium channels and by opening the calcium channels in β-cell membranes [88]. Repaglinide has also been explored for noninvasive PET imaging of β-cells [89–91]. More recently, Kimura et al. synthesized several novel mitiglinide derivatives and found that one of these compounds, (+)-(*S*)-o-FMIT, showed the highest affinity for SUR1 and specifically accumulated in pancreatic β-cells as revealed by *ex vivo* autoradiography, suggesting that (+)-(*S*)-o-$^{18}$F-FMIT could be a candidate PET tracer for *in vivo* molecular imaging of pancreatic β-cells [92]. However, several other radiolabeled SUR1 ligands had low, non-specific concentration in the pancreas but high uptake in adjacent organs [89,93].

## 5. Imaging of glucagon-like peptide-1 receptor (GLP-1R)

### 5.1. Agonists of GLP-1R/GLP-1 pathway

Glucagon-like peptide-1 (GLP-1), a gut-derived peptide secreted by intestinal L-cells after food ingestion, is the endogenous agonist to GLP-1R. The GLP-1R/GLP-1-complex activates the adenylyl cyclase pathway, resulting in β-cell proliferation and neogenesis, increased synthesis and release of insulin in a glucose-dependent manner [94,95]. GLP-1R was first cloned from rat islets and was found abundantly expressed on native islet β-cells [95,96]. Peptides targeting GLP-1R are promising agents for use in the treatment of diabetes or in the imaging of β-cells. Endogenous GLP-1 is degraded within minutes *in vivo*, and, as a result, this native peptide is not a suitable candidate for β-cell imaging. Therefore, many efforts have been devoted to the modifications of GLP-1 to increase its *in vivo* efficacy and its biological half-life. To this end, a more stable GLP-1R agonist, exendin-4 (Exenatide), has been isolated from the salivary glands of Gila monster lizards and binds to the extracellular domain of GLP-1R with picomolar affinity [97]. Exendin-4 is currently used as a GLP-1R agonist for treating T2DM [98–100]. Exendin-4 and its derivatives have been extensively developed for fluorescence, nuclear medicine, and/or MR imaging of endogenous BCM [101–108]. Moreover, exendin (9-39) is a GLP-1R antagonist from Gila monster saliva and has also been used in determining BCM [97,109]. Of note, different from exendin-4, exendin (9-39) had no agonist activity because it did not modify cellular cAMP levels [97].

### 5.2. Exendin-based PET/SPECT probes

Gotthardt and co-authors synthesized an $^{111}$In-labeled exendin-4 analogue ($^{111}$In-DTPA-Lys40-exendin-4) and examined its *in vivo* imaging efficacy in rats and mice. *In vivo* high-resolution SPECT imaging results from the study showed specific uptake of this tracer in the stomach, pancreas, lung, adrenal glands, and pituitary gland [110]. In 2009, Mukai et al. tested exendin (9-39) as another potential probe for pancreatic β-cell imaging. $^{125}$I-BH-exendin (9-39) showed the highest concentration in the lungs and the second highest concentration in the pancreas, and pre-dosing of an excess amount of unlabeled exendin (9-39) significantly reduced the pancreatic uptake, indicating that radiolabeled exendin (9-39) could be another useful probe for β-cell imaging [111]. The same team then developed another probe, [Lys$^{12}$($^{111}$In-BnDTPA-Ahx)]exendin-4, and reported that SPECT imaging with this probe enabled noninvasive visualization of β-cells and measurement of BCM [112]. More recently, SPECT imaging after *in vivo* injection of $^{111}$In-labeled exendin-3 showed specific targeting of the radiotracer to β-cells, facilitating noninvasive visualization and quantification of BCM in the pancreas of rodents, as well as in healthy and diabetic patients [103,113]. In the study including five type 1 diabetic patients and five healthy controls, Brom et al. reported that, although inter-individual variation of the tracer uptake existed, a substantially lower uptake was observed in patients with T1DM [113]. Currently, it is quite difficult to perform quantitative analysis of SPECT images, especially for pancreatic β-cell imaging data. Therefore, development of a quantitative method that could allow for quantification of BCM is of great importance. In one possible solution, three-dimensionally printed phantom images were used to quantify pancreatic $^{111}$In-exendin uptake and initial results showed that this technique is reliable in the quantification of pancreatic uptake [114].

Several groups have used different labeling strategies and developed $^{18}$F-labeled exendin (9-39) derivatives [115,116], or exendin-4 analogs [117], for quantitative analysis of BCM. Connolly et al. labeled Lys$^{40}$(DOTA)NH$_2$Exendin-4 with $^{64}$Cu and *ex vivo* autoradiographic and immunohistochemical studies showed the specific binding of $^{64}$Cu-(Lys$^{40}$(DOTA)NH$_2$)exendin-4 to islet β-cells [118]. Although Selvaraju et al. reported a marked decrease in the uptake of $^{68}$Ga-DO3A-VS-Cys40-exendin-4 ($^{68}$Ga-DO3A-exendin-4) in STZ-induced diabetic rats compared to non-diabetics (Fig. 2D) [105], a confirmation study from the same group demonstrated that the pancreatic accumulation patterns of the imaging agent failed to show differences between non-diabetic and diabetic pigs (Fig. 2E) [108]. This implied that GLP-1R is also expressed on other cells in the diabetic pig pancreas in significant amounts. Additionally, unexpected high retention of the tracer was retained in the bilateral lungs of the diabetic pigs but no background uptake was observed in the porcine liver, indicating that this tracer may be alternatively used as an imaging agent for GLP-1R-expressing β-cells transplanted to the liver. From these studies and a study by Willekens et al. [119], one can learn that animal models matter a great deal in assessing the efficacy of β-cell targeting probes in the *in vivo* determination of BCM.

## 6. Molecular imaging with β-cell specific antibodies

β-Cell specific antibodies, or humanized high affinity antibody fragments, may meet the requirements of β-cell specific imaging after conjugation with radioactive isotopes [120–122]. Radiolabeled monoclonal antibodies (mAbs) targeting pancreatic β-cells have been reported by several studies [122,123]. Therefore, by utilizing these mAbs which specifically bind to insulin-producing β-cells, development of antibody-based imaging probes has shown enormous promise and could potentially result in important tools for evaluating BCM.

Transmembrane protein 27 (TMEM27) stimulates pancreatic β-cell proliferation, is predominantly expressed on the β-cell surface [124], and thus may serve as a potential marker for pancreatic BCM [125]. Using a mAb (8/9-mAb) specific to human TMEM27 (hTMEM27), Rudin and colleagues reported multimodal imaging strategies to target β-cells on human samples and in animal models. $^{89}$Zr-8/9-mAb showed high signal-to-background contrast in subcutaneous insulinoma models one day after tracer injection, and fluorescently-labeled 8/9-mAb showed β-cell specific staining on both human and mouse pancreatic sections [126]. However, the specificity of 8/9-mAb for human TMEM27 may limit its use for BCM assessment in preclinical diabetic animal models. Cross species-selective antibodies against TMEM27 are still needed to further evaluate the potential value of TMEM27 in noninvasive β-cell imaging.

IC2 is a rat mAb specifically binding to insulin granula [127,128]. Although this mAb was discovered 30 years ago, it has only recently been

used for β-cell imaging *in vivo*. Moore et al. used this mAb for β-cell imaging in 2001 [129]. After DTPA conjugation, IC2 was labeled with $^{111}$In. Both *in vitro* and *in vivo* studies demonstrated the specific targeting of $^{111}$In-DTPA-IC2 to β-cell surface structures. The authors further found that the uptake of $^{125}$I-labeled IC2 directly correlated with BCM in diabetic and normal animals [129]. However, in addition to the slow blood clearance of this probe due to its large size, no experimental or clinical studies verify the application of this mAb in human diagnostics.

Alternatively, single-chain antibodies other antibody fragments may show high pancreas uptake and fast blood clearance. For example, Ueberberg and colleagues screened a single-chain antibody library and reported that $^{125}$I-labeled single-chain antibodies successfully monitored BCM in rats [130]. Eriksson et al. radiolabeled a novel Zinc transporter 8 (ZnT8)-targeting antibody fragment, Ab31, using $^{125}$I and reported that the binding affinity of this probe to insulinomas and the pancreatic accumulation of this tracer was higher than that of $^{125}$I-labeled exendin-4 [131]. These initial results indicate that antibody fragments and single-chain antibodies may be promising alternatives for β-cell imaging, since they have similar specificities and affinities toward their corresponding targets with faster clearance because of their much smaller sizes [132].

## 7. Imaging agents for other emerging targets

### 7.1. Zinc-based MRI probes

ZnT8 is a specialized zinc transporter found predominantly in the insulin secretory granules of pancreatic β-cells and controls the accumulation and transportation of zinc from the cytoplasm into the lumen of intracellular vesicles [133]. Recent studies have confirmed that the zinc transporter 8 autoantibody is a major biomarker for T1DM diagnosis [134]. ZnT8 itself may act as a very promising target for β-cell imaging [135,136]. Insulin granules contain high concentrations of Zn(II) ions, of which a small but important fraction (1–100 μM) is unbound [137]. Given the significant proportion of Zn(II) in the secretory granules and the relative scarcity of zinc ions throughout other components of the pancreas [138], Zn(II)-based imaging agents may be useful tools to quantify BCM *in vivo* [139]. Using the $Zn^{2+}$-responsive MRI agent, GdDOTA-diBPEN, Lubag et al. demonstrated that divalent zinc ions were secreted together with insulin from β-cells after glucose stimulation. Additionally, serial MR imaging of mice fed with a prolonged high-fat diet (60%) showed a dramatic increase in abdominal contrast, which was in line with expansion of the pancreas volume and a concomitant overall increase in function of β-cells [140]. A dual-modal MRI/optical probe that senses Zn(II) has also been developed by Stasiuk and colleagues. This probe specifically accumulated into secretory granules and isolated islets *in vitro*, and *in vivo* MRI experiments using this probe clearly outlined the enhanced pancreas [141]. These results indicate that MR imaging using Zn(II)-sensing probes could potentially detect BCM and β-cell function, but the application of this imaging method in humans remains to be tested.

### 7.2. FFAR1 targeting probe

FFAR1 is a part of the class of the seven-transmembrane domain G-protein-coupled receptors. Medium and long-chain free fatty acids, which can enhance glucose-dependent insulin secretion, are the main endogenous ligands of the receptor and can activate the receptor in a dose-dependent manner. FFAR1 was found to be expressed in defined human brain areas and in the intestine [142], but the receptor is predominantly expressed in human and rodent β-cells [143,144]. Due to this relatively high expression of FFAR1 in islets, Bertrand et al. modified the scaffold of the FFAR1 agonist TAK875 and then conjugated the compound with different fluorophores, of which probe 16 conjugated with Alexa488 maintained its agonistic properties and enhanced insulin secretion in a glucose-stimulated manner [145]. The same group further labeled derivatives of TAK875 with $^{18}$F and yielded good radiochemical results [146]. Although further studies assessing the *in vivo* efficacy of these probes in imaging β-cells are still needed, these initial results represented the first important steps toward successful β-cell imaging by targeting FFAR1.

### 7.3. SSTR targeting probe

Natural somatostatin is a cyclic peptide hormone generated by and found in many human tissues such as hypothalamus, adrenals, and pancreas. Somatostatin produced by the pancreas inhibits the secretion of other pancreatic hormones like insulin and glucagon. Somatostatin receptors (SSTRs) are expressed on 87% of β-cells [147], and therefore may act as a potential target for imaging [148]. In 2006, Amartey et al. explored the potential application of SSTRs in imaging of β-cells. The authors synthesized and evaluated $^{131}$I-IPC-β-AL3 *in vitro* and *in vivo*, and found that the accumulation of this probe in normal mice was significantly higher in the pancreas over other organs, implying the value of $^{131}$I-IPC-β-AL3 as a potential pancreatic β-cell imaging agent [149]. The same group then monitored the progression of diabetes in diabetic mice models and demonstrated that pancreatic uptake of this probe was lower in nonobese diabetic mice than in normal mice, and that the radioligand accumulation correlated with the number of islets in tissue sections of both control and nonobese diabetic mice [150].

### 7.4. VAChT targeting probe

Besides probes targeting VMAT2, another promising neural imaging target for β-cell imaging is the vesicular acetylcholine transporter (VAChT). One such probe targeting this transporter is $^{18}$F-FBT, which binds to VAChT with high specificity and was initially used for mapping vesamicol receptor density in the rat brain [151]. In 2004, Clark et al. first reported that the pancreas was intensely $^{18}$F-FBT avid and was clearly visualized in the $^{18}$F-FBT PET images of mice, rhesus monkeys, and adult human volunteers [152]. $^{18}$F-FBT was further used as a tool to investigate glucose tolerance in adult female monkeys [153]. Considering the reduced cholinergic innervation in T1DM and the role of the parasympathetic neurotransmitter ACh in insulin production, Clark and co-authors further tested the feasibility of dual radiotracer analysis in identifying neurofunctional changes in T1DM using $^{18}$F-FBT and 4-$^{3}$H-DAMP, with the former probe targeting VAChT and the latter probe binding to M3 muscarinic receptors on β-cells [154]. The authors found that the combined use of these two tracers may efficiently assess insulin production ability, indicating that noninvasive synergistic imaging of pancreatic cholinergic activity and M3 muscarinic receptor density may be an effective method for evaluating BCM and β-cell function. Even considering these studies, the use of $^{18}$F-FBT PET as a means of assessing BCM and β-cell function needs to be further explored.

## 8. Optical imaging probes

### 8.1. Bioluminescence

Optical imaging of BCM can be achieved using either bioluminescence or probes conjugated with fluorescent dyes [155]. Bioluminescence, the emission of light produced during enzyme (luciferase)-mediated catalysis of luciferin, can be visualized using highly sensitive cameras [156]. When applied to β-cell imaging, bioluminescence mainly employs the insulin promoter for tissue-specific expression of luciferase in pancreatic β-cells [157,158]. Studies have reported that this imaging modality can be used to monitor BCM over time [157,159–162], to monitor the fate of transplanted islets [65,163], or to assess the regeneration of β-cells [164]. Virostko et al. developed a transgenic mouse with β-cell-specific expression of luciferase and the human diphtheria toxin receptor, and found that bioluminescence

rather than radiolabeled VMAT2-targeted ligands ($^{18}$F-FP-DTBZ, $^{18}$F-AV-266 and $^{18}$F-AV-300) precisely monitored BCM following diphtheria toxin administration. This finding indicated that these three VMAT2-directed ligands were binding to other parts of mouse pancreas but not specifically to pancreatic β-cells [65]. This study also demonstrated that multimodal imaging, rather than a single modal imaging technique, is more powerful for precisely evaluating and validating the value of potential radioligands for imaging β-cells.

### 8.2. GLP-1R-specific near-infrared probe

Brand et al. designed a bimodal imaging probe $^{64}$Cu-E4-Fl, which was produced by conjugating a near-infrared fluorescent dye and a copper chelator (sarcophagine) to exendin-4 and was radiolabeled with $^{64}$Cu, and found that this probe was able to detect individual pancreatic islets in a GLP-1R-specific manner. Small animal PET imaging easily visualized subcutaneous insulinomas in GLP-1R positive 916-1 tumor models as well (Fig. 3A, B) [165]. This study highlighted that PET imaging as well as optical imaging are possible in the same animal, combining the advantages of whole-body information from the former and high resolution imaging from the latter. Other fluorescent exendin-4 imaging agents based on alkyne modification have also been reported [101,166,167], but one should remember that different positions of the alkyne modification in the peptide sequence may impact the binding affinity of the corresponding molecular imaging agent [102]. Of note, Berclaz et al. developed a tracer (designated as Cy5.5-exendin-3) and found that time-lapse Optical Coherence Microscopy imaging using the ligand could facilitate longitudinal monitoring of the rapid and specific tracer accumulation in murine islets, revealing promising feasibility of optical platforms for research and diagnosis of diabetes or other β-cell related conditions [168].

While great interest and intense efforts have been focused on developing imaging probes for monitoring BCM, few studies have investigated imaging β-cell function (insulin release) through targeting GLP-1R. Li et al. developed a peptide conjugate of a fluorescent zinc sensor for the functional imaging of islet β-cells and found that this probe could further perform functional imaging of insulin secretion [169].

### 8.3. SUR1 targeting fluorescent probe

Considering glibenclamide does not contain any functional groups amenable for further covalent attachment to nanocarriers, Lange and colleagues designed and developed 11 glibenclamide derivatives and then obtained multivalent glibenclamide-polyamidoamine (PAMAM) derivatives, which were further used to produce fluorescently-labeled probes for multifunctional imaging. Their results showed that one of the synthesized multivalent agents, a PAMAM-rhodamine-5-glibenclamide conjugate (denoted as probe C), showed specific labeling of insulin-containing cells and distinctly outlined insulin-containing β-cells (Fig. 3C–F) [170]. These findings together with aforementioned results showed that multivalent probes modified from glibenclamide may provide a versatile platform for future development of multimodality β-cell specific imaging probes.

## 9. Imaging transplanted islets

### 9.1. Optical/SPECT/PET probes

In the last few years, islet transplantation has arisen as a treatment alternative for T1DM. To visualize transplanted islets and monitor their fate, various noninvasive probes and functionalized nanoparticles have been investigated and significant success has been achieved in basic trials to date [171–173]. The first successful *in vivo* imaging and detection of transplanted islets was reported by Lu et al. in 2004, wherein the authors transfected islets with a recombinant adenovirus coding for the luciferase gene and demonstrated that introduction of

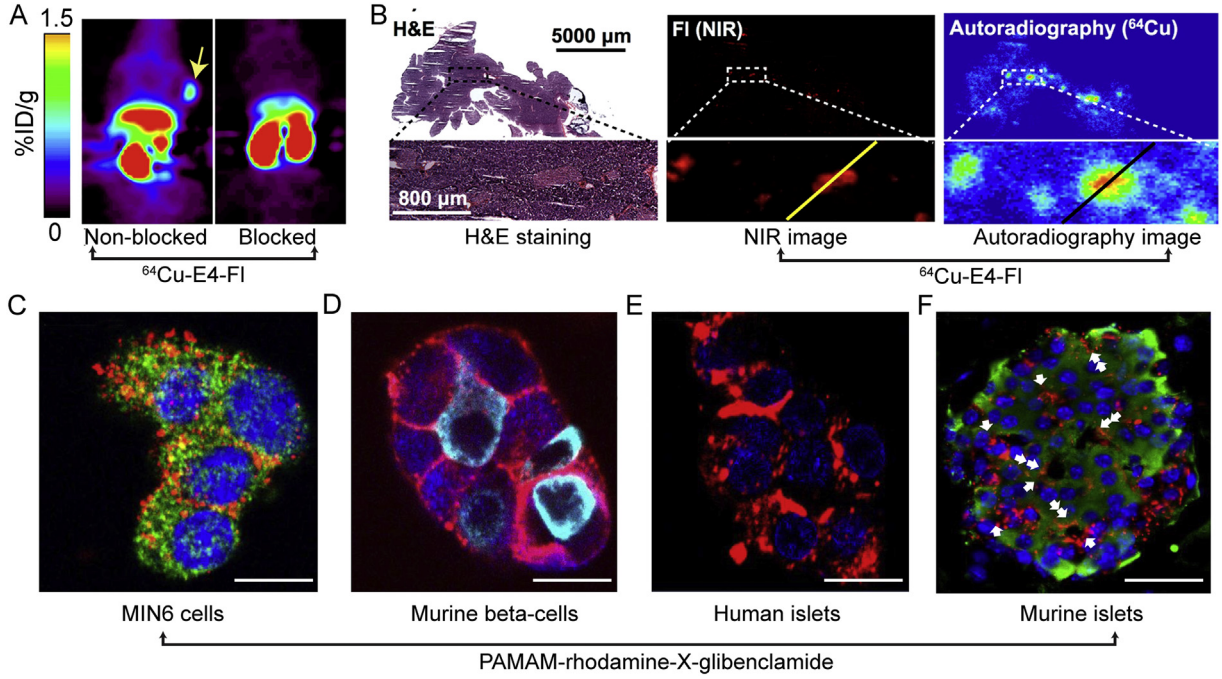


**Fig. 3.** Representative optical imaging probes specific for β-cells. (A) PET imaging using the bimodal imaging (PET/fluorescence) probe $^{64}$Cu-E4-Fl successfully detected GLP-1R positive 916-1 insulinoma in a female nude mouse (left). $^{64}$Cu-E4-Fl was specific to GLP-1R because blocking studies with unmodified peptide substantially reduced tracer uptake (right). The tumor is indicated by a yellow arrow. (B) H&E, NIR, and phosphor autoradiography images of a resected pancreatic slide. As fluorescently labeled sarcophagine 5 was conjugated with $^{64}$Cu in the $^{64}$Cu-E4-Fl probe, excellent correlation of both imaging modalities with regard to islet visualization was observed. PAMAM-rhodamine-X-glibenclamide conjugates (probe C) showed specific binding to SUR1 positive MIN6 cells (C), primary β-cells obtained from murine pancreas (D) and human islets (E). (F) After *in vivo* injection of probe C, both murine islet vessels (single arrows) and β-cells (double arrows) were labeled. Images are merged after staining with DAPI (blue), insulin (green), glucagon (turquoise) and probe C (red). Scale bar = 10 μm.
Adapted with permission from [165,170].

reporter gene-directed luciferase expression into the isolated islets allowed the long-term monitoring of grafted islets [174]. The same group further visualized islet grafts by PET imaging using reporter gene techniques [175,176]. In the latter study, the authors used recombinant lentivirus rather than recombinant adenovirus to direct the expression of the reporter gene (sr39tk, a mutant HSV1 thymidine kinase gene) to isolated islets, and found that PET imaging using [$^{18}$F]FHBG (a substrate specific for HSV thymidine kinase) allowed noninvasive detection of transplanted islets in the axillary cavity of NOD-scid mice. Notably, this imaging strategy realized longitudinal monitoring of the transplanted islets as long as 90 days after implantation [176]. By expressing a reporter gene which was under the control of the insulin promoter, another study used PET imaging of islets and found that PET signal directly correlated with insulin production [177]. Although the potential clinical application of these reporter gene-based β-cell imaging strategies mainly lies in monitoring of transplanted islets, they may also be exploited to investigate the initiation and development of diabetes [178].

Pre-labeling of islets with $^{18}$F-FDG also allowed monitoring of transplanted islets for up to 6 h [19]. Most notably, the widely-investigated exendin analogs have also been radiolabeled and exploited for imaging transplanted islets in rodents [118,179], and in humans [180]. Using an ultra-efficient $^{18}$F-labeling method [181,182], Wu et al. further developed $^{18}$F-TTCO-Cys$^{40}$-exendin-4 and found that this probe demonstrated great potential for transplanted islet imaging because of its much lower kidney uptake and higher specificity [183]. Intramuscular or subcutaneous islet transplants particularly appear to be reasonable foci for PET or SPECT imaging [184]. Transplanted islets at these known locations will possibly provide a chance to perform partial volume correction and an opportunity to quantitatively evaluate the exact concentration of imaging probes in the transplanted tissue [185]. These encouraging works have shown the feasibility of noninvasive *in vivo* imaging and monitoring of transplanted β-cells; however, the necessity to perform *ex vivo* transfection of cells and the short half-life of $^{18}$F (110 min) may limit further clinical translation of these technologies. Additionally, questions related to the distribution and persistence of the genetically altered cells need to be thoroughly investigated before clinical translation.

D2 receptors, also known as D2R, have been explored as a target for brain imaging since the 1980s [186,187]. Based on the neuroendocrine nature of islets, D2R were expected to be expressed on β-cells and this hypothesis was confirmed by several studies. In 2005, Rubi et al. showed excellent co-localization of D2R and insulin expression in both human and rodent islets [188]. Since then, the D2R has been exploited for noninvasively imaging insulinomas, congenital hyperinsulinism, and transplanted islets [189–192]. Iodobenzamide (IBZM) is another tracer which has high affinity and specificity for the D2R and has been previously used as a SPECT radiotracer in neurodegenerative diseases after labeling with $^{123}$I or $^{125}$I [193]. More recently, Willekens et al. found that $^{125}$I-IBZM specifically binds to isolated islets *in vitro*, and the authors further demonstrated the technical feasibility of $^{123}$I-IBZM SPECT/CT for non-invasively visualizing intramuscular islet grafts by targeting the D2 receptor *in vivo* [194]. More importantly, the intensity of $^{123}$I-IBZM on SPECT/CT images correlated with the volume of the insulin-positive grafts and also the revascularization, indicating the potential application of $^{123}$I-IBZM SPECT/CT in the quantification and longitudinal monitoring of grafted islets [195,196].

### 9.2. MRI probes

MRI contrast agents enhance the local contrast of an image, of which superparamagnetic iron oxides (SPIOs, also known as Feridex) were the most widely-used contrast agent for MR imaging of the liver and for MR cellular imaging because of their low toxicity and good sensitivity [197–200]. In general, SPIOs had relatively higher sensitivity than several other contrast agents and MRI-based cell tracking using SPIO particles had successfully been used clinically [201]. Although SPIO particles were able to modify local contrast, they were biodegradable and were also greatly affected by the *in vivo* microenvironment [202,203]. This was especially evident in the liver, because the liver is intrinsically rich in iron and Küpffer cells in liver can take up and then break down SPIO particles quickly [204]. In one study, SPIO-labeled islets were transplanted to the liver in four patients with T1DM, and MR imaging was performed prior to and after transplantation at several time points. For the first patient, diffuse hypointense signals caused by spontaneous high iron content in the liver were observed on her initial MRI images; therefore, she had to be excluded. For the remaining three patients, hypointense iron-loaded islets could be observed after transplantation on MR images [205]. However, due to lack of sales and poor performance in clinical trials, manufacturers ceased commercial production of Feridex and several other similar agents such as Resovist and Sinarem by 2009.

The feasibility of MR imaging and MR/optical dual-modality imaging in the monitoring of transplanted pancreatic islets has also been reported [197,206–208]. Studies have demonstrated that co-encapsulation of islets together with iron oxide nanoparticles [209], or perfluorocarbons [210], allowed noninvasive tracking of transplanted islets with MR or multimodal imaging, respectively. To further minimize the potential toxicity of the nanoparticles, Kim et al. fabricated "capsule-in-capsules" which consisted of gold, iron oxide, and islets, and further reported that this method enabled multimodality (MRI, CT, and US) imaging of the transplanted islets and maintained cell viability and glucose responsiveness. This formula had an improved insulin secretion and restored normal glycemia levels in STZ-induced diabetic mice models [211]. Lee et al. prepared magnetosome-like nanoparticles by coating ferromagnetic iron oxide nanocubes (FIONs) with polyethylene glycol-phospholipid, incubated rat pancreatic islets with the FIONs, and then intraportally infused the FION-labeled islets into STZ-induced diabetic rats. *In vivo* MRI studies showed that, while the transplanted syngeneic islets were clearly delineated as dark spots in the liver on T2 MR images and the signal lasted for up to 150 d, the hypointense spots of the transplanted allogeneic islets decreased gradually after transplantation (Fig. 4A–F) [212]. However, the long-term toxicity of these nanoparticles is still unknown, and these studies need to be performed before any clinical application.

Despite the promising progress of the above-mentioned approaches, noninvasive short-term imaging and long-term tracking of transplanted islets remains an obstacle in clinical settings. These reported techniques require manipulation of the transplanted islets either by pre-labeling or by genetic modification. Therefore, efforts are still needed to develop an *in vivo* imaging tracer with safe profiles to enable simple, reproducible monitoring of transplanted β-cells in patients [16].

## 10. Imaging insulinomas and β-cell hyperplasia

One of the most promising and useful clinical applications of noninvasive β-cell imaging lies in the visualization of insulinomas and β-cell hyperplasia [213,214]. Insulinoma, the most common cause of hypoglycemia in adult patients not diagnosed with diabetes, occurs in 1–4 cases per million of the general population and accounts for 1%–2% of all pancreatic malignancies [215,216]. Several radiotracers, including $^{18}$F-FDOPA [217–220], $^{11}$C-5-hydroxytryptophan ($^{11}$C-5-HTP) [221], and various imaging probes derived from exendin analogs [222,223], have been successfully used to detect insulinomas. Sweet et al. initially screened and identified several candidate molecules including L-DOPA as potential β-cell imaging agents [224]. Although several studies have shown that the relatively low *in vitro* binding specificity of L-DOPA to β-cells did not qualify this small molecule for further development as a PET imaging tracer to assess BCM, $^{18}$F-FDOPA could be used to noninvasively assess hyperinsulinism [27,225–228]. In addition to its role in detecting BCM and transplanted islets [229–231], $^{11}$C-5-HTP can also be used to detect neuroendocrine tumors due to high intracellular uptake of 5-HTP [232]. However, to increase tumor uptake and lower

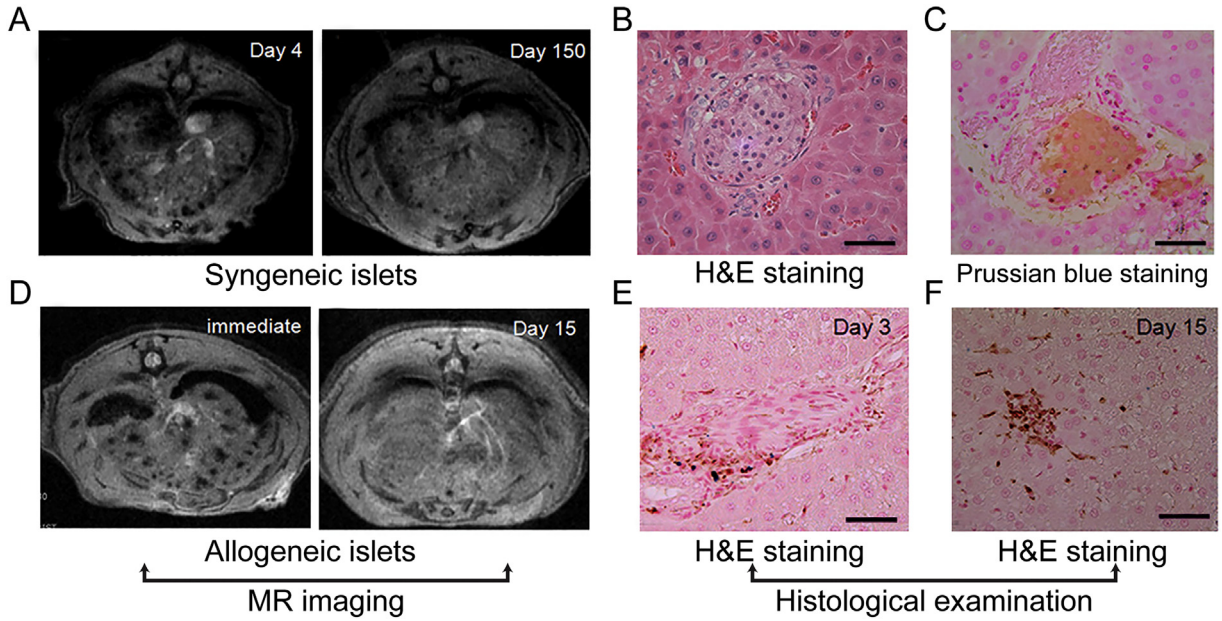


**Fig. 4.** MR images of intrahepatically transplanted syngeneic and allogeneic islets. (A) MR images of rat liver infused with FIONs-labeled syngeneic pancreatic islets at 4 d and 150 d after transplantation. The hypointense spots which represented labeled islets lasted for up to 150 d after transplantation. (B) H&E staining showed the normal structure of transplanted pancreatic islets in liver. (C) Prussian blue staining showed the presence of FIONs in islet β cells. (D) MR images of rat liver infused with FIONs-labeled allogeneic pancreatic islets immediately and 15 d after transplantation. The number of dark hypointense spots in the T2 MR image rapidly decreased after transplantation, indicating allograft rejection following the transplantation. (E) Immunohistochemical examination revealed iron in the islets 3 d after transplantation. (F) Clearance of the FIONs and infiltration of macrophages into the islets were observed.
Adapted with permission from [212].

physiological pancreatic uptake, patient premedication with carbidopa is generally needed for $^{18}$F-FDOPA and $^{11}$C-5-HTP PET imaging [233,234]. Furthermore, the dosage and the optimal protocol for carbidopa premedication are not definitively standardized in clinical practice [220].

While benign insulinomas express the GLP-1R at a high density and somatostatin receptors (SSTRs) in low levels, 73% of malignant insulinomas have high expression levels of SSTRs, with the remaining malignant insulinomas overexpressing GLP-1R [235,236]. In order to enhance the circulation and overcome the rapid degradation of GLP-1 *in vivo* by enzymes, a series of conformationally-constrained GLP-1 analogs have been developed [237]. One such example is EM3106B, which has an unnatural α-aminoisobutyric acid and multiple lactam bridges and has been labeled with $^{18}$F-FBEM [238]. Due to the challenge in synthesizing derivatives of EM3106B, Kiesewetter and colleagues modified exendin-4 with a cysteine to allow site-specific labeling with $^{18}$F-FBEM or aluminum $^{18}$F-fluoride [239,240]. Based on these encouraging preclinical results, initial clinical attempts found that $^{68}$Ga-labeled exendin-4 identified both occult and metastatic insulinomas [241–243]. A recent comparative study showed $^{68}$Ga-NOTA-exendin-4 identified 42 out of 43 histopathologically-proven insulinomas (Fig. 5), superior to $^{99m}$Tc-HYNIC-TOC SPECT/CT or other traditional imaging modalities [28]. The advantageous diagnostic value of PET over SPECT may result from improvements in partial-volume effects and superior spatial resolution, as was demonstrated by a recent study which compared the detection efficacies of $^{68}$Ga-DOTA-exendin-4 PET/CT and $^{111}$In-DOTA-exendin-4 SPECT/CT in patients with hidden insulinomas [243]. One of the critical factors in the realization of routine clinical examinations with an agent is the accessibility of the radiopharmaceutical. Considering that [$^{68}$Ga]Ga-DO3A-VSCys40-exendin-4 successfully localized multiple small liver and lymph node metastases from insulinomas and the fact that the tracer was prepared manually [241], Velikyan et al. further established automated production and quality control methods for preparing [$^{68}$Ga]Ga-DO3A-VSCys40-exendin-4 [244]. These efforts will certainly pave the way for broader clinical use of these tracers in the early and precise diagnosis of insulinomas.

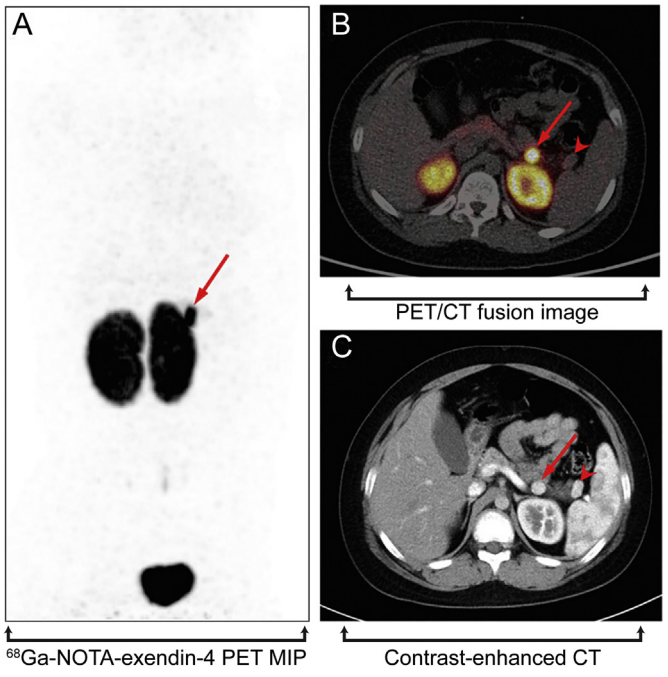


**Fig. 5.** Value of $^{68}$Ga-NOTA-exendin-4 in the preoperative localization of insulinoma. Maximum-intensity-projection PET image (A) and axial PET/CT fusion image (B) obtained from a 10-y-old boy 1 h after injection of 48.1 MBq of $^{68}$Ga-NOTA-exendin-4. Red arrow showed intense uptake in the body of the pancreas ($SUV_{max}$, 27.1) and a mass near the spleen without obvious radiotracer concentration. (C) Arterial-phase contrast-enhanced CT image from same patient further showed an enhanced insulinoma (red arrow) and intrapancreatic accessory spleen (red arrowhead), both of which were subsequently confirmed by pathological examination.
Adapted with permission from [28].

Notably, $^{64}$Cu-labeled dimeric exendin-4 subunit, which was designated as $^{64}$Cu-Mal$_2$Sar-(exendin-4)$_2$, showed higher tumor uptake than that of the monomeric exendin-4 subunit [245]. Besides the most commonly-used GLP-1R agonists exendin-3 and -4 and their derivatives, exendin (9-39) exhibits strong binding affinity for GLP-1R but is less likely to cause hypoglycemia [246,247]. As a result, radiolabeled derivatives of this peptide have also been investigated in the context of insulinoma. Kimura et al. reported that $^{111}$In-BnDTPA-exendin (9-39) clearly depicted tumors at 30 min post-injection in INS-1 tumor-bearing mice [248]. Theoretically, dual-targeting of GLP1-R and SSTR could thus localize all insulinomas. To this purpose, a hybrid peptide targeting both GLP-1R and SSTR has also been prepared and evaluated after labeling using $^{99m}$Tc, and the preliminary results from Medina-García et al. showed that the probe is successful in identifying GRP-1R- and SSTR- double positive tumors or tumors with either GRP-1R or SSTR expression [249,250].

## 11. Conclusions and future perspectives

Currently, diabetes mellitus is usually diagnosed by blood tests that measure glucose tolerance or abnormal glycosylation of hemoglobin (termed HbA$_{1c}$) [5, 251]. Ideally, diabetes should be diagnosed at a very early stage when the BCM and β-cell function have just changed. As the relatively small β-cell islets are scattered throughout the pancreas and constitute a minor part of the pancreas, and a highly β-cell-specific ligand for labeling is currently not available, imaging them is still very challenging [16,106,252]. Possible imaging techniques require several properties, such as high sensitivity, high spatial resolution, and low cost, which limit the feasible choices. Although the path leading from encouraging preclinical outcomes to bedside applications is not always easy, great efforts and long-term investments have been devoted to improve the diagnostic accuracy of diabetes/BCM in the laboratory using highly β-cell-specific molecular imaging probes [253]. Of the probes discussed above, GLP1-based imaging probes [28,101,107,118,179,254,255], manganese-based probes [34,45], and zinc-based probes [140], and several other probes emerge as the most promising candidates for β-cell imaging (Table 1).

Clinical translation of selected probes will facilitate early diagnosis of patients with diabetes and therefore timely intervention. Considering the fact that β-cells comprise only a small proportion of the total pancreatic mass and substantial variation in BCM exists between different individuals, the major value of β-cell imaging may lie in longitudinal studies where imaging results of two or more time points will indicate the dynamic changes of BCM in the same individual over time. In addition, noninvasive β-cell imaging methods will enable assessment of survival of transplanted islets [256], and precise detection of insulinomas [214].

For future development, there are several aspects that we may take into consideration when developing β-cell-specific probes. First, since tracers nonspecific for β-cells may lead to an overestimation of the BCM, future efforts should be devoted to discovering tracers of high sensitivity and specificity for β-cells. Hopefully, the most optimal candidates can be obtained by genome-wide loss-of-function screening and screening of the concomitant epigenetic, proteomic and metabolomic libraries [130,257–259]. For example, a recent study using proteomic screening methods identified G coupled protein GPR44 as a surrogate marker for β-cells [260], and follow-up studies reported that radiolabeled GPR44 ligands, [$^3$H]AZD 3825 [261], and [$^{11}$C]AZ12204657 [262], could be used to visualize β-cells *in vivo*. Interdisciplinary research and collaboration from the fields of chemistry, biology, radiology, and pharmacy will also allow great strides toward developing β-cell specific probes.

Secondly, longitudinal quantification and measurement are necessary to track the dynamic changes of BCM over time, especially for transplanted islets. This means that the tracer applied for imaging has to be non-toxic without damaging β-cells or other tissue. For this reason, radiomanganese PET/CT imaging, rather than other $Mn^{2+}$-based agents, seems to be a feasible method to assess BCM, since it uses far less tracer [45]. Radiolabeled exendin analogs can also be alternative options, as dosimetry studies showed that those probes had acceptable radiation-induced damage to islets in rats and humans [263]. While reporter gene-based β-cell imaging approaches showed great promise for monitoring islet transplantation [176,177], these methods rely on the *ex vivo* transfection of β-cells. Therefore, whether the manipulation and expression of foreign proteins will trigger immune responses or malignant transformation of the transfected cells needs to be addressed [264,265].

Additionally, molecular imaging has great potential for noninvasive and quantitative imaging of pancreatic β-cells, but each single imaging modality has its own intrinsic strengths and limitations. Functional imaging modalities have high sensitivity (such as SPECT and PET) and anatomical imaging techniques have high spatial resolution (such as CT and MRI) [266]. Therefore, a bimodal or multimodal approach may provide complementary quantitative and spatial information [165].

To conclude, the field of noninvasive β-cell imaging has progressed rapidly in the past two decades. With further development and clinical translation of β-cell imaging probes, it is hopeful that more personalized management strategies will be developed for patients with diabetes/insulinoma, and for patients who receive islet transplantation.

**Table 1**
Summary of representative β-cell specific probes illustrated in the present review.

| Probe | Target | Isotope | Imaging modality | Preclinical/clinical | Ref. |
|---|---|---|---|---|---|
| $^{18}$F-FDG | GLUT | $^{18}$F | PET | Clinical | [21] |
| Mn-DPDP | $Ca^{2+}$ channel | / | MRI | Clinical | [24] |
| $MnCl_2$ | $Ca^{2+}$ channel | / | MRI | Preclinical | [35] |
| $^{52}Mn^{2+}$ | $Ca^{2+}$ channel | $^{52}Mn^{2+}$ | PET | Preclinical | [45] |
| $^{11}$C-DTBZ | VMAT2 | $^{11}$C | PET | Clinical | [25] |
| $^{18}$F-AV-133 | VMAT2 | $^{18}$F | PET | Clinical | [26] |
| (+)-(*S*)-o-$^{18}$F-FMIT | SUR1 | $^{18}$F | PET | Preclinical | [92] |
| $^{111}$In-exendin | GLP-1R | $^{111}$In | SPECT | Preclinical | [103] |
| $^{68}$Ga-DO3A-exendin-4 | GLP-1R | $^{68}$Ga | PET | Preclinical | [105,108] |
| $^{89}$Zr-8/9-mAb | TMEM27 | $^{89}$Zr | PET | Preclinical | [126] |
| TAK875 | FFAR1 | $^{18}$F | PET | Preclinical | [146] |
| $^{18}$F-FBT | VAChT | $^{18}$F | PET | Preclinical | [152] |
| $^{64}$Cu-E4-Fl | GLP-1R | $^{64}$Cu | PET/NIR | Preclinical | [165] |
| Probe C | SUR1 | / | Fluorescence | Preclinical | [170] |
| $^{18}$F-TTCO-Cys40-exendin-4 | GLP-1R | $^{18}$F | PET | Preclinical | [183] |
| $^{123}$I-IBZM | D2 receptor | $^{123}$I | SPECT | Preclinical | [194] |
| $^{18}$F-FDOPA | Multiple targets | $^{18}$F | PET | Clinical | [27,227] |
| $^{11}$C-5-HTP | LAT | $^{11}$C | PET | Clinical | [230] |
| $^{68}$Ga-NOTA-exendin-4 | GLP-1R | $^{68}$Ga | PET | Clinical | [28] |

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## References

[1] P. Zhang, X. Zhang, J. Brown, D. Vistisen, R. Sicree, J. Shaw, G. Nichols, Global healthcare expenditure on diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (2010) 293–301.
[2] D. Dabelea, E.J. Mayer-Davis, S. Saydah, G. Imperatore, B. Linder, J. Divers, R. Bell, A. Badaru, J.W. Talton, T. Crume, A.D. Liese, A.T. Merchant, J.M. Lawrence, K. Reynolds, L. Dolan, L.L. Liu, R.F. Hamman, S.f.D.i.Y. Study, Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009, JAMA 311 (2014) 1778–1786.
[3] W.H. Organization, Global Report on Diabetes, World Health Organization, 2016.
[4] D.R. Whiting, L. Guariguata, C. Weil, J. Shaw, IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030, Diabetes Res. Clin. Pract. 94 (2011) 311–321.
[5] A. American Diabetes, 2. Classification and diagnosis of diabetes: standards of medical Care in diabetes-2018, Diabetes Care 41 (2018) S13–S27.
[6] T.L. van Belle, K.T. Coppieters, M.G. von Herrath, Type 1 diabetes: etiology, immunology, and therapeutic strategies, Physiol. Rev. 91 (2011) 79–118.
[7] J.F. Caro, L.G. Dohm, W.J. Pories, M.K. Sinha, Cellular alterations in liver, skeletal muscle, and adipose tissue responsible for insulin resistance in obesity and type II diabetes, Diabetes Metab. Rev. 5 (1989) 665–689.
[8] S. Guo, Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models into disease mechanisms, J. Endocrinol. 220 (2014) T1–T23.
[9] A.V. Matveyenko, P.C. Butler, Relationship between beta-cell mass and diabetes onset, Diabetes Obes. Metab. 10 (Suppl. 4) (2008) 23–31.
[10] A.E. Butler, J. Janson, S. Bonner-Weir, R. Ritzel, R.A. Rizza, P.C. Butler, β-Cell deficit and increased β-cell apoptosis in humans with type 2 diabetes, Diabetes 52 (2003) 102–110.
[11] D.R. Laybutt, H. Kaneto, W. Hasenkamp, S. Grey, J.-C. Jonas, D.C. Sgroi, A. Groff, C. Ferran, S. Bonner-Weir, A. Sharma, Increased expression of antioxidant and antiapoptotic genes in islets that may contribute to β-cell survival during chronic hyperglycemia, Diabetes 51 (2002) 413–423.
[12] G.C. Weir, S. Bonner-Weir, Five stages of evolving beta-cell dysfunction during progression to diabetes, Diabetes 53 (2004) S16–S21.
[13] R.P. Robertson, Estimation of beta-cell mass by metabolic tests: necessary, but how sufficient? Diabetes 56 (2007) 2420–2424.
[14] O. Eriksson, M. Laughlin, M. Brom, P. Nuutila, M. Roden, A. Hwa, R. Bonadonna, M. Gotthardt, In vivo imaging of beta cells with radiotracers: state of the art, prospects and recommendations for development and use, Diabetologia 59 (2016) 1340–1349.
[15] V. Di Gialleonardo, E.F. de Vries, M. Di Girolamo, A.M. Quintero, R.A. Dierckx, A. Signore, Imaging of beta-cell mass and insulitis in insulin-dependent (Type 1) diabetes mellitus, Endocr. Rev. 33 (2012) 892–919.
[16] K. Andralojc, M. Srinivas, M. Brom, L. Joosten, I.J. de Vries, D.L. Eizirik, O.C. Boerman, P. Meda, M. Gotthardt, Obstacles on the way to the clinical visualisation of beta cells: looking for the Aeneas of molecular imaging to navigate between Scylla and Charybdis, Diabetologia 55 (2012) 1247–1257.
[17] B.A. Blomberg, I. Codreanu, G. Cheng, T.J. Werner, A. Alavi, Beta-cell imaging: call for evidence-based and scientific approach, Mol. Imaging Biol. 15 (2013) 123–130.
[18] D. Laurent, L. Vinet, S. Lamprianou, M. Daval, G. Filhoulaud, A. Ktorza, H. Wang, S. Sewing, H.P. Juretschke, H. Glombik, P. Meda, R. Boisgard, D.L. Nguyen, G.J. Stasiuk, N.J. Long, X. Montet, P. Hecht, W. Kramer, G.A. Rutter, J. Hecksher-Sorensen, Pancreatic beta-cell imaging in humans: fiction or option? Diabetes Obes. Metab. 18 (2016) 6–15.
[19] C. Toso, H. Zaidi, P. Morel, M. Armanet, A. Andres, N. Pernin, R. Baertschiger, D. Slosman, L.H. Buhler, D. Bosco, T. Berney, Positron-emission tomography imaging of early events after transplantation of islets of Langerhans, Transplantation 79 (2005) 353–355.
[20] O. Eriksson, T. Eich, A. Sundin, A. Tibell, G. Tufveson, H. Andersson, M. Felldin, A. Foss, L. Kyllonen, B. Langstrom, B. Nilsson, O. Korsgren, T. Lundgren, Positron emission tomography in clinical islet transplantation, Am. J. Transplant. 9 (2009) 2816–2824.
[21] W.J. Malaisse, P. Damhaut, F. Malaisse-Lagae, L. Ladriere, E. Olivares, S. Goldman, Fate of 2-deoxy-2-[18F]fluoro-D-glucose in control and diabetic rats, Int. J. Mol. Med. 5 (2000) 525–532.
[22] Z. Wu, F. Kandeel, Radionuclide probes for molecular imaging of pancreatic beta-cells, Adv. Drug Deliv. Rev. 62 (2010) 1125–1138.
[23] P.E. Harris, R.L. Leibel, Neurofunctional imaging of beta-cell dynamics, Diabetes Obes. Metab. 14 (Suppl. 3) (2012) 91–100.
[24] D. Botsikas, S. Terraz, L. Vinet, S. Lamprianou, C.D. Becker, D. Bosco, P. Meda, X. Montet, Pancreatic magnetic resonance imaging after manganese injection distinguishes type 2 diabetic and normoglycemic patients, Islets 4 (2012) 243–248.
[25] R. Goland, M. Freeby, R. Parsey, Y. Saisho, D. Kumar, N. Simpson, J. Hirsch, M. Prince, A. Maffei, J.J. Mann, P.C. Butler, R. Van Heertum, R.L. Leibel, M. Ichise, P.E. Harris, 11C-dihydrotetrabenazine PET of the pancreas in subjects with long-standing type 1 diabetes and in healthy controls, J. Nucl. Med. 50 (2009) 382–389.
[26] M.D. Normandin, K.F. Petersen, Y.S. Ding, S.F. Lin, S. Naik, K. Fowles, D.M. Skovronsky, K.C. Herold, T.J. McCarthy, R.A. Calle, R.E. Carson, J.L. Treadway, G.W. Cline, In vivo imaging of endogenous pancreatic beta-cell mass in healthy and type 1 diabetic subjects using 18F-fluoropropyl-dihydrotetrabenazine and PET, J. Nucl. Med. 53 (2012) 908–916.
[27] H. Minn, S. Kauhanen, M. Seppanen, P. Nuutila, 18F-FDOPA: a multiple-target molecule, J. Nucl. Med. 50 (2009) 1915–1918.
[28] Y. Luo, Q. Pan, S. Yao, M. Yu, W. Wu, H. Xue, D.O. Kiesewetter, Z. Zhu, F. Li, Y. Zhao, X. Chen, Glucagon-like peptide-1 receptor PET/CT with 68Ga-NOTA-exendin-4 for detecting localized insulinoma: a prospective cohort study, J. Nucl. Med. 57 (2016) 715–720.
[29] L. Leoni, S.D. Serai, M.E. Haque, R.L. Magin, B.B. Roman, Functional MRI characterization of isolated human islet activation, NMR Biomed. 23 (2010) 1158–1165.
[30] B. Gimi, L. Leoni, J. Oberholzer, M. Braun, J. Avila, Y. Wang, T. Desai, L.H. Philipson, R.L. Magin, B.B. Roman, Functional MR microimaging of pancreatic beta-cell activation, Cell Transplant. 15 (2006) 195–203.
[31] M. Nagata, T. Kagawa, D. Koutou, T. Matsushita, Y. Yamazaki, K. Murase, Measurement of manganese content in various organs in rats with or without glucose stimulation, Radiol. Phys. Technol. 4 (2011) 7–12.
[32] P.F. Antkowiak, S.A. Tersey, J.D. Carter, M.H. Vandsburger, J.L. Nadler, F.H. Epstein, R.G. Mirmira, Noninvasive assessment of pancreatic beta-cell function in vivo with manganese-enhanced magnetic resonance imaging, Am. J. Physiol. Endocrinol. Metab. 296 (2009) E573–E578.
[33] S. Lamprianou, R. Immonen, C. Nabuurs, A. Gjinovci, L. Vinet, X.C. Montet, R. Gruetter, P. Meda, High-resolution magnetic resonance imaging quantitatively detects individual pancreatic islets, Diabetes 60 (2011) 2853–2860.
[34] P.F. Antkowiak, B.K. Stevens, C.S. Nunemaker, M. McDuffie, F.H. Epstein, Manganese-enhanced magnetic resonance imaging detects declining pancreatic beta-cell mass in a cyclophosphamide-accelerated mouse model of type 1 diabetes, Diabetes 62 (2013) 44–48.
[35] A. Meyer, K. Stolz, W. Dreher, J. Bergemann, V. Holebasavanahalli Thimmashetty, N. Lueschen, Z. Azizi, V. Khobragade, K. Maedler, E. Kuestermann, Manganese-mediated MRI signals correlate with functional beta-cell mass during diabetes progression, Diabetes 64 (2015) 2138–2147.
[36] D. Bosco, M. Armanet, P. Morel, N. Niclauss, A. Sgroi, Y.D. Muller, L. Giovannoni, G. Parnaud, T. Berney, Unique arrangement of alpha- and beta-cells in human islets of Langerhans, Diabetes 59 (2010) 1202–1210.
[37] C.W. Olanow, Manganese-induced parkinsonism and Parkinson's disease, Ann. N. Y. Acad. Sci. 1012 (2004) 209–223.
[38] J.A. Roth, M.D. Garrick, Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese, Biochem. Pharmacol. 66 (2003) 1–13.
[39] J.H. Lee, A.C. Silva, H. Merkle, A.P. Koretsky, Manganese-enhanced magnetic resonance imaging of mouse brain after systemic administration of MnCl2: dose-dependent and temporal evolution of T1 contrast, Magn. Reson. Med. 53 (2005) 640–648.
[40] A. Jodal, R. Schibli, M. Behe, Targets and probes for non-invasive imaging of beta-cells, Eur. J. Nucl. Med. Mol. Imaging 44 (2017) 712–727.
[41] S. Goel, C.G. England, F. Chen, W. Cai, Positron emission tomography and nanotechnology: a dynamic duo for cancer theranostics, Adv. Drug Deliv. Rev. 113 (2017) 157–176.
[42] J. Culver, W. Akers, S. Achilefu, Multimodality molecular imaging with combined optical and SPECT/PET modalities, J. Nucl. Med. 49 (2008) 169–172.
[43] E.B. Ehlerding, W. Cai, Harnessing the power of molecular imaging for precision medicine, J. Nucl. Med. 57 (2016) 171–172.
[44] S.A. Graves, R. Hernandez, H.F. Valdovinos, P.A. Ellison, J.W. Engle, T.E. Barnhart, W. Cai, R.J. Nickles, Preparation and in vivo characterization of 51MnCl2 as PET tracer of Ca2+ channel-mediated transport, Sci. Rep. 7 (2017) 3033.
[45] R. Hernandez, S.A. Graves, T. Gregg, H.R. VanDeusen, R.J. Fenske, H.N. Wienkes, C.G. England, H.F. Valdovinos, J.J. Jeffery, T.E. Barnhart, G.W. Severin, R.J. Nickles, M.E. Kimple, M.J. Merrins, W. Cai, Radiomanganese PET detects changes in functional beta-cell mass in mouse models of diabetes, Diabetes 66 (2017) 2163–2174.
[46] A. Maffei, Z. Liu, P. Witkowski, F. Moschella, G. Del Pozzo, E. Liu, K. Herold, R.J. Winchester, M.A. Hardy, P.E. Harris, Identification of tissue-restricted transcripts in human islets, Endocrinology 145 (2004) 4513–4521.
[47] M. Anlauf, R. Eissele, M.K. Schafer, L.E. Eiden, R. Arnold, U. Pauser, G. Kloppel, E. Weihe, Expression of the two isoforms of the vesicular monoamine transporter (VMAT1 and VMAT2) in the endocrine pancreas and pancreatic endocrine tumors, J. Histochem. Cytochem. 51 (2003) 1027–1040.
[48] E. Weihe, L.E. Eiden, Chemical neuroanatomy of the vesicular amine transporters, FASEB J. 14 (2000) 2435–2449.
[49] J.N. DaSilva, M.R. Kilbourn, T.J. Mangner, Synthesis of a [11C]methoxy derivative of alpha-dihydrotetrabenazine: a radioligand for studying the vesicular monoamine transporter, Appl. Radiat. Isot. 44 (1993) 1487–1489.
[50] J.N. DaSilva, J.E. Carey, P.S. Sherman, T.J. Pisani, M.R. Kilbourn, Characterization of [11C]tetrabenazine as an in vivo radioligand for the vesicular monoamine transporter, Nucl. Med. Biol. 21 (1994) 151–156.
[51] R.A. Koeppe, K.A. Frey, T.M. Vander Borght, A. Karlamangla, D.M. Jewett, L.C. Lee, M.R. Kilbourn, D.E. Kuhl, Kinetic evaluation of [11C]dihydrotetrabenazine by dynamic PET: measurement of vesicular monoamine transporter, J. Cereb. Blood Flow Metab. 16 (1996) 1288–1299.

[52] N.R. Simpson, F. Souza, P. Witkowski, A. Maffei, A. Raffo, A. Herron, M. Kilbourn, A. Jurewicz, K. Herold, E. Liu, M.A. Hardy, R. Van Heertum, P.E. Harris, Visualizing pancreatic beta-cell mass with [11C]DTBZ, Nucl. Med. Biol. 33 (2006) 855–864.

[53] F. Souza, N. Simpson, A. Raffo, C. Saxena, A. Maffei, M. Hardy, M. Kilbourn, R. Goland, R. Leibel, J.J. Mann, R. Van Heertum, P.E. Harris, Longitudinal noninvasive PET-based beta cell mass estimates in a spontaneous diabetes rat model, J. Clin. Invest. 116 (2006) 1506–1513.

[54] P.E. Harris, C. Ferrara, P. Barba, T. Polito, M. Freeby, A. Maffei, VMAT2 gene expression and function as it applies to imaging beta-cell mass, J. Mol. Med. (Berl.) 86 (2008) 5–16.

[55] M. Freeby, R. Goland, M. Ichise, A. Maffei, R. Leibel, P. Harris, VMAT2 quantitation by PET as a biomarker for beta-cell mass in health and disease, Diabetes Obes. Metab. 10 (Suppl. 4) (2008) 98–108.

[56] W.B. Inabnet, L. Milone, P. Harris, E. Durak, M.J. Freeby, L. Ahmed, M. Sebastian, J.C. Lifante, M. Bessler, J. Korner, The utility of [(11)C] dihydrotetrabenazine positron emission tomography scanning in assessing beta-cell performance after sleeve gastrectomy and duodenal-jejunal bypass, Surgery 147 (2010) 303–309.

[57] H.F. Kung, B.P. Lieberman, Z.P. Zhuang, S. Oya, M.P. Kung, S.R. Choi, K. Poessl, E. Blankemeyer, C. Hou, D. Skovronsky, M. Kilbourn, In vivo imaging of vesicular monoamine transporter 2 in pancreas using an (18)F epoxide derivative of tetrabenazine, Nucl. Med. Biol. 35 (2008) 825–837.

[58] M.P. Kung, C. Hou, B.P. Lieberman, S. Oya, D.E. Ponde, E. Blankemeyer, D. Skovronsky, M.R. Kilbourn, H.F. Kung, In vivo imaging of beta-cell mass in rats using 18F-FP-(+)-DTBZ: a potential PET ligand for studying diabetes mellitus, J. Nucl. Med. 49 (2008) 1171–1176.

[59] T. Singhal, Y.S. Ding, D. Weinzimmer, M.D. Normandin, D. Labaree, J. Ropchan, N. Nabulsi, S.F. Lin, M.B. Skaddan, W.C. Soeller, Y. Huang, R.E. Carson, J.L. Treadway, G.W. Cline, Pancreatic beta cell mass PET imaging and quantification with [11C] DTBZ and [18F]FP-(+)-DTBZ in rodent models of diabetes, Mol. Imaging Biol. 13 (2011) 973–984.

[60] O. Eriksson, M. Jahan, P. Johnstrom, O. Korsgren, A. Sundin, C. Halldin, L. Johansson, In vivo and in vitro characterization of [18F]-FE-(+)-DTBZ as a tracer for beta-cell mass, Nucl. Med. Biol. 37 (2010) 357–363.

[61] H.H. Tsao, K.J. Lin, J.H. Juang, D.M. Skovronsky, T.C. Yen, S.P. Wey, M.P. Kung, Binding characteristics of 9-fluoropropyl-(+)-dihydrotetrabenzazine (AV-133) to the vesicular monoamine transporter type 2 in rats, Nucl. Med. Biol. 37 (2010) 413–419.

[62] K.J. Lin, Y.H. Weng, S.P. Wey, I.T. Hsiao, C.S. Lu, D. Skovronsky, H.P. Chang, M.P. Kung, T.C. Yen, Whole-body biodistribution and radiation dosimetry of 18F-FP-(+)-DTBZ (18F-AV-133): a novel vesicular monoamine transporter 2 imaging agent, J. Nucl. Med. 51 (2010) 1480–1485.

[63] M.J. Freeby, P. Kringas, R.S. Goland, R.L. Leibel, A. Maffei, C. Divgi, M. Ichise, P.E. Harris, Cross-sectional and test-retest characterization of PET with [(18)F]FP-(+)-DTBZ for beta cell mass estimates in diabetes, Mol. Imaging Biol. 18 (2016) 292–301.

[64] V. Fagerholm, K.K. Mikkola, T. Ishizu, E. Arponen, S. Kauhanen, K. Nagren, O. Solin, P. Nuutila, M. Haaparanta, Assessment of islet specificity of dihydrotetrabenazine radiotracer binding in rat pancreas and human pancreas, J. Nucl. Med. 51 (2010) 1439–1446.

[65] J. Virostko, J. Henske, L. Vinet, S. Lamprianou, C. Dai, A. Radhika, R.M. Baldwin, M.S. Ansari, F. Hefti, D. Skovronsky, H.F. Kung, P.L. Herrera, T.E. Peterson, P. Meda, A.C. Powers, Multimodal image coregistration and inducible selective cell ablation to evaluate imaging ligands, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 20719–20724.

[66] T.C. Kwee, S. Basu, B. Saboury, D.A. Torigian, A. Naji, A. Alavi, Beta-cell imaging: opportunities and limitations, J. Nucl. Med. 52 (2011) 493 (author reply 493–495).

[67] M. Ichise, P.E. Harris, Imaging of beta-cell mass and function, J. Nucl. Med. 51 (2010) 1001–1004.

[68] M. Naganawa, S.F. Lin, K. Lim, D. Labaree, J. Ropchan, P. Harris, Y. Huang, M. Ichise, R.E. Carson, G.W. Cline, Evaluation of pancreatic VMAT2 binding with active and inactive enantiomers of 18F-FP-DTBZ in baboons, Nucl. Med. Biol. 43 (2016) 743–751.

[69] M. Naganawa, K. Lim, N.B. Nabulsi, S.F. Lin, D. Labaree, J. Ropchan, K.C. Herold, Y. Huang, P. Harris, M. Ichise, G.W. Cline, R.E. Carson, Evaluation of pancreatic VMAT2 binding with active and inactive enantiomers of [(18)F]FP-DTBZ in healthy subjects and patients with type 1 diabetes, Mol. Imaging Biol. (2018) 1–11.

[70] K. Goda, E. Sasaki, K. Nagata, M. Fukai, N. Ohsawa, T. Hahafusa, Pancreatic volume in type 1 and type 2 diabetes mellitus, Acta Diabetol. 38 (2001) 145–149.

[71] A.J. Williams, W. Chau, M.P. Callaway, C.M. Dayan, Magnetic resonance imaging: a reliable method for measuring pancreatic volume in Type 1 diabetes, Diabet. Med. 24 (2007) 35–40.

[72] M. Hickeson, M. Yun, A. Matthies, H. Zhuang, L.E. Adam, L. Lacorte, A. Alavi, Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET, Eur. J. Nucl. Med. Mol. Imaging 29 (2002) 1639–1647.

[73] A. Sanchez-Crespo, P. Andreo, S.A. Larsson, Positron flight in human tissues and its influence on PET image spatial resolution, Eur. J. Nucl. Med. Mol. Imaging 31 (2004) 44–51.

[74] S. Basu, H. Zaidi, M. Houseni, G. Bural, J. Udupa, P. Acton, D.A. Torigian, A. Alavi, Novel quantitative techniques for assessing regional and global function and structure based on modern imaging modalities: implications for normal variation, aging and diseased states, Semin. Nucl. Med. 37 (2007) 223–239.

[75] Y. Saisho, P.E. Harris, A.E. Butler, R. Galasso, T. Gurlo, R.A. Rizza, P.C. Butler, Relationship between pancreatic vesicular monoamine transporter 2 (VMAT2) and insulin expression in human pancreas, J. Mol. Histol. 39 (2008) 543–551.

[76] P.E. Harris, M.D. Farwell, M. Ichise, PET quantification of pancreatic VMAT 2 binding using (+) and (−) enantiomers of [(1)(8)F]FP-DTBZ in baboons, Nucl. Med. Biol. 40 (2013) 60–64.

[77] K.F. Raab-Graham, L.J. Cirilo, A.A. Boettcher, C.M. Radeke, C.A. Vandenberg, Membrane topology of the amino-terminal region of the sulfonylurea receptor, J. Biol. Chem. 274 (1999) 29122–29129.

[78] L. Aguilar-Bryan, J.P. Clement IV, G. Gonzalez, K. Kunjilwar, A. Babenko, J. Bryan, Toward understanding the assembly and structure of KATP channels, Physiol. Rev. 78 (1998) 227–245.

[79] L. Ladriere, F. Malaisse-Lagae, W.J. Malaisse, Uptake of tritiated glibenclamide by endocrine and exocrine pancreas, Endocrine 12 (2000) 329–332.

[80] P.E. MacDonald, J.W. Joseph, P. Rorsman, Glucose-sensing mechanisms in pancreatic beta-cells, Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 360 (2005) 2211–2225.

[81] Y. Guiot, M. Stevens, I. Marhfour, P. Stiernet, M. Mikhailov, S.J. Ashcroft, J. Rahier, J.C. Henquin, C. Sempoux, Morphological localisation of sulfonylurea receptor 1 in endocrine cells of human, mouse and rat pancreas, Diabetologia 50 (2007) 1889–1899.

[82] J.L. Carpentier, F. Sawano, M. Ravazzola, W.J. Malaisse, Internalization of 3H-glibenclamide in pancreatic islet cells, Diabetologia 29 (1986) 259–261.

[83] G.G. Shiue, R. Schirrmacher, C.Y. Shiue, A.A. Alavi, Synthesis of fluorine-18 labeled sulfonureas as β-cell imaging agents, J. Label. Compd. Radiopharm. 44 (2001) 127–139.

[84] R. Schirrmacher, M. Weber, A. Schmitz, C.Y. Shiue, A.A. Alavi, P. Feilen, S. Schneider, P. Kann, F. Rösch, Radiosynthesis of 1-(4-(2-[18F] fluoroethoxy) benzenesulfonyl)-3-butyl urea: a potential β-cell imaging agent, J. Label. Compd. Radiopharm. 45 (2002) 763–774.

[85] S. Schneider, P.J. Feilen, M. Schreckenberger, M. Schwanstecher, C. Schwanstecher, H.G. Buchholz, O. Thews, K. Oberholzer, A. Korobeynikov, A. Bauman, S. Comagic, M. Piel, E. Schirrmacher, C.Y. Shiue, A.A. Alavi, P. Bartenstein, F. Rosch, M.M. Weber, H.H. Klein, R. Schirrmacher, In vitro and in vivo evaluation of novel glibenclamide derivatives as imaging agents for the non-invasive assessment of the pancreatic islet cell mass in animals and humans, Exp. Clin. Endocrinol. Diabetes 113 (2005) 388–395.

[86] N. Tournier, W. Saba, S. Cisternino, M.A. Peyronneau, A. Damont, S. Goutal, A. Dubois, F. Dolle, J.M. Scherrmann, H. Valette, B. Kuhnast, M. Bottlaender, Effects of selected OATP and/or ABC transporter inhibitors on the brain and whole-body distribution of glyburide, AAPS J. 15 (2013) 1082–1090.

[87] S. Schneider, S. Ueberberg, A. Korobeynikov, W. Schechinger, C. Schwanstecher, M. Schwanstecher, H.H. Klein, E. Schirrmacher, Synthesis and evaluation of a glibenclamide glucose-conjugate: a potential new lead compound for substituted glibenclamide derivatives as islet imaging agents, Regul. Pept. 139 (2007) 122–127.

[88] L.J. Scott, Repaglinide: a review of its use in type 2 diabetes mellitus, Drugs 72 (2012) 249–272.

[89] B. Wangler, S. Schneider, O. Thews, E. Schirrmacher, S. Comagic, P. Feilen, C. Schwanstecher, M. Schwanstecher, C.Y. Shiue, A. Alavi, S. Hohnemann, M. Piel, F. Rosch, R. Schirrmacher, Synthesis and evaluation of (*S*)-2-(2-[18F]fluoroethoxy)-4-([3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbam oyl]-methyl)-benzoic acid ([18F]repaglinide): a promising radioligand for quantification of pancreatic beta-cell mass with positron emission tomography (PET), Nucl. Med. Biol. 31 (2004) 639–647.

[90] B. Wangler, C. Beck, C.Y. Shiue, S. Schneider, C. Schwanstecher, M. Schwanstecher, P.J. Feilen, A. Alavi, F. Rosch, R. Schirrmacher, Synthesis and in vitro evaluation of (*S*)-2-([11C]methoxy)-4-[3-methyl-1-(2-piperidine-1-yl-phenyl)-butyl-carbamoyl]-be nzoic acid ([11C]methoxy-repaglinide): a potential beta-cell imaging agent, Bioorg. Med. Chem. Lett. 14 (2004) 5205–5209.

[91] W.J. Malaisse, K. Louchami, A. Sener, Noninvasive imaging of pancreatic beta cells, Nat. Rev. Endocrinol. 5 (2009) 394–400.

[92] H. Kimura, H. Matsuda, H. Fujimoto, K. Arimitsu, K. Toyoda, E. Mukai, H. Nakamura, Y. Ogawa, M. Takagi, M. Ono, N. Inagaki, H. Saji, Synthesis and evaluation of 18F-labeled mitiglinide derivatives as positron emission tomography tracers for beta-cell imaging, Bioorg. Med. Chem. 22 (2014) 3270–3278.

[93] A. Schmitz, C.Y. Shiue, Q. Feng, G.G. Shiue, S. Deng, M.T. Pourdehnad, R. Schirrmacher, M. Vatamaniuk, N. Doliba, F. Matschinsky, B. Wolf, F. Rosch, A. Naji, A.A. Alavi, Synthesis and evaluation of fluorine-18 labeled glyburide analogs as beta-cell imaging agents, Nucl. Med. Biol. 31 (2004) 483–491.

[94] A.R. Meloni, M.B. DeYoung, C. Lowe, D.G. Parkes, GLP-1 receptor activated insulin secretion from pancreatic beta-cells: mechanism and glucose dependence, Diabetes Obes. Metab. 15 (2013) 15–27.

[95] M.E. Doyle, J.M. Egan, Mechanisms of action of glucagon-like peptide 1 in the pancreas, Pharmacol. Ther. 113 (2007) 546–593.

[96] P. Richards, H.E. Parker, A.E. Adriaenssens, J.M. Hodgson, S.C. Cork, S. Trapp, F.M. Gribble, F. Reimann, Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model, Diabetes 63 (2014) 1224–1233.

[97] B.L. Furman, The development of Byetta (exenatide) from the venom of the Gila monster as an anti-diabetic agent, Toxicon 59 (2012) 464–471.

[98] S. Runge, H. Thogersen, K. Madsen, J. Lau, R. Rudolph, Crystal structure of the ligand-bound glucagon-like peptide-1 receptor extracellular domain, J. Biol. Chem. 283 (2008) 11340–11347.

[99] M. Briones, M. Bajaj, Exenatide: a GLP-1 receptor agonist as novel therapy for Type 2 diabetes mellitus, Expert. Opin. Pharmacother. 7 (2006) 1055–1064.

[100] J. Eng, W.A. Kleinman, L. Singh, G. Singh, J.P. Raufman, Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas, J. Biol. Chem. 267 (1992) 7402–7405.

[101] T. Reiner, G. Thurber, J. Gaglia, C. Vinegoni, C.W. Liew, R. Upadhyay, R.H. Kohler, L. Li, R.N. Kulkarni, C. Benoist, D. Mathis, R. Weissleder, Accurate measurement of pancreatic islet beta-cell mass using a second-generation fluorescent exendin-4 analog, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 12815–12820.
[102] S.M. Clardy, E.J. Keliher, J.F. Mohan, M. Sebas, C. Benoist, D. Mathis, R. Weissleder, Fluorescent exendin-4 derivatives for pancreatic beta-cell analysis, Bioconjug. Chem. 25 (2014) 171–177.
[103] M. Brom, L. Joosten, C. Frielink, O. Boerman, M. Gotthardt, (111)In-exendin uptake in the pancreas correlates with the beta-cell mass and not with the alpha-cell mass, Diabetes 64 (2015) 1324–1328.
[104] K. Mikkola, C.B. Yim, V. Fagerholm, T. Ishizu, V.V. Elomaa, J. Rajander, J. Jurttila, T. Saanijoki, T. Tolvanen, M. Tirri, E. Gourni, M. Behe, M. Gotthardt, J.C. Reubi, H. Macke, A. Roivainen, O. Solin, P. Nuutila, 64Cu- and 68Ga-labelled [Nle(14),Lys(40)(Ahx-NODAGA)NH2]-exendin-4 for pancreatic beta cell imaging in rats, Mol. Imaging Biol. 16 (2014) 255–263.
[105] R.K. Selvaraju, I. Velikyan, L. Johansson, Z. Wu, I. Todorov, J. Shively, F. Kandeel, O. Korsgren, O. Eriksson, In vivo imaging of the glucagonlike peptide 1 receptor in the pancreas with 68Ga-labeled DO3A-exendin-4, J. Nucl. Med. 54 (2013) 1458–1463.
[106] P. Wang, B. Yoo, J. Yang, X. Zhang, A. Ross, P. Pantazopoulos, G. Dai, A. Moore, GLP-1R-targeting magnetic nanoparticles for pancreatic islet imaging, Diabetes 63 (2014) 1465–1474.
[107] D. Wild, M. Behe, A. Wicki, D. Storch, B. Waser, M. Gotthardt, B. Keil, G. Christofori, J.C. Reubi, H.R. Macke, [Lys40(Ahx-DTPA-111In)NH2]exendin-4, a very promising ligand for glucagon-like peptide-1 (GLP-1) receptor targeting, J. Nucl. Med. 47 (2006) 2025–2033.
[108] L. Nalin, R.K. Selvaraju, I. Velikyan, M. Berglund, S. Andreasson, A. Wikstrand, A. Ryden, M. Lubberink, F. Kandeel, G. Nyman, O. Korsgren, O. Eriksson, M. Jensen-Waern, Positron emission tomography imaging of the glucagon-like peptide-1 receptor in healthy and streptozotocin-induced diabetic pigs, Eur. J. Nucl. Med. Mol. Imaging 41 (2014) 1800–1810.
[109] J. Eng, Exendin peptides, Mt Sinai J. Med. 59 (1992) 147–149.
[110] M. Gotthardt, G. Lalyko, J. van Eerd-Vismale, B. Keil, T. Schurrat, M. Hower, P. Laverman, T.M. Behr, O.C. Boerman, B. Goke, M. Behe, A new technique for in vivo imaging of specific GLP-1 binding sites: first results in small rodents, Regul. Pept. 137 (2006) 162–167.
[111] E. Mukai, K. Toyoda, H. Kimura, H. Kawashima, H. Fujimoto, M. Ueda, T. Temma, K. Hirao, K. Nagakawa, H. Saji, N. Inagaki, GLP-1 receptor antagonist as a potential probe for pancreatic beta-cell imaging, Biochem. Biophys. Res. Commun. 389 (2009) 523–526.
[112] H. Kimura, N. Fujita, K. Kanbe, H. Matsuda, H. Watanabe, K. Arimitsu, H. Fujimoto, K. Hamamatsu, Y. Yagi, M. Ono, N. Inagaki, H. Saji, Synthesis and biological evaluation of an (111)In-labeled exendin-4 derivative as a single-photon emission computed tomography probe for imaging pancreatic beta-cells, Bioorg. Med. Chem. 25 (2017) 5772–5778.
[113] M. Brom, W. Woliner-van der Weg, L. Joosten, C. Frielink, T. Bouckenooghe, P. Rijken, K. Andralojc, B.J. Goke, M. de Jong, D.L. Eizirik, M. Behe, T. Lahoutte, W.J. Oyen, C.J. Tack, M. Janssen, O.C. Boerman, M. Gotthardt, Non-invasive quantification of the beta cell mass by SPECT with (1)(1)(1)In-labelled exendin, Diabetologia 57 (2014) 950–959.
[114] W. Woliner-van der Weg, L.N. Deden, A.P. Meeuwis, M. Koenrades, L.H. Peeters, H. Kuipers, G.J. Laanstra, M. Gotthardt, C.H. Slump, E.P. Visser, A 3D-printed anatomical pancreas and kidney phantom for optimizing SPECT/CT reconstruction settings in beta cell imaging using 111In-exendin, EJNMMI Phys. 3 (2016) 29.
[115] Y. Wang, K. Lim, M. Normandin, X. Zhao, G.W. Cline, Y.S. Ding, Synthesis and evaluation of [18F]exendin (9-39) as a potential biomarker to measure pancreatic beta-cell mass, Nucl. Med. Biol. 39 (2012) 167–176.
[116] H. Kimura, Y. Ogawa, H. Fujimoto, E. Mukai, H. Kawashima, K. Arimitsu, K. Toyoda, N. Fujita, Y. Yagi, K. Hamamatsu, T. Murakami, A. Murakami, M. Ono, Y. Nakamoto, K. Togashi, N. Inagaki, H. Saji, Evaluation of (18)F-labeled exendin(9-39) derivatives targeting glucagon-like peptide-1 receptor for pancreatic beta-cell imaging, Bioorg. Med. Chem. 26 (2018) 463–469.
[117] B. Mi, Y. Xu, D. Pan, L. Wang, R. Yang, C. Yu, W. Wan, Y. Wu, M. Yang, Non-invasive glucagon-like peptide-1 receptor imaging in pancreas with (18)F-Al labeled Cys(39)-exendin-4, Biochem. Biophys. Res. Commun. 471 (2016) 47–51.
[118] B.M. Connolly, A. Vanko, P. McQuade, I. Guenther, X. Meng, D. Rubins, R. Waterhouse, R. Hargreaves, C. Sur, E. Hostetler, Ex vivo imaging of pancreatic beta cells using a radiolabeled GLP-1 receptor agonist, Mol. Imaging Biol. 14 (2012) 79–87.
[119] S.M. Willekens, L. Joosten, O.C. Boerman, A. Balhuizen, D.L. Eizirik, M. Gotthardt, M. Brom, Strain differences determine the suitability of animal models for noninvasive in vivo beta cell mass determination with radiolabeled exendin, Mol. Imaging Biol. 18 (2016) 705–714.
[120] C. Konidaris, W. Simonson, B. Michelsen, G.K. Papadopoulos, Specific monoclonal antibodies against the surface of rat islet beta cells, Cell Biol. Int. 26 (2002) 817–828.
[121] B. Ziegler, S. Lucke, E. Kohler, B. Hehmke, M. Schlosser, S. Witt, W. Besch, M. Ziegler, Monoclonal antibody-mediated cytotoxicity against rat beta cells detected in vitro does not cause beta-cell destruction in vivo, Diabetologia 35 (1992) 608–613.
[122] F. Saudek, C.H. Brogren, S. Manohar, Imaging the Beta-cell mass: why and how, Rev. Diabet. Stud. 5 (2008) 6–12.
[123] L. Ladriere, F. Malaisse-Lagae, R. Alejandro, W.J. Malaisse, Pancreatic fate of a (125)I-labelled mouse monoclonal antibody directed against pancreatic B-cell surface ganglioside(s) in control and diabetic rats, Cell Biochem. Funct. 19 (2001) 107–115.
[124] J. Altirriba, R. Gasa, S. Casas, M.J. Ramirez-Bajo, S. Ros, A. Gutierrez-Dalmau, M.C. Ruiz de Villa, A. Barbera, R. Gomis, The role of transmembrane protein 27 (TMEM27) in islet physiology and its potential use as a beta cell mass biomarker, Diabetologia 53 (2010) 1406–1414.
[125] P. Akpinar, S. Kuwajima, J. Krutzfeldt, M. Stoffel, Tmem27: a cleaved and shed plasma membrane protein that stimulates pancreatic beta cell proliferation, Cell Metab. 2 (2005) 385–397.
[126] D. Vats, H. Wang, D. Esterhazy, K. Dikaiou, C. Danzer, M. Honer, F. Stuker, H. Matile, C. Migliorini, E. Fischer, J. Ripoll, R. Keist, W. Krek, R. Schibli, M. Stoffel, M. Rudin, Multimodal imaging of pancreatic beta cells in vivo by targeting transmembrane protein 27 (TMEM27), Diabetologia 55 (2012) 2407–2416.
[127] K. Buschard, C.H. Brogren, C. Ropke, J. Rygaard, Antigen expression of the pancreatic beta-cells is dependent on their functional state, as shown by a specific, BB rat monoclonal autoantibody IC2, APMIS 96 (1988) 342–346.
[128] C.H. Brogren, F. Hirsch, P. Wood, P. Druet, P. Poussier, Production and characterization of a monoclonal islet cell surface autoantibody from the BB rat, Diabetologia 29 (1986) 330–333.
[129] A. Moore, S. Bonner-Weir, R. Weissleder, Noninvasive in vivo measurement of beta-cell mass in mouse model of diabetes, Diabetes 50 (2001) 2231–2236.
[130] S. Ueberberg, J.J. Meier, C. Waengler, W. Schechinger, J.W. Dietrich, A. Tannapfel, I. Schmitz, R. Schirrmacher, M. Koller, H.H. Klein, S. Schneider, Generation of novel single-chain antibodies by phage-display technology to direct imaging agents highly selective to pancreatic beta- or alpha-cells in vivo, Diabetes 58 (2009) 2324–2334.
[131] O. Eriksson, O. Korsgren, R.K. Selvaraju, M. Mollaret, Y. de Boysson, F. Chimienti, M. Altai, Pancreatic imaging using an antibody fragment targeting the zinc transporter type 8: a direct comparison with radio-iodinated Exendin-4, Acta Diabetol. 55 (2018) 49–57.
[132] C.S. Hampe, A.R. Wallen, M. Schlosser, M. Ziegler, I.R. Sweet, Quantitative evaluation of a monoclonal antibody and its fragment as potential markers for pancreatic beta cell mass, Exp. Clin. Endocrinol. Diabetes 113 (2005) 381–387.
[133] F. Chimienti, S. Devergnas, A. Favier, M. Seve, Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules, Diabetes 53 (2004) 2330–2337.
[134] H. Wan, C. Merriman, M.A. Atkinson, C.H. Wasserfall, K.M. McGrail, Y. Liang, D. Fu, H. Dai, Proteoliposome-based full-length ZnT8 self-antigen for type 1 diabetes diagnosis on a plasmonic platform, Proc. Natl. Acad. Sci. U. S. A. 114 (38) (2017) 10196–10201.
[135] E.A. Bellomo, G. Meur, G.A. Rutter, Glucose regulates free cytosolic Zn(2)(+) concentration, Slc39 (ZiP), and metallothionein gene expression in primary pancreatic islet beta-cells, J. Biol. Chem. 286 (2011) 25778–25789.
[136] T.J. Nicolson, E.A. Bellomo, N. Wijesekara, M.K. Loder, J.M. Baldwin, A.V. Gyulkhandanyan, V. Koshkin, A.I. Tarasov, R. Carzaniga, K. Kronenberger, T.K. Taneja, G. da Silva Xavier, S. Libert, P. Froguel, R. Scharfmann, V. Stetsyuk, P. Ravassard, H. Parker, F.M. Gribble, F. Reimann, R. Sladek, S.J. Hughes, P.R. Johnson, M. Masseboeuf, R. Burcelin, S.A. Baldwin, M. Liu, R. Lara-Lemus, P. Arvan, F.C. Schuit, M.B. Wheeler, F. Chimienti, G.A. Rutter, Insulin storage and glucose homeostasis in mice null for the granule zinc transporter ZnT8 and studies of the type 2 diabetes-associated variants, Diabetes 58 (2009) 2070–2083.
[137] J.L. Vinkenborg, T.J. Nicolson, E.A. Bellomo, M.S. Koay, G.A. Rutter, M. Merkx, Genetically encoded FRET sensors to monitor intracellular Zn2+ homeostasis, Nat. Methods 6 (2009) 737–740.
[138] L.G. Sondergaard, M. Stoltenberg, P. Doering, A. Flyvbjerg, J. Rungby, Zinc ions in the endocrine and exocrine pancreas of zinc deficient rats, Histol. Histopathol. 21 (2006) 619–625.
[139] A.C. Esqueda, J.A. Lopez, G. Andreu-de-Riquer, J.C. Alvarado-Monzon, J. Ratnakar, A.J. Lubag, A.D. Sherry, L.M. De Leon-Rodriguez, A new gadolinium-based MRI zinc sensor, J. Am. Chem. Soc. 131 (2009) 11387–11391.
[140] A.J. Lubag, L.M. De Leon-Rodriguez, S.C. Burgess, A.D. Sherry, Noninvasive MRI of beta-cell function using a Zn2+-responsive contrast agent, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 18400–18405.
[141] G.J. Stasiuk, F. Minuzzi, M. Sae-Heng, C. Rivas, H.P. Juretschke, L. Piemonti, P.R. Allegrini, D. Laurent, A.R. Duckworth, A. Beeby, G.A. Rutter, N.J. Long, Dual-modal magnetic resonance/fluorescent zinc probes for pancreatic beta-cell mass imaging, Chemistry 21 (2015) 5023–5033.
[142] C.P. Briscoe, M. Tadayyon, J.L. Andrews, W.G. Benson, J.K. Chambers, M.M. Eilert, C. Ellis, N.A. Elshourbagy, A.S. Goetz, D.T. Minnick, P.R. Murdock, H.R. Sauls Jr., U. Shabon, L.D. Spinage, J.C. Strum, P.G. Szekeres, K.B. Tan, J.M. Way, D.M. Ignar, S. Wilson, A.I. Muir, The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids, J. Biol. Chem. 278 (2003) 11303–11311.
[143] Y. Itoh, Y. Kawamata, M. Harada, M. Kobayashi, R. Fujii, S. Fukusumi, K. Ogi, M. Hosoya, Y. Tanaka, H. Uejima, H. Tanaka, M. Maruyama, R. Satoh, S. Okubo, H. Kizawa, H. Komatsu, F. Matsumura, Y. Noguchi, T. Shinohara, S. Hinuma, Y. Fujisawa, M. Fujino, Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40, Nature 422 (2003) 173–176.
[144] T. Tomita, H. Masuzaki, M. Noguchi, H. Iwakura, J. Fujikura, T. Tanaka, K. Ebihara, J. Kawamura, I. Komoto, Y. Kawaguchi, K. Fujimoto, R. Doi, Y. Shimada, K. Hosoda, M. Imamura, K. Nakao, GPR40 gene expression in human pancreas and insulinoma, Biochem. Biophys. Res. Commun. 338 (2005) 1788–1790.
[145] R. Bertrand, A. Wolf, Y. Ivashchenko, M. Lohn, M. Schafer, M. Bronstrup, M. Gotthardt, V. Derdau, O. Plettenburg, Synthesis and characterization of a promising novel FFAR1/GPR40 targeting fluorescent probe for beta-cell imaging, ACS Chem. Biol. 11 (2016) 1745–1754.
[146] R. Bertrand, I. Hamp, M. Bronstrup, R. Weck, M. Lukacevic, A. Polyak, T.L. Ross, M. Gotthardt, O. Plettenburg, V. Derdau, Synthesis of GPR40 targeting 3 H- and 18 F-probes towards selective beta cell imaging, J. Label. Compd. Radiopharm. 59 (2016) 604–610.

[147] U. Kumar, R. Sasi, S. Suresh, A. Patel, M. Thangaraju, P. Metrakos, S.C. Patel, Y.C. Patel, Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis, Diabetes 48 (1999) 77–85.

[148] S. Moldovan, A. Atiya, T.E. Adrian, R.M. Kleinman, K. Lloyd, K. Olthoff, D. Imagawa, L. Shevlin, D. Coy, J. Walsh, et al., Somatostatin inhibits B-cell secretion via a subtype-2 somatostatin receptor in the isolated perfused human pancreas, J. Surg. Res. 59 (1995) 85–90.

[149] J.K. Amartey, C. Esguerra, I. Al-Jammaz, R.S. Parhar, B. Al-Otaibi, Synthesis and evaluation of radioiodinated substituted beta-naphthylalanine as a potential probe for pancreatic beta-cells imaging, Appl. Radiat. Isot. 64 (2006) 769–777.

[150] J.K. Amartey, Y. Shi, I. Al-Jammaz, C. Esguerra, B. Al-Otaibi, F. Al-Mohanna, Radioiodinated naphthylalanine derivatives targeting pancreatic beta cells in normal and nonobese diabetic mice, Exp. Diabetes Res. 2008 (2008) 371716.

[151] S.M. Efange, R.H. Mach, A. Khare, R.H. Michelson, P.A. Nowak, P.H. Evora, *p*-[18F] fluorobenzyltrozamicol ([18F]FBT): molecular decomposition-reconstitution approach to vesamicol receptor radioligands for positron emission tomography, Appl. Radiat. Isot. 45 (1994) 465–472.

[152] P.B. Clark, H.D. Gage, C. Brown-Proctor, N. Buchheimer, J. Calles-Escandon, R.H. Mach, K.A. Morton, Neurofunctional imaging of the pancreas utilizing the cholinergic PET radioligand [18F]4-fluorobenzyltrozamicol, Eur. J. Nucl. Med. Mol. Imaging 31 (2004) 258–260.

[153] P.B. Clark, K. Kavanagh, H.D. Gage, P. Garg, S. Garg, J. Calles-Escandon, J.D. Wagner, K. Morton, Enhanced cholinergic response in pancreata of nonhuman primates with impaired glucose tolerance shown on [18F]fluorobenzyltrozamicol positron emission tomography, Diabetes Technol. Ther. 11 (2009) 451–455.

[154] P.B. Clark, M.J. Plaza, J. Kraas, N. Burbank, A.W. Elster II, P. Garg, S. Garg, H.D. Gage, J. Calles-Escandon, J.D. Wagner, K. Morton, Dual radiotracer analysis of cholinergic neuronal changes in prediabetic mouse pancreas, Diabetes Technol. Ther. 11 (2009) 107–111.

[155] W.A. Eter, S. Parween, L. Joosten, C. Frielink, M. Eriksson, M. Brom, U. Ahlgren, M. Gotthardt, SPECT-OPT multimodal imaging enables accurate evaluation of radiotracers for beta-cell mass assessments, Sci. Rep. 6 (2016) 24576.

[156] L.F. Greer III, A.A. Szalay, Imaging of light emission from the expression of luciferases in living cells and organisms: a review, Luminescence 17 (2002) 43–74.

[157] J. Virostko, A. Radhika, G. Poffenberger, Z. Chen, M. Brissova, J. Gilchrist, B. Coleman, M. Gannon, E.D. Jansen, A.C. Powers, Bioluminescence imaging in mouse models quantifies beta cell mass in the pancreas and after islet transplantation, Mol. Imaging Biol. 12 (2010) 42–53.

[158] A. Zumsteg, K. Strittmatter, D. Klewe-Nebenius, H. Antoniadis, G. Christofori, A bioluminescent mouse model of pancreatic {beta}-cell carcinogenesis, Carcinogenesis 31 (2010) 1465–1474.

[159] S.J. Smith, H. Zhang, A.O. Clermont, A.C. Powers, D.B. Kaufman, A.F. Purchio, D.B. West, In vivo monitoring of pancreatic beta-cells in a transgenic mouse model, Mol. Imaging 5 (2006) 65–75.

[160] D. Sever, R. Eldor, G. Sadoun, L. Amior, D. Dubois, C. Boitard, C. Aflalo, D. Melloul, Evaluation of impaired beta-cell function in nonobese-diabetic (NOD) mouse model using bioluminescence imaging, FASEB J. 25 (2011) 676–684.

[161] J. Virostko, A. Radhika, G. Poffenberger, A.N. Dula, D.J. Moore, A.C. Powers, Bioluminescence imaging reveals dynamics of beta cell loss in the non-obese diabetic (NOD) mouse model, PLoS One 8 (2013), e57784. .

[162] M. Patel, A. Gleason, S. O'Malley, B. Connolly, D. Suresch, J. Virostko, N. Phillips, S.A. Lin, T.B. Chen, M. Klimas, R.J. Hargreaves, C. Sur, D.L. Williams Jr., A.C. Powers, B. Bednar, Non-invasive bioluminescence imaging of beta-cell function in obese-hyperglycemic [ob/ob] mice, PLoS One 9 (2014), e106693. .

[163] J. Virostko, Z. Chen, M. Fowler, G. Poffenberger, A.C. Powers, E.D. Jansen, Factors influencing quantification of in vivo bioluminescence imaging: application to assessment of pancreatic islet transplants, Mol. Imaging 3 (2004) 333–342.

[164] D.Z. Balla, S. Gottschalk, G. Shajan, S. Ueberberg, S. Schneider, M. Hardtke-Wolenski, E. Jaeckel, V. Hoerr, C. Faber, K. Scheffler, R. Pohmann, J. Engelmann, In vivo visualization of single native pancreatic islets in the mouse, Contrast Media Mol. Imaging 8 (2013) 495–504.

[165] C. Brand, D. Abdel-Atti, Y. Zhang, S. Carlin, S.M. Clardy, E.J. Keliher, W.A. Weber, J.S. Lewis, T. Reiner, In vivo imaging of GLP-1R with a targeted bimodal PET/fluorescence imaging agent, Bioconjug. Chem. 25 (2014) 1323–1330.

[166] T. Reiner, R.H. Kohler, C.W. Liew, J.A. Hill, J. Gaglia, R.N. Kulkarni, R. Weissleder, Near-infrared fluorescent probe for imaging of pancreatic beta cells, Bioconjug. Chem. 21 (2010) 1362–1368.

[167] E.J. Keliher, T. Reiner, G.M. Thurber, R. Upadhyay, R. Weissleder, Efficient 18F-labeling of synthetic exendin-4 analogues for imaging beta cells, ChemistryOpen 1 (2012) 177–183.

[168] C. Berclaz, C. Pache, A. Bouwens, D. Szlag, A. Lopez, L. Joosten, S. Ekim, M. Brom, M. Gotthardt, A. Grapin-Botton, T. Lasser, Combined Optical Coherence and Fluorescence Microscopy to assess dynamics and specificity of pancreatic beta-cell tracers, Sci. Rep. 5 (2015) 10385.

[169] D. Li, Z. Huang, S. Chen, Z. Hu, W.H. Li, GLP-1 receptor mediated targeting of a fluorescent Zn(2+) sensor to beta cell surface for imaging insulin/Zn(2+) release, Bioconjug. Chem. 26 (2015) 1443–1450.

[170] A. Babic, S. Lamprianou, L. Vinet, N. Stransky-Heilkron, C. Xayaphoummine, M.A. Campo, H. Glombik, A. Schulte, H.P. Juretschke, X. Montet, P. Meda, N. Lange, Multivalent glibenclamide to generate islet specific imaging probes, Biomaterials 75 (2016) 1–12.

[171] P. Wang, A. Moore, Theranostic magnetic resonance imaging of type 1 diabetes and pancreatic islet transplantation, Quant. Imaging Med. Surg. 2 (2012) 151–162.

[172] Y. Liu, B. Song, X. Ran, Q. Jiang, J. Hu, S.M. Vance Chiang, Molecular imaging of pancreatic islet transplantation, Exp. Clin. Endocrinol. Diabetes 122 (2014) 79–86.

[173] J. Li, J. Karunananthan, B. Pelham, F. Kandeel, Imaging pancreatic islet cells by positron emission tomography, World J. Radiol. 8 (2016) 764–774.

[174] Y. Lu, H. Dang, B. Middleton, Z. Zhang, L. Washburn, M. Campbell-Thompson, M.A. Atkinson, S.S. Gambhir, J. Tian, D.L. Kaufman, Bioluminescent monitoring of islet graft survival after transplantation, Mol. Ther. 9 (2004) 428–435.

[175] Y. Lu, H. Dang, B. Middleton, Z. Zhang, L. Washburn, D.B. Stout, M. Campbell-Thompson, M.A. Atkinson, M. Phelps, S.S. Gambhir, J. Tian, D.L. Kaufman, Noninvasive imaging of islet grafts using positron-emission tomography, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 11294–11299.

[176] Y. Lu, H. Dang, B. Middleton, M. Campbell-Thompson, M.A. Atkinson, S.S. Gambhir, J. Tian, D.L. Kaufman, Long-term monitoring of transplanted islets using positron emission tomography, Mol. Ther. 14 (2006) 851–856.

[177] S.J. Kim, D.J. Doudet, A.R. Studenov, C. Nian, T.J. Ruth, S.S. Gambhir, C.H. McIntosh, Quantitative micro positron emission tomography (PET) imaging for the in vivo determination of pancreatic islet graft survival, Nat. Med. 12 (2006) 1423–1428.

[178] J. Yong, J. Rasooly, H. Dang, Y. Lu, B. Middleton, Z. Zhang, L. Hon, M. Namavari, D.B. Stout, M.A. Atkinson, J. Tian, S.S. Gambhir, D.L. Kaufman, Multimodality imaging of beta-cells in mouse models of type 1 and 2 diabetes, Diabetes 60 (2011) 1383–1392.

[179] Z. Wu, I. Todorov, L. Li, J.R. Bading, Z. Li, I. Nair, K. Ishiyama, D. Colcher, P.E. Conti, S.E. Fraser, J.E. Shively, F. Kandeel, In vivo imaging of transplanted islets with 64Cu-DO3A-VS-Cys40-Exendin-4 by targeting GLP-1 receptor, Bioconjug. Chem. 22 (2011) 1587–1594.

[180] F. Pattou, J. Kerr-Conte, D. Wild, GLP-1-receptor scanning for imaging of human beta cells transplanted in muscle, N. Engl. J. Med. 363 (2010) 1289–1290.

[181] Z. Li, H. Cai, M. Hassink, M.L. Blackman, R.C. Brown, P.S. Conti, J.M. Fox, Tetrazine-trans-cyclooctene ligation for the rapid construction of 18F labeled probes, Chem. Commun. (Camb.) 46 (2010) 8043–8045.

[182] S. Liu, M. Hassink, R. Selvaraj, L.P. Yap, R. Park, H. Wang, X. Chen, J.M. Fox, Z. Li, P.S. Conti, Efficient 18F labeling of cysteine-containing peptides and proteins using tetrazine-trans-cyclooctene ligation, Mol. Imaging 12 (2013) 121–128.

[183] Z. Wu, S. Liu, M. Hassink, I. Nair, R. Park, L. Li, I. Todorov, J.M. Fox, Z. Li, J.E. Shively, P.S. Conti, F. Kandeel, Development and evaluation of 18F-TTCO-Cys40-Exendin-4: a PET probe for imaging transplanted islets, J. Nucl. Med. 54 (2013) 244–251.

[184] W.A. Eter, I. Van der Kroon, K. Andralojc, M. Buitinga, S.M.A. Willekens, C. Frielink, D. Bos, L. Joosten, O.C. Boerman, M. Brom, M. Gotthardt, Non-invasive in vivo determination of viable islet graft volume by 111In-exendin-3, Sci. Rep. 7 (2017) 7232.

[185] O. Eriksson, A. Alavi, Imaging the islet graft by positron emission tomography, Eur. J. Nucl. Med. Mol. Imaging 39 (2012) 533–542.

[186] H.F. Kung, Y.Z. Guo, J. Billings, X. Xu, R.H. Mach, M. Blau, R.E. Ackerhalt, Preparation and biodistribution of [125I]IBZM: a potential CNS D-2 dopamine receptor imaging agent, Int. J. Rad. Appl. Instrum. B 15 (1988) 195–201.

[187] U. Saeed, J. Compagnone, R.I. Aviv, A.P. Strafella, S.E. Black, A.E. Lang, M. Masellis, Imaging biomarkers in Parkinson's disease and Parkinsonian syndromes: current and emerging concepts, Transl. Neurodegener. 6 (2017) 8.

[188] B. Rubi, S. Ljubicic, S. Pournourmohammadi, S. Carobbio, M. Armanet, C. Bartley, P. Maechler, Dopamine D2-like receptors are expressed in pancreatic beta cells and mediate inhibition of insulin secretion, J. Biol. Chem. 280 (2005) 36824–36832.

[189] A. Becherer, M. Szabo, G. Karanikas, P. Wunderbaldinger, P. Angelberger, M. Raderer, A. Kurtaran, R. Dudczak, K. Kletter, Imaging of advanced neuroendocrine tumors with (18)F-FDOPA PET, J. Nucl. Med. 45 (2004) 1161–1167.

[190] T. Otonkoski, K. Nanto-Salonen, M. Seppanen, R. Veijola, H. Huopio, K. Hussain, P. Tapanainen, O. Eskola, R. Parkkola, K. Ekstrom, Y. Guiot, J. Rahier, M. Laakso, R. Rintala, P. Nuutila, H. Minn, Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography, Diabetes 55 (2006) 13–18.

[191] O. Eriksson, A. Mintz, C. Liu, M. Yu, A. Naji, A. Alavi, On the use of [18F]DOPA as an imaging biomarker for transplanted islet mass, Ann. Nucl. Med. 28 (2014) 47–52.

[192] A. Garcia, A. Venugopal, M.L. Pan, J. Mukherjee, Imaging pancreas in healthy and diabetic rodent model using [18F]fallypride positron emission tomography/computed tomography, Diabetes Technol. Ther. 16 (2014) 640–643.

[193] G. Pizzolato, F. Chierichetti, M. Fabbri, A. Cagnin, M. Dam, G. Ferlin, L. Battistin, Reduced striatal dopamine receptors in Alzheimer's disease: single photon emission tomography study with the D2 tracer [123I]-IBZM, Neurology 47 (1996) 1065–1068.

[194] S.M. Willekens, I. van der Kroon, L. Joosten, C. Frielink, O.C. Boerman, S.A. van den Broek, M. Brom, M. Gotthardt, SPECT of transplanted islets of Langerhans by dopamine 2 receptor targeting in a rat model, Mol. Pharm. 13 (2016) 85–91.

[195] S.M. Willekens, I. van der Kroon, D. Bos, L. Joosten, C. Frielink, O.C. Boerman, M. Brom, M. Gotthardt, Quantitative and longitudinal imaging of intramuscular transplanted islets of Langerhans with SPECT using [ 123 I]IBZM, Diabetes Obes. Metab. 19 (2017) 604–608.

[196] W.A. Eter, D. Bos, C. Frielink, O.C. Boerman, M. Brom, M. Gotthardt, Graft revascularization is essential for non-invasive monitoring of transplanted islets with radiolabeled exendin, Sci. Rep. 5 (2015) 15521.

[197] N.V. Evgenov, Z. Medarova, G. Dai, S. Bonner-Weir, A. Moore, In vivo imaging of islet transplantation, Nat. Med. 12 (2006) 144–148.

[198] Z. Medarova, P. Vallabhajosyula, A. Tena, N. Evgenov, P. Pantazopoulos, V. Tchipashvili, G. Weir, D. Sachs, A. Moore, In vivo imaging of autologous islet grafts in the liver and under the kidney capsule in non-human primates, Transplantation 87 (2009) 1659–1666.

[199] J.H. Tai, P. Foster, A. Rosales, B. Feng, C. Hasilo, V. Martinez, S. Ramadan, J. Snir, C.W. Melling, S. Dhanvantari, B. Rutt, D.J. White, Imaging islets labeled with magnetic nanoparticles at 1.5 Tesla, Diabetes 55 (2006) 2931–2938.

[200] Y.X. Wang, Superparamagnetic iron oxide based MRI contrast agents: current status of clinical application, Quant. Imaging Med. Surg. 1 (2011) 35–40.

[201] I.J. de Vries, W.J. Lesterhuis, J.O. Barentsz, P. Verdijk, J.H. van Krieken, O.C. Boerman, W.J. Oyen, J.J. Bonenkamp, J.B. Boezeman, G.J. Adema, J.W. Bulte, T.W. Scheenen, C.J. Punt, A. Heerschap, C.G. Figdor, Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy, Nat. Biotechnol. 23 (2005) 1407–1413.
[202] E.T. Ahrens, J.W. Bulte, Tracking immune cells in vivo using magnetic resonance imaging, Nat. Rev. Immunol. 13 (2013) 755–763.
[203] D.R. Arifin, J.W. Bulte, Imaging of pancreatic islet cells, Diabetes Metab. Res. Rev. 27 (2011) 761–766.
[204] R. Weissleder, D.D. Stark, B.L. Engelstad, B.R. Bacon, C.C. Compton, D.L. White, P. Jacobs, J. Lewis, Superparamagnetic iron oxide: pharmacokinetics and toxicity, AJR Am. J. Roentgenol. 152 (1989) 167–173.
[205] C. Toso, J.P. Vallee, P. Morel, F. Ris, S. Demuylder-Mischler, M. Lepetit-Coiffe, N. Marangon, F. Saudek, A.M. James Shapiro, D. Bosco, T. Berney, Clinical magnetic resonance imaging of pancreatic islet grafts after iron nanoparticle labeling, Am. J. Transplant. 8 (2008) 701–706.
[206] K. Oishi, Y. Miyamoto, H. Saito, K. Murase, K. Ono, M. Sawada, M. Watanabe, Y. Noguchi, T. Fujiwara, S. Hayashi, H. Noguchi, In vivo imaging of transplanted islets labeled with a novel cationic nanoparticle, PLoS One 8 (2013), e57046. .
[207] N.V. Evgenov, Z. Medarova, J. Pratt, P. Pantazopoulos, S. Leyting, S. Bonner-Weir, A. Moore, In vivo imaging of immune rejection in transplanted pancreatic islets, Diabetes 55 (2006) 2419–2428.
[208] Z. Medarova, N.V. Evgenov, G. Dai, S. Bonner-Weir, A. Moore, In vivo multimodal imaging of transplanted pancreatic islets, Nat. Protoc. 1 (2006) 429–435.
[209] B.P. Barnett, A. Arepally, P.V. Karmarkar, D. Qian, W.D. Gilson, P. Walczak, V. Howland, L. Lawler, C. Lauzon, M. Stuber, D.L. Kraitchman, J.W. Bulte, Magnetic resonance-guided, real-time targeted delivery and imaging of magnetocapsules immunoprotecting pancreatic islet cells, Nat. Med. 13 (2007) 986–991.
[210] B.P. Barnett, J. Ruiz-Cabello, P. Hota, R. Liddell, P. Walczak, V. Howland, V.P. Chacko, D.L. Kraitchman, A. Arepally, J.W. Bulte, Fluorocapsules for improved function, immunoprotection, and visualization of cellular therapeutics with MR, US, and CT imaging, Radiology 258 (2011) 182–191.
[211] J. Kim, D.R. Arifin, N. Muja, T. Kim, A.A. Gilad, H. Kim, A. Arepally, T. Hyeon, J.W. Bulte, Multifunctional capsule-in-capsules for immunoprotection and trimodal imaging, Angew. Chem. Int. Ed. Eng. 50 (2011) 2317–2321.
[212] N. Lee, H. Kim, S.H. Choi, M. Park, D. Kim, H.C. Kim, Y. Choi, S. Lin, B.H. Kim, H.S. Jung, H. Kim, K.S. Park, W.K. Moon, T. Hyeon, Magnetosome-like ferrimagnetic iron oxide nanocubes for highly sensitive MRI of single cells and transplanted pancreatic islets, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 2662–2667.
[213] R.K. Selvaraju, T.N. Bulenga, D. Espes, M. Lubberink, J. Sorensen, B. Eriksson, S. Estrada, I. Velikyan, O. Eriksson, Dosimetry of [(68)Ga]Ga-DO3A-VS-Cys(40)-Exendin-4 in rodents, pigs, non-human primates and human - repeated scanning in human is possible, Am. J. Nucl. Med. Mol. Imaging 5 (2015) 259–269.
[214] D.A. Pattison, R.J. Hicks, Molecular imaging in the investigation of hypoglycaemic syndromes and their management, Endocr. Relat. Cancer 24 (2017) R203–R221.
[215] A. Mehrabi, L. Fischer, M. Hafezi, A. Dirlewanger, L. Grenacher, M.K. Diener, H. Fonouni, M. Golriz, C. Garoussi, N. Fard, N.N. Rahbari, J. Werner, M.W. Buchler, A systematic review of localization, surgical treatment options, and outcome of insulinoma, Pancreas 43 (2014) 675–686.
[216] T. Okabayashi, Y. Shima, T. Sumiyoshi, A. Kozuki, S. Ito, Y. Ogawa, M. Kobayashi, K. Hanazaki, Diagnosis and management of insulinoma, World J. Gastroenterol. 19 (2013) 829–837.
[217] S. Kauhanen, M. Seppanen, H. Minn, R. Gullichsen, A. Salonen, K. Alanen, R. Parkkola, O. Solin, J. Bergman, T. Sane, J. Salmi, M. Valimaki, P. Nuutila, Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients, J. Clin. Endocrinol. Metab. 92 (2007) 1237–1244.
[218] L. Tessonnier, F. Sebag, C. Ghander, C. De Micco, R. Reynaud, F.F. Palazzo, B. Conte-Devolx, J.F. Henry, O. Mundler, D. Taieb, Limited value of 18F-F-DOPA PET to localize pancreatic insulin-secreting tumors in adults with hyperinsulinemic hypoglycemia, J. Clin. Endocrinol. Metab. 95 (2010) 303–307.
[219] J.S. Gopal-Kothandapani, K. Hussain, Congenital hyperinsulinism: role of fluorine-18L-3, 4 hydroxyphenylalanine positron emission tomography scanning, World J. Radiol. 6 (2014) 252–260.
[220] A. Imperiale, F. Sebag, M. Vix, F. Castinetti, L. Kessler, F. Moreau, P. Bachellier, B. Guillet, I.J. Namer, O. Mundler, D. Taieb, 18F-FDOPA PET/CT imaging of insulinoma revisited, Eur. J. Nucl. Med. Mol. Imaging 42 (2015) 409–418.
[221] H. Orlefors, A. Sundin, U. Garske, C. Juhlin, K. Oberg, B. Skogseid, B. Langstrom, M. Bergstrom, B. Eriksson, Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography, J. Clin. Endocrinol. Metab. 90 (2005) 3392–3400.
[222] E. Christ, D. Wild, S. Ederer, M. Behe, G. Nicolas, M.E. Caplin, M. Brandle, T. Clerici, S. Fischli, C. Stettler, P.J. Ell, J. Seufert, B. Gloor, A. Perren, J.C. Reubi, F. Forrer, Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study, Lancet Diabetes Endocrinol. 1 (2013) 115–122.
[223] M. Brom, W.J. Oyen, L. Joosten, M. Gotthardt, O.C. Boerman, 68Ga-labelled exendin-3, a new agent for the detection of insulinomas with PET, Eur. J. Nucl. Med. Mol. Imaging 37 (2010) 1345–1355.
[224] I.R. Sweet, D.L. Cook, A. Lernmark, C.J. Greenbaum, A.R. Wallen, E.S. Marcum, S.A. Stekhova, K.A. Krohn, Systematic screening of potential beta-cell imaging agents, Biochem. Biophys. Res. Commun. 314 (2004) 976–983.
[225] C. Capito, N. Khen-Dunlop, M.J. Ribeiro, F. Brunelle, Y. Aigrain, C. Cretolle, F. Jaubert, P. De Lonlay, C. Nihoul-Fekete, Value of 18F-fluoro-L-dopa PET in the preoperative localization of focal lesions in congenital hyperinsulinism, Radiology 253 (2009) 216–222.
[226] W. Barthlen, O. Blankenstein, H. Mau, M. Koch, C. Hohne, W. Mohnike, T. Eberhard, F. Fuechtner, B. Lorenz-Depiereux, K. Mohnike, Evaluation of [18F]fluoro-L-DOPA positron emission tomography-computed tomography for surgery in focal congenital hyperinsulinism, J. Clin. Endocrinol. Metab. 93 (2008) 869–875.
[227] M.J. Ribeiro, N. Boddaert, C. Bellanne-Chantelot, S. Bourgeois, V. Valayannopoulos, T. Delzescaux, F. Jaubert, C. Nihoul-Fekete, F. Brunelle, P. De Lonlay, The added value of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy: a retrospective study involving 49 children, Eur. J. Nucl. Med. Mol. Imaging 34 (2007) 2120–2128.
[228] O.T. Hardy, M. Hernandez-Pampaloni, J.R. Saffer, J.S. Scheuermann, L.M. Ernst, R. Freifelder, H. Zhuang, C. MacMullen, S. Becker, N.S. Adzick, C. Divgi, A. Alavi, C.A. Stanley, Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism, J. Clin. Endocrinol. Metab. 92 (2007) 4706–4711.
[229] O. Eriksson, R.K. Selvaraju, L. Johansson, J.W. Eriksson, A. Sundin, G. Antoni, J. Sorensen, B. Eriksson, O. Korsgren, Quantitative imaging of serotonergic biosynthesis and degradation in the endocrine pancreas, J. Nucl. Med. 55 (2014) 460–465.
[230] O. Eriksson, D. Espes, R.K. Selvaraju, E. Jansson, G. Antoni, J. Sorensen, M. Lubberink, A.R. Biglarnia, J.W. Eriksson, A. Sundin, H. Ahlstrom, B. Eriksson, L. Johansson, P.O. Carlsson, O. Korsgren, Positron emission tomography ligand [11C]5-hydroxy-tryptophan can be used as a surrogate marker for the human endocrine pancreas, Diabetes 63 (2014) 3428–3437.
[231] O. Eriksson, R. Selvaraju, T. Eich, M. Willny, T.B. Brismar, L. Carlbom, H. Ahlstrom, G. Tufvesson, T. Lundgren, O. Korsgren, Positron emission tomography to assess the outcome of intraportal islet transplantation, Diabetes 65 (2016) 2482–2489.
[232] H. Orlefors, A. Sundin, B. Eriksson, B. Skogseid, K. Oberg, G. Akerstrom, P. Hellman, PET-guided surgery - high correlation between positron emission tomography with 11C-5-hydroxytryptophane (5-HTP) and surgical findings in abdominal neuroendocrine tumours, Cancers (Basel) 4 (2012) 100–112.
[233] J. Detour, A. Pierre, F. Boisson, G. Kreutter, T. Lavaux, I.J. Namer, L. Kessler, D. Brasse, P. Marchand, A. Imperiale, Effect of carbidopa on 18F-FDOPA uptake in insulinoma: from cell culture to small-animal PET imaging, J. Nucl. Med. 58 (2017) 36–41.
[234] H. Orlefors, A. Sundin, L. Lu, K. Oberg, B. Langstrom, B. Eriksson, M. Bergstrom, Carbidopa pretreatment improves image interpretation and visualisation of carcinoid tumours with 11C-5-hydroxytryptophan positron emission tomography, Eur. J. Nucl. Med. Mol. Imaging 33 (2006) 60–65.
[235] L. Bodei, J. Mueller-Brand, R.P. Baum, M.E. Pavel, D. Horsch, M.S. O'Dorisio, T.M. O'Dorisio, J.R. Howe, M. Cremonesi, D.J. Kwekkeboom, J.J. Zaknun, The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours, Eur. J. Nucl. Med. Mol. Imaging 40 (2013) 800–816.
[236] D. Wild, E. Christ, M.E. Caplin, T.R. Kurzawinski, F. Forrer, M. Brandle, J. Seufert, W.A. Weber, J. Bomanji, A. Perren, P.J. Ell, J.C. Reubi, Glucagon-like peptide-1 versus somatostatin receptor targeting reveals 2 distinct forms of malignant insulinomas, J. Nucl. Med. 52 (2011) 1073–1078.
[237] E.N. Murage, G. Gao, A. Bisello, J.M. Ahn, Development of potent glucagon-like peptide-1 agonists with high enzyme stability via introduction of multiple lactam bridges, J. Med. Chem. 53 (2010) 6412–6420.
[238] H. Gao, G. Niu, M. Yang, Q. Quan, Y. Ma, E.N. Murage, J.M. Ahn, D.O. Kiesewetter, X. Chen, PET of insulinoma using (1)(8)F-FBEM-EM3106B, a new GLP-1 analogue, Mol. Pharm. 8 (2011) 1775–1782.
[239] D.O. Kiesewetter, H. Gao, Y. Ma, G. Niu, Q. Quan, N. Guo, X. Chen, 18F-radiolabeled analogs of exendin-4 for PET imaging of GLP-1 in insulinoma, Eur. J. Nucl. Med. Mol. Imaging 39 (2012) 463–473.
[240] D.O. Kiesewetter, N. Guo, J. Guo, H. Gao, L. Zhu, Y. Ma, G. Niu, X. Chen, Evaluation of an [(18)F]AlF-NOTA analog of exendin-4 for imaging of GLP-1 receptor in insulinoma, Theranostics 2 (2012) 999–1009.
[241] O. Eriksson, I. Velikyan, R.K. Selvaraju, F. Kandeel, L. Johansson, G. Antoni, B. Eriksson, J. Sorensen, O. Korsgren, Detection of metastatic insulinoma by positron emission tomography with [(68)ga]exendin-4-a case report, J. Clin. Endocrinol. Metab. 99 (2014) 1519–1524.
[242] Y. Luo, M. Yu, Q. Pan, W. Wu, T. Zhang, D.O. Kiesewetter, Z. Zhu, F. Li, X. Chen, Y. Zhao, 68Ga-NOTA-exendin-4 PET/CT in detection of occult insulinoma and evaluation of physiological uptake, Eur. J. Nucl. Med. Mol. Imaging 42 (2015) 531–532.
[243] K. Antwi, M. Fani, G. Nicolas, C. Rottenburger, T. Heye, J.C. Reubi, B. Gloor, E. Christ, D. Wild, Localization of hidden insulinomas with (6)(8)Ga-DOTA-Exendin-4 PET/CT: a pilot study, J. Nucl. Med. 56 (2015) 1075–1078.
[244] I. Velikyan, U. Rosenstrom, O. Eriksson, Fully automated GMP production of [68Ga]Ga-DO3A-VS-Cys40-Exendin-4 for clinical use, Am. J. Nucl. Med. Mol. Imaging 7 (2017) 111–125.
[245] Z. Wu, S. Liu, I. Nair, K. Omori, S. Scott, I. Todorov, J.E. Shively, P.S. Conti, Z. Li, F. Kandeel, (64)Cu labeled sarcophagine exendin-4 for microPET imaging of glucagon like peptide-1 receptor expression, Theranostics 4 (2014) 770–777.
[246] M. Brom, L. Joosten, W.J. Oyen, M. Gotthardt, O.C. Boerman, Radiolabelled GLP-1 analogues for in vivo targeting of insulinomas, Contrast Media Mol. Imaging 7 (2012) 160–166.
[247] B. Waser, J.C. Reubi, Radiolabelled GLP-1 receptor antagonist binds to GLP-1 receptor-expressing human tissues, Eur. J. Nucl. Med. Mol. Imaging 41 (2014) 1166–1171.
[248] H. Kimura, H. Matsuda, Y. Ogawa, H. Fujimoto, K. Toyoda, N. Fujita, K. Arimitsu, K. Hamamatsu, Y. Yagi, M. Ono, N. Inagaki, H. Saji, Development of 111In-labeled exendin(9-39) derivatives for single-photon emission computed tomography imaging of insulinoma, Bioorg. Med. Chem. 25 (2017) 1406–1412.
[249] V. Medina-Garcia, B.E. Ocampo-Garcia, G. Ferro-Flores, C.L. Santos-Cuevas, L. Aranda-Lara, R. Garcia-Becerra, D. Ordaz-Rosado, L. Melendez-Alafort, A freeze-

dried kit formulation for the preparation of Lys(27)(99mTc-EDDA/HYNIC)-Exendin(9-39)/99mTc-EDDA/HYNIC-Tyr3-Octreotide to detect benign and malignant insulinomas, Nucl. Med. Biol. 42 (2015) 911–916.
[250] B.E. Ocampo-Garcia, C.L. Santos-Cuevas, M.A. Luna-Gutierrez, E. Ignacio-Alvarez, M. Pedraza-Lopez, C. Manzano-Mayoral, 99mTc-exendin(9-39)/octreotide: biokinetics and radiation dosimetry in healthy individuals, Nucl. Med. Commun. 38 (2017) 912–918.
[251] D.L. Kim, S.D. Kim, S.K. Kim, S. Park, K.H. Song, Is an oral glucose tolerance test still valid for diagnosing diabetes mellitus? Diabetes Metab. J. 40 (2016) 118–128.
[252] M. Gotthardt, A therapeutic insight in beta-cell imaging? Diabetes 60 (2011) 381–382.
[253] J. Dimastromatteo, T. Brentnall, K.A. Kelly, Imaging in pancreatic disease, Nat. Rev. Gastroenterol. Hepatol. 14 (2017) 97–109.
[254] A. Wicki, D. Wild, D. Storch, C. Seemayer, M. Gotthardt, M. Behe, S. Kneifel, M.J. Mihatsch, J.C. Reubi, H.R. Macke, G. Christofori, [Lys40(Ahx-DTPA-111In)NH2]-Exendin-4 is a highly efficient radiotherapeutic for glucagon-like peptide-1 receptor-targeted therapy for insulinoma, Clin. Cancer Res. 13 (2007) 3696–3705.
[255] B. Behnam Azad, V. Rota, L. Yu, R. McGirr, A.H. St Amant, T.Y. Lee, S. Dhanvantari, L.G. Luyt, Synthesis and evaluation of optical and PET GLP-1 peptide analogues for GLP-1R imaging, Mol. Imaging 14 (2015).
[256] D. Kim, H.S. Jun, In vivo imaging of transplanted pancreatic islets, Front. Endocrinol. (Lausanne) 8 (2017) 382.
[257] T. Bouckenooghe, D. Flamez, F. Ortis, S. Goldman, D.L. Eizirik, Identification of new pancreatic beta cell targets for in vivo imaging by a systems biology approach, Curr. Pharm. Des. 16 (2010) 1609–1618.
[258] H. Singh, Y. Yu, M.J. Suh, M.G. Torralba, R.D. Stenzel, A. Tovchigrechko, V. Thovarai, D.M. Harkins, S.V. Rajagopala, W. Osborne, F.R. Cogen, P.B. Kaplowitz, K.E. Nelson, R. Madupu, R. Pieper, Type 1 diabetes: urinary proteomics and protein network analysis support perturbation of lysosomal function, Theranostics 7 (2017) 2704–2717.
[259] M. Ghasemi, I. Nabipour, A. Omrani, Z. Alipour, M. Assadi, Precision medicine and molecular imaging: new targeted approaches toward cancer therapeutic and diagnosis, Am. J. Nucl. Med. Mol. Imaging 6 (2016) 310–327.
[260] C. Lindskog, O. Korsgren, F. Ponten, J.W. Eriksson, L. Johansson, A. Danielsson, Novel pancreatic beta cell-specific proteins: antibody-based proteomics for identification of new biomarker candidates, J. Proteome 75 (2012) 2611–2620.
[261] E. Hellstrom-Lindahl, A. Danielsson, F. Ponten, P. Czernichow, O. Korsgren, L. Johansson, O. Eriksson, GPR44 is a pancreatic protein restricted to the human beta cell, Acta Diabetol. 53 (2016) 413–421.
[262] O. Eriksson, P. Johnstrom, Z. Cselenyi, M. Jahan, R.K. Selvaraju, M. Jensen-Waern, A. Takano, M. Sorhede Winzell, C. Halldin, S. Skrtic, O. Korsgren, In vivo visualization of beta-cells by targeting of GPR44, Diabetes 67 (2018) 182–192.
[263] I. van der Kroon, W. Woliner-van der Weg, M. Brom, L. Joosten, C. Frielink, M.W. Konijnenberg, E.P. Visser, M. Gotthardt, Whole organ and islet of Langerhans dosimetry for calculation of absorbed doses resulting from imaging with radiolabeled exendin, Sci. Rep. 7 (2017) 39800.
[264] W. Wei, D. Jiang, E.B. Ehlerding, Q. Luo, W. Cai, Noninvasive PET imaging of T cells, Trends in Cancer 2018.
[265] S.S. Yaghoubi, D.O. Campbell, C.G. Radu, J. Czernin, Positron emission tomography reporter genes and reporter probes: gene and cell therapy applications, Theranostics 2 (2012) 374–391.
[266] J. Rieffel, U. Chitgupi, J.F. Lovell, Recent advances in higher-order, multimodal, biomedical imaging agents, Small 11 (2015) 4445–4461.