SPECIAL ISSUE REVIEW

Exendin-4 analogs in insulinoma theranostics

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Insulinomas are neuroendocrine tumors arising from the pancreatic beta cells. Currently, surgical resection is the therapy of choice, and therefore, preoperative localization of insulinomas is essential. Nearly all insulinomas show overexpression of the glucagon-like peptide-1 receptor (GLP-1R), and therefore, radiolabeled GLP-1 peptide analog exendin-4 can be used for diagnosis and preoperative localization with nuclear imaging. Here, we present an overview of the development and clinical implementation of exendin-4–based tracers for single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging of insulinomas, and we address the potential use of this molecule for optical imaging. At last, we discuss the possibilities and pitfalls of the use of exendin-4–based tracers for therapeutic applications such as peptide receptor radionuclide therapy (PRRT) or targeted photodynamic therapy (tPDT), giving a future outlook on the use of exendin-4 in insulinoma theranostics.

KEYWORDS
exendin-4, GLP-1 receptor, insulinoma, peptide receptor radionuclide therapy (PRRT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), targeted photodynamic therapy (tPDT), theranostics

1 | CLINICAL CHARACTERISTICS AND THERAPY OF INSULINOMA

Insulinoma is a subtype of pancreatic neuroendocrine tumors (pNETs) that arises from the insulin-producing beta cells in the islets of Langerhans. Although the majority of insulinomas are benign (90%), symptoms due to the excessive insulin secretion by the tumor cells can be severe and have a major impact on the patient's quality

of life. Symptoms include hypoglycemia, impaired consciousness, disturbances of speech and vision, seizures, and sensorimotor function impairment. Furthermore, behavioral changes, personality changes, and weight gain due to continuous eating may occur.[1,2] Insulinoma is currently diagnosed biochemically by measuring plasma glucose, insulin, C-peptide, and proinsulin during a 12- to 72-hour period of fasting, showing low glucose levels with inappropriately high insulin levels. Treatment options include surgical resection, radiofrequency ablation, alcohol ablation, embolization, chemotherapy, medication, and peptide receptor radionuclide therapy (PRRT).[3-7] Since surgical resection is the only curative treatment

option for insulinoma, patients are eligible for surgery once the clinical diagnosis has been made and the tumor has been localized using preoperative imaging.

2 | PREOPERATIVE IMAGING OF INSULINOMA

Preoperative imaging is essential to localize the lesion, plan the surgical procedure (eg, enucleation of the lesion or partial pancreatic resection), and determine whether laparoscopic resection is feasible. Typically, the size of insulinomas is small (82% < 2 cm and 47% < 1 cm).[8] This hampers detection by noninvasive imaging methods such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), which have mean sensitivities of only 32.6%, 43.9%, and 53.3%, respectively.[3] Methods with higher sensitivity are angiography with intraarterial calcium stimulation and venous sampling (ASVS), with a sensitivity of 85%, and endoscopic ultrasound (EUS), with a sensitivity of 74.8%. However, shortcomings of these methods are their invasive nature, with concomitant risk of complications, and that they are operator dependent.[3,9-12] Since the majority of neuroendocrine tumors (NETs) express somatostatin receptors (SSTRs) at high levels, somatostatin receptor scintigraphy (SRS) with the radiolabeled peptide octreotide (binding SSTR subtypes 2 and 5) and its derivatives is a very efficient detection method.[13,14] In benign insulinoma however, the receptor density of SSTR subtypes 2 and 5 is low, and therefore, sensitivity of SRS is relatively poor (<50%).[15,16] Recently, the use of SSTR positron emission tomography (PET) tracers [Ga^{68}]Ga-DOTA-TOC and [Ga^{68}]Ga-DOTA-TATE for detection of insulinomas resulted in improved sensitivity of 87%,[17,18] which is mainly due to the better spatial resolution and sensitivity of PET when compared with scintigraphy and due to better affinity of the PET tracers for SSTRs. In contrast to low SSTR expression, benign insulinomas do express high levels of the glucagon-like peptide-1 receptor (GLP-1R) in nearly 100% of cases and are therefore suitable candidates for single-photon emission computed tomography (SPECT) or PET imaging with glucagon-like peptide-1 (GLP-1) analogs.[19] Iodinated GLP-1(7-36) was the first tracer to be investigated as a possible tool for insulinoma detection targeting the GLP-1R, and it showed specific tumor targeting in preclinical models for insulinoma.[20] However, low peptide stability of GLP-1 in blood and rapid deinodination limits clinical use, and therefore, multiple radiolabeled tracers of the natural GLP-1 analog exendin-4 have been developed. Exendin-4 is isolated from the saliva of the Gila monster (*Heloderma suspectum*),[21] and since the dipeptidyl peptidase-IV enzymatic cleavage site is not present in this peptide, it is resistant to degradation in serum, resulting in an increased biological half-life of ≥20 minutes compared with GLP-1 (≤2 min).[22]

In this review, we will give an overview of development of exendin-4–based tracers and their clinical implementation for insulinoma imaging. We will also address some pitfalls of exendin-4–based imaging. Furthermore, we will discuss on the future outlook of the use of exendin-4 in insulinoma theranostics (for an overview, see Figure 1).

3 | IMAGING OF INSULINOMA WITH EXENDIN-4–BASED TRACERS

3.1 | Tracer development and clinical implementation

The first exendin-4–based imaging tracer that was developed is the diethylenetriaminepentaacetic acid (DTPA) conjugate [Lys^{40}(Ahx-DTPA-[^{111}In]In)NH$_2$]-exendin-4.[23,24] This tracer showed high receptor affinity and remarkably high tumor uptake (287 ± 62 %IA/g) in the Rip1Tag2 mouse model[24] (for an overview of exendin-based SPECT tracers and characteristics, see Tables 1 and 2). [Lys^{40}(Ahx-DOTA-[^{111}In]In)NH$_2$]-exendin-4 was also the first tracer to be used in clinical diagnosis of insulinoma.[25] In a prospective pilot study, whole-body planar and SPECT/CT imaging with this tracer successfully detected an insulinoma in all six patients that presented with biochemically proven endogenous hyperinsulinemic hypoglycemia, whereas it was missed in five out of six patients with MRI and in two out of six patients with endosonography. In a second prospective study including 30 patients, [Lys^{40}(Ahx-DTPA-[^{111}In]In)NH$_2$]-exendin-4 SPECT/CT was proven to be a more sensitive method for insulinoma detection than conventional imaging (CT or MRI) (sensitivity of 95% vs. 47%, respectively).[26]

The use of indium-111 has drawbacks since it is costly and carries a relatively high radiation burden for the patient. Technetium-99m can be used to overcome these drawbacks because of its low energy and shorter half-life. To this end, [Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc)NH$_2$]-exendin-4 was developed, and tumor and organ uptake in the Rip1Tag2 mice was lower compared with [Lys^{40}(Ahx-DTPA-[^{111}In]In)NH$_2$]-exendin-4,[27] which could be explained by less efficient internalization of the ^{99m}Tc-labeled tracer. Although the tumor uptake is lower, small lesions (1.0-3.2 mm in diameter) could still be detected with SPECT. [Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc/EDDA)NH$_2$]-exendin-4 was injected in eight patients with clinical and biochemical signs of insulinoma, and in all patients, focal uptake of the tracer was found. In six out of eight patients, surgical excision of the lesion was performed, and these lesions were insulin-producing G1 NETs as confirmed by
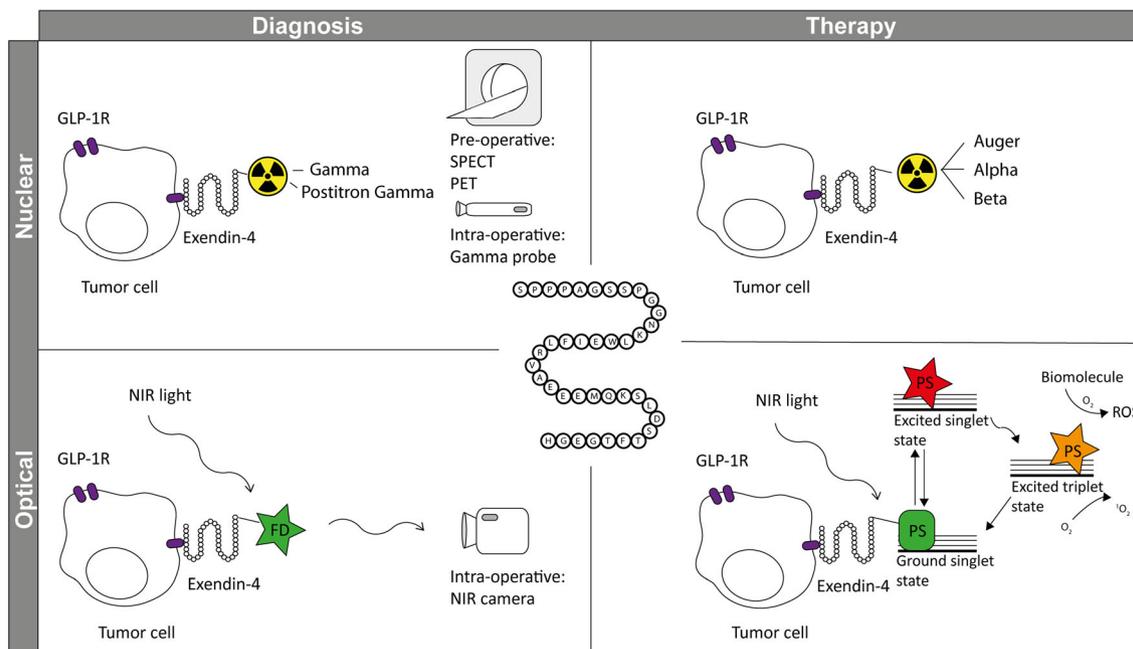
FIGURE 1 Exendin-4 in theranostics of insulinoma. Exendin-4 can be used for diagnosis of GLP-1 receptor (GLP-1R) expressing tumor cells upon conjugation with 1) a radionuclide and preoperative SPECT or PET imaging or intraoperative detection with a gamma probe or 2) a fluorescent dye (FD) and intraoperative imaging with a near-infrared (NIR) light camera. The same molecule can be used for therapy of GLP-1R expressing tumor cells upon conjugation with 1) a therapeutic radionuclide for peptide receptor radionuclide therapy (PRRT) and 2) a photosensitizer (PS) for targeted photodynamic therapy (tPDT).

histopathology.[28] In a second study, 40 patients experiencing episodes of hypoglycemia with no signs of an insulinoma based on conventional imaging methods were included. In 28 of these patients, the [Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc/EDDA)NH$_2$]-exendin-4 scan was positive, and in 18 patients, the presence of an insulinoma was confirmed histopathologically. The other 10 patients could not undergo surgery.[29]

PET imaging has a number of advantages over SPECT imaging, such as higher sensitivity so that lower amounts of a tracer molecule can be detected, better spatial resolution, and more accurate quantification. Therefore, multiple exendin-4–based PET tracers have been developed (for an overview of developed PET tracers and their characteristics, see Tables 3 and 4). Fluorine-18 is a favorable radionuclide for PET imaging because of the low positron emission energy, which provides a short tissue range and thus the potential for achieving a high resolution. As the conditions typically required for ^{18}F-fluorination are very harsh (eg, high temperatures and strong bases), prosthetic groups that can be labeled and conjugated to functional moieties of the exendin-4 have been developed.[30-35] Interestingly, kidney uptake of these tracers is high at first, but clearance from the kidneys is more rapid compared with radiometal-labeled exendin. To overcome the time-consuming synthesis of prosthetic groups, other strategies such as aluminum complexation were applied and showed high tracer uptake by the tumor as well.[36-38]

The use of generator-produced positron emitting gallium-68 makes tracers affordable, and it eliminates the need for a cyclotron on site. Lys^{40}(Ahx-DOTA-[^{68}Ga]Ga)NH2]-exendin-4 showed high tumor uptake (205 ± 59 %IA/g) 4 hours after injection in Rip1Tag2 mice.[27] The [^{68}Ga]Ga-DO3A-VS-Cys40-exendin-4 tracer could be labeled with six times higher specific activity compared with Lys^{40}(Ahx-DOTA-[^{68}Ga]Ga)NH2]-exendin-4, thereby enabling injection of lower peptide dose, and this tracer also showed good tumor uptake in INS-1 xenografts.[39] During the recent years, multiple case reports have been published in which ^{68}Ga-labeled exendin-4 tracers enabled successful detection of insulinomas with PET/CT, while other imaging methods were negative[11,40-44] (for an overview of clinical PET tracers, see Table 4). Antwi et al performed the first pilot study directly comparing [^{111}In]In-DOTA-exendin-4 SPECT/CT with [^{68}Ga]Ga-DOTA-exendin-4 for detection of insulinoma in five patients. In the four patients that were operated on, better spatial resolution and better tumor-to-background ratios allowed for detection of four out of four lesions with [^{68}Ga]Ga-DOTA-exendin-4, while [^{111}In]In-DOTA-exendin-4 detected two out of four lesions.[45] One patient refused surgery, despite a positive [^{68}Ga]Ga-DOTA-exendin-4 scan. In a prospective cohort study, 52 patients with hyperinsulinemic hypoglycemia were included, and various imaging modalities including [^{68}Ga]Ga-NOTA-exendin-4 PET/CT were applied. Forty-three patients that

TABLE 1 Overview of preclinical SPECT tracers and their characteristics

Author + Year	Compound	Tumor Model	Peptide Dose	Activity Dose	Tumor Uptake	Kidney Uptake
Indium-111						
Wild et al. 2006	[Lys^{40}(Ahx-[^{111}In]In-DTPA)NH2]exendin-4	RipTag2 and C57BL/6J RipTag2	10 ng (BD) 50 pmol (Im)	185-370 kBq (BD) 37 MBq (Im)	287 ± 62 %IA/g (4 h)	209 ± 35 %IA/g (4 h)
Wild et al. 2010	[Lys^{40}(Ahx-DTPA-[^{111}In]In)NH2]exendin-4	RipTag2	10 pmol	70-110 kBq	213 ± 75 %IA/g (4 h)	243 ± 17 %IA/g (4 h)
Brom et al. 2012	[Lys^{40}(Ahx-[^{111}In]In-DTPA)NH2]exendin-3	INS-1	20 pmol	370 kBq	25.0 ± 6.0 %ID/g (30 min) 26.5 ± 8.9 %ID/g (4 h)	150.7 ± 14.9 %ID/g (30 min) 188.8 ± 14.4 %ID/g (4 h)
Brom et al. 2012	[Lys^{40}(Ahx-[^{111}In]In-DTPA)NH2]exendin-4	INS-1	20 pmol	370 kBq	30.7 ± 6.1 %ID/g (30 min) 41.9 ± 7.2 %ID/g (4 h)	150.9 ± 9.6 %ID/g (30 min) 173.6 ± 24.3 %ID/g (4 h)
Brom et al. 2012	[Lys^{40}(Ahx-[^{111}In]In-DTPA)NH2]exendin(9-39)	INS-1	20 pmol	370 kBq	3.2 ± 0.7 %ID/g (30 min) 0.71 ± 0.2 %ID/g (4 h)	65.7 ± 6.1 %ID/g (30 min) 70.7 ± 4.0 %ID/g (4 h)
Bauman et al. 2015	[Lys^{40}-(AHX-DTPA-[^{111}In]In)NH$_2$]exendin-4	RIN-m5f	10 pmol, 52 ng	385 kBq	14.74 ± 5.91 %ID/g (1 h) 15.56 ± 5.32 %ID/g (4 h) 9.31 ± 2.35 %ID/g (24 h) 3.47 ± 0.52 %ID/g (48 h)	152.70 ± 24.86 %ID/g (1 h) 178.41 ± 33.66 %ID/g (4 h) 144.09 ± 20.94 %ID/g (24 h) 84.80 ± 19.26 %ID/g (48 h)
Kimura et al. 2017	[Lys^{12}([^{111}In]In-BnDTPA)]exendin-9-39	INS-1	1.5 ng 790 ng	37 kBq/100 μL (BD) 19.9 MBq/220 μL (Im)	7.83 ± 1.86 %ID/g (30 min) 1.87 ± 0.52 %ID/g (4 h) –	193.6 ± 15.1 %ID/g (30 min) 180.9 ± 52.7 %ID/g (4 h) –
Technetium-99m						
Wild et al. 2010	[Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc/EDDA)NH2]exendin-4	RipTag2	10 pmol (BD) –	70-110 kBq (BD) 37 MBq (Im)	67 ± 13 %IA/g (30 min) 93.1 ± 19.9 %IA/g (4 h) –	63 ± 10 %IA/g (30 min) 60 ± 12 %IA/g (4 h) –
Medina-Garcia et al. 2015	[Lys^{27}([^{99m}Tc]Tc-EDDA/HYNIC)]exendin(9-39)	AR42J induced	–	1.85 MBq	2.41 ± 0.38 %ID/g (2 h)	95.01 ± 1.95 %ID/g (2 h)

Abbreviations: BD, biodistribution; Im, imaging; SPECT, single-photon emission computed tomography.

were operated on and had histopathologically proven insulinoma were included for analysis. [^{68}Ga]Ga-NOTA-exendin-4 PET/CT showed a very high sensitivity of 97.7%, in contrast to 74.4% for CT, 56% for MRI, 84% for EUS, and 19.5% for [^{99m}Tc]Tc-HYNIC-TOC SPECT/CT.[43]

In a prospective crossover imaging study with GLP-1R PET/CT, GLP-1R SPECT/CT, and 3T MRI, 52 patients with biochemically proven endogenous hyperinsulinemic hypoglycemia were included. For each patient, a [^{68}Ga]Ga-DOTA-exendin-4 PET/CT scan,

TABLE 2 Overview of clinical single-photon emission computed tomography (SPECT) tracers and study outcomes

Author + Year	Compound	Patients	Peptide Dose	Activity Dose	Results	Adverse Events
Indium-111						
Christ et al. 2009	[Lys^{40}(AHX-DOTA-[In^{111}]In)NH$_2$] exendin-4	6	30 µg	82-97 MBq	In all six patients, the insulinoma was correctly localized.	- Decrease in blood glucose levels 0.3-2.4 mmol/L, glucose infusion needed in three patients - Vomiting (n = 1)
Wild et al. 2011	[Lys^{40}(AHX-DTPA-[In^{111}]In)NH$_2$] exendin-4	11	10 ± 2 µg	108-136 MBq	Uptake in four patients was observed with malignant insulinomas that were expressing the GLP-1R.	- Decrease in blood glucose levels 1.1-3.3 mmol/L in GLP-1R–positive patients, 0.5-0.6 mmol/L in GLP-1R–negative patients
Christ et al. 2013	[Lys^{40}(AHX-DTPA-[In^{111}]In)NH$_2$] exendin-4	30	8-14 µg	80-128 MBq	95% (75-100) sensitivity 20% (2-64) specificity 83% (62-94) positive predictive value	- Decrease in blood glucose levels 0-2.6 mmol/L, glucose infusion needed in 20 patients
Antwi et al. 2015	[Nle$_{14}$, Lys$_{40}$(Ahx-DOTA-[^{111}In]In)NH$_2$] exendin-4]	5	10.5-14.4 µg	79.2 ± 9.3 MBq (66-90 MBq)	In four out of five patients that had surgery, an insulinoma was found in two of four patients.	- Prophylactic glucose infusion was given before the injection - Nausea (n = 2) and vomiting (n = 2)
Antwi et al. 2018	[^{111}In]In-DOTA-exendin-4	52	11.0-16.9 µg	87.5 ± 10.7 MBq (52-111 MBq)	Sensitivity 68.5% (59.0-77.0)	- No hypoglycemia due to continuous infusion of glucose - Nausea (n = 27) and vomiting (n = 23)
Fluorine-18						
Sowa-Staszczak et al. 2013	[Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc/EDDA)NH$_2$]-exendin-4	11	–	740 MBq (mean)	Focal uptake in all eight cases with suspicion of benign insulinomas was observed. In six of the eight patients, surgery was performed and the presence of an insulinoma was confirmed.	- Most patients with benign insulinoma needed glucose infusion
Sowa-Staszczak et al. 2016	[Lys^{40}(Ahx-HYNIC-[^{99m}Tc]Tc/EDDA)NH$_2$]-exendin-4	40	–	740 MBq (mean)	Uptake was seen in 28 patients. In 18 out of 28 cases, insulinomas were identified histopathologically.	- All patients with suspected benign insulinoma needed glucose infusion

[^{111}In]In-DOTA-exendin-4 SPECT/CT scans (4 and 72 h), and an MRI scan were performed. In 38 out of 52 patients, histological confirmation could be obtained, and this resulted in sensitivities of 94.6%, 68.5%, and 69.4% for [^{68}Ga]Ga-DOTA-exendin-4, [^{111}In]In-DOTA-exendin-4, and MRI, respectively.[46] Although spatial resolution of PET/CT is better compared with SPECT/CT, small lesions can still be missed as is illustrated by the only false-negative PET/CT finding of a 5 × 5 × 10 mm insulinoma in this study.

High kidney accumulation of exendin-4–based tracers can complicate imaging applications, since the tail of the pancreas is located close to the kidney. For both indium-111 and technetium-99m exendin-based tracers, tumor-to-kidney ratios do increase over time, and therefore, authors suggest that additional late scans should be made

TABLE 3 Overview of preclinical PET tracers and their characteristics

Author + Year	Compound	Tumor Model	Peptide Dose	Activity Dose	Tumor Uptake	Kidney Uptake
Gallium-68						
Wild et al. 2010	[Lys^{40}(Ahx-DOTA-[^{68}Ga]Ga)NH2]exendin-4	RipTag2	10 pmol	70-110 kBq	185 $\pm$ 33 %IA/g (30 min) 205 $\pm$ 59 %IA/g (4 h)	255 $\pm$ 14 %IA/g 202 $\pm$ 34 %IA/g
Selvaraju et al. 2014	[^{68}Ga]Ga-DO3A-VS-Cys^{40}-Exendin-4	INS-1 xenografts	2.5 µg/kg	0.6 $\pm$ 0.1 MBq	Tumor-to-muscle ratio 44.8 (80 min)	–
Bauman et al. 2015	[Lys^{40}-(AHX-DFO-[^{68}Ga]Ga)NH$_2$]exendin-4	RIN-m5f xenografts	10 pmol, 52 ng	385 kBq	32.48 $\pm$ 8.26 %ID/g (1 h)	141.51 $\pm$ 25.14 %ID/g (1 h)
Rylova et al. 2016	[Nle^{14},Lys^{40}(Ahx-DOTA-[^{68}Ga]Ga)NH$_2$]exendin-4	INS-1 xenografts	100 pmol (BD) 100 pmol (Im)	0.4-0.9 MBq (BD) 0.4-0.9 MBq (Im)	40.2 $\pm$ 8.2 %IA/g (1 h) –	235.8 $\pm$ 17.0 %IA/g (1 h) –
Rylova et al. 2016	[Lys^{27}(Ahx-DOTA-[^{68}Ga]Ga]exendin(9-39)NH$_2$	INS-1 xenografts	100 pmol (BD)	0.4-0.9 MBq (BD)	–	113.8 $\pm$ 23.8 %IA/g (1 h)
Rylova et al. 2016	[Lys^{27}(NODAGA-[^{68}Ga]Ga]exendin(9-39)NH$_2$	INS-1 xenografts	100 pmol (BD)	0.4-0.9 MBq (BD)	0.7 $\pm$ 0.2 %IA/g (1 h)	101.0 $\pm$ 21.0 %IA/g (1 h)
Rylova et al. 2016	[Lys^{40}(NODAGA-[^{68}Ga]Ga)NH$_2$]exendin(9-39)	INS-1 xenografts	100 pmol (BD) 100 pmol (Im)	0.4-0.9 MBq (BD) 0.4-0.9 MBq (Im)	2.2 $\pm$ 0.2 %IA/g (1 h) –	78.4 $\pm$ 8.5 %IA/g (1 h) –
Läppchen et al. 2017	[Nle^{14},Lys^{40}(Ahx-DOTA-[^{68}Ga]Ga)NH$_2$]exendin-4	INS-1 xenografts	10 pmol (BD)	–	58.3 $\pm$ 15.6 %IA/g (1 h)	201.3 $\pm$ 30.6 %IA/g (1 h)
Fluorine-18						
Kiesewetter et al. 2012	[^{18}F]FBEM-[Cys^{40}]exendin-4	INS-1 xenografts	0.5-1 µg (BD) 0.5-1 µg (Im)	3.44 $\pm$ 0.26 MBq (BD) 3.44 $\pm$ 0.26 MBq (Im)	– 25.25 $\pm$ 3.39 %ID/g (1 h)	Tumor-to-kidney ratio 7.4 (2 h) Tumor-to-kidney ratio 4.94 (2 h)
Kiesewetter et al. 2012	[^{18}F]FBEM-[Cys^{0}]-exendin-4	INS-1 xenografts	0.5-1 µg (BD) 0.5-1 µg (Im)	3.44 $\pm$ 0.26 MBq (BD) 3.44 $\pm$ 0.26 MBq (Im)	– 7.2 $\pm$ 1.26 %ID/g (1 h)	Tumor-to-kidney ratio 0.48 (2 h) Tumor-to-kidney ratio 0.74 (2 h)
Kiesewetter et al. 2012	[^{18}F]AlF-NOTA-MAL-Cys^{40}-exendin-4	INS-1 xenografts	300 pmol (BD) 300 pmol (Im)	3.44 $\pm$ 0.26 MBq (BD) 3.44 $\pm$ 0.26 MBq (Im)	17.9 $\pm$ 1.4 %ID/g (1 h) 15.7 $\pm$ 1.4 %ID/g (30 min) 14.6 $\pm$ 1.3 %ID/g (1 h)	– 79.3 $\pm$ 3.7 %ID/g (30 min) 74.7 $\pm$ 6.2 %ID/g (1 h)
Wu et al. 2013	[^{18}F]FB-exendin-4	RIN-m5f xenografts	40 µg (BD) 40 µg (Im)	3.7 MBq (BD) 3.7 MBq (Im)	0.15 %ID/g (2 h) –	0.27 %ID/g (2 h) –
Yue et al. 2013	[^{18}F]FPenM-[cys^{40}]-exendin-4	INS-1 xenografts	– –	3.7 MBq (Im) 3.7 MBq (BD)	21.30 $\pm$ 4.55 %ID/g (30 min) 20.32 $\pm$ 4.36 %ID/g (1 h) – 33.21 $\pm$ 4.79 %ID/g (1 h)	34.41 $\pm$ 4.59 %ID/g (30 min) 11.30 $\pm$ 2.41 %ID/g (1 h) 33 %ID/g (30 min) 11 %ID/g (1 h)
Xu et al. 2014	[^{18}F]FBEM-Cys^{39}-exendin-4	INS-1 xenografts	106 pmol (BD) 21 pmol (Im)	0.74 MBq (BD) 3.7 MBq (Im)	12.85 $\pm$ 2.21 %ID/g (30 min)	29.64 $\pm$ 3.47 %ID/g (30 min)

TABLE 3 (Continued)

Author + Year	Compound	Tumor Model	Peptide Dose	Activity Dose	Tumor Uptake	Kidney Uptake
					10.06 ± 1.93 %ID/g (2 h)	12.43 ± 0.75 %ID/g (2 h)
					10.71 ± 1.46 %ID/g (30 min)	21.27 ± 4.10 %ID/g (30 min)
					9.19 ± 0.86 %ID/g (2 h)	11.62 ± 2.08 %ID/g (2 h)
Xu et al. 2015	[^{18}F]AlF-NOTA-MAL-Cys39-exendin-4	INS-1 xenografts	128 pmol (BD) 638 pmol (Im)	0.74 MBq (BD) 3.7 MBq (Im)	8.68 ± 0.46 %ID/g (30 min) 7.59 ± 0.60 %ID/g (1 h) 9.15 ± 1.6 %ID/g (30 min) 7.74 ± 0.87 %ID/g (1 h)	86.19 ± 4.87 %ID/g (30 min) 95.91 ± 9.20 %ID/g (1 h) 75.12 ± 4.35 %ID/g (30 min) 85.32 ± 5.89 %ID/g (1 h)
Dialer et al. 2018	[^{18}F]F-2	CHL-GLP-1R xenografts	1.3 pmol, 5.9 ng (BD) 1.3 nmol (Im)	200 kBq (BD) 13 MBq (Im)	15 ± 7 %ID/g (30 min) 14 ± 7 %ID/g (1 h) 13 ± 10 %ID/g (2 h) SUV_{tumor} of 2.2 (2 h)	33.3 ± 2.4 %ID/g (30 min) 49 ± 18 %ID/g (1 h) 39 ± 12 %ID/g (2 h) $SUV_{kidneys}$ of 4.1 (2 h)
Zirconium-89						
Bauman et al. 2015	[Lys^{40}-(AHX-DFO-[^{89}Zr]Zr)NH$_2$]exendin-4	RIN-m5f xenografts	10 pmol, 52 ng	385 kBq	13.46 ± 0.79 %ID/g (1 h) 11.73 ± 3.17 %ID/g (4 h) 8.23 ± 1.61 %ID/g (24 h) 3.1 ± 0.17 %ID/g (48 h)	216.89 ± 56.22 %ID/g (1 h) 188.25 ± 52.22 %ID/g (4 h) 169.12 ± 44.87 %ID/g (24 h) 144.27 ± 1.68 %ID/g (48 h)
Iodine-125						
Rylova et al. 2016	[[^{125}I]I-BH-Lys^{27}]exendin(9-39)NH$_2$	INS-1 xenografts	–	0.037 MBq (BD)	42.5 ± 8.1 %IA/g (1 h) 19.8 ± 4.3 %IA/g (4 h)	12.1 ± 1.4 %IA/g (1 h) 4.2 ± 0.7 %IA/g (4 h)
Läppchen et al. 2017	[Nle^{14},[^{125}I]I-Tyr^{40}-NH$_2$]exendin-4	INS-1 xenografts	0.5 pmol (BD) –	40 KBq (BD) 2.5-3.0 MBq (Im)	72.8 ± 12.2 %IA/g (1 h) 22.4 ± 2.9 %IA/g (4 h) 3.7 ± 2.5 %IA/g (24 h)	7.5 ± 0.7 %IA/g (1 h) 3.2 ± 0.3 %IA/g (4 h) 0.2 ± 0.0 %IA/g (24 h)
Läppchen et al. 2017	[Nle^{14},[^{125}I]I-Tyr^{40}-NH$_2$]exendin(9-39)	INS-1 xenografts	0.5 pmol (BD)	40 KBq (BD)	12.7 ± 4.1 %IA/g (1 h) 1.9 ± 0.5 %IA/g (4 h)	7.6 ± 1.2 %IA/g (1 h) 2.0 ± 0.3 %IA/g (4 h)

Abbreviations: BD, biodistribution; Im, imaging; PET, positron emission tomography.

in case of negative scans early after injection,[28,29,47,48] as has been suggested for longer-lived positron-emitting radionuclides such as zirconium-89 as well.[49] The use of radioiodinated exendin-based tracers should also be considered to reduce renal accumulation.[50,51]

3.2 | Imaging of benign versus malignant insulinoma

Nearly all benign insulinomas express GLP-1R whereas expression of SSTR is low or not present. This while

TABLE 4 Overview of clinical positron emission tomography (PET) tracers and study outcomes

Author + Year	Compound	Patients	Peptide Dose	Activity Dose	Results	Adverse Events
Gallium-68						
Eriksson et al. 2014	[^{68}Ga]Ga-DO3A-VS-Cys^{40}-Exendin-4	1	0.17 µg/kg	0.88 MBq/kg	Detection of liver and lymph node metastases	–
Antwi et al. 2015	[Nle$_{14}$, Lys$_{40}$(Ahx-DOTA-[^{68}Ga]Ga)NH$_2$] exendin-4]	5	12.0-15.3 µg	79.8 ± 3.9 MBq (76-97 MBq)	In four out of 5 patients that had surgery, an insulinoma was found in four of four patients	- Prophylactic glucose infusion was given before the injection - Nausea (n = 1)
Luo et al. 2015	[^{68}Ga]Ga-NOTA-exendin-4	1	–	–	Detection of insulinoma in the pancreas tail (SUV$_{max}$ of 20.7)	–
Cuthbertson et al. 2015	[^{68}Ga]Ga-NOTA-exendin-4	1	–	–	Detection of insulinoma	–
Luo et al. 2016	[^{68}Ga]Ga-NOTA-exendin-4	1	–	51.8 MBq	Detection of insulinoma in the pancreas tail (SUV$_{mean}$ of 20.0 and SUV$_{max}$ of 52.9)	–
Luo et al. 2016	[^{68}Ga]Ga-NOTA-MAL-Cys^{40}-exendin-4	52	7-25 µg	18.5-185 MBq	In 43 of 52 patients, surgery was performed. In 42 patients, an insulinoma was found (sensitivity of 97.7%)	- No hypoglycemia was observed because of continuous infusion of glucose - Nausea (n = 2) - Vomiting (n = 2)
Luo et al. 2017	[^{68}Ga]Ga-exendin-4	1	–	–	Detection of a lesion that was ablated with ethanol ablation (SUV$_{mean}$ of 5.7 and SUV$_{max}$ of 10.8)	–
Bongetti et al. 2018	[^{68}Ga]Ga-DOTA-exendin-4	1	–	–	The ^{68}Ga-DOTA-exendin-4 was suggestive of nesidioblastosis; however, an insulinoma as identified with SACST and EUS was missed, noting that the insulinoma was negative for GLP-1R	–
Parihar et al. 2018	[^{68}Ga]Ga-DOTA-exendin-4	1	–	–	Detection of insulinoma (SUV$_{max}$ of 21)	–
Antwi et al. 2018	[^{68}Ga]Ga-DOTA-exendin-4	52	11.6-23.8 µg	82.4 ± 14.9 MBq (43-106 MBq)	Sensitivity 94.6% (88.6-98.0)	- No hypoglycemia due to continuous infusion of glucose - Nausea (n = 14) and vomiting (n = 1)

malignant insulinomas often lack expression of GLP-1R but have high expression of SSTR.[16,52] This is reflected in various clinical imaging studies with exendin-4–based tracers, where false-negative cases were proven to be malignant insulinomas.[28,29,48,53] Interestingly, also differences in uptake between primary tumor and metastases[28,29] and uptake of both tracers in one lesion[43] were observed, stressing the variability in molecular phenotype of insulinomas, which should be taking into account when selecting the appropriate tracer. To be able to detect both benign and malignant lesions with one imaging procedure, a hybrid Lys^{27}([^{99m}Tc]Tc-EDDA/HYNIC)-exendin$^{9-39}$/[^{99m}Tc]Tc-EDDA/HYNIC-Tyr^3-octreotide formulation was prepared for simultaneous imaging of SSTR and GLP-1R.[54] Uptake of this tracer in SSTR and GLP-1R positive AR42J tumor xenografts was observed, and specificity for both targets was confirmed with blocking studies. In clinical practice, GLP-1R and SSTR

expression cannot be distinguished on the SPECT scan; however, evidence of local invasiveness and lymph node or liver metastases is indicative of malignant disease.[55] Alternatively, octreotide and exendin-4 in the hybrid tracer could be labeled with different radionuclides, enabling dual-radioisotope imaging.

3.3 | Prevent GLP-1R stimulation; reduction of peptide dose and use of receptor antagonists

Exendin-4 is a GLP-1R agonist and can therefore induce hypoglycemia because of receptor stimulation. GLP-1R agonists can induce insulin secretion, but this is dependent on elevated blood glucose levels, especially when levels exceed euglycemic concentrations of glucose. The effect of exendin-4 is thus self-regulating, and this lowers the risk of hypoglycemic events.[56] Other known side effects that may occur are nausea and vomiting. It is therefore important to minimize the peptide dose that is injected into patients, and various efforts have been made to increase specific activity. Christ et al first performed clinical SPECT imaging using a peptide dose of 30 μg, whereas in later clinical studies, doses of approximately 2 to 17 μg were used and also higher specific activities were achieved.[28,29,45-48,52] For PET imaging studies, peptide doses of 7 to 25 μg were injected, in which a wide range in peptide dose can be observed within and between studies.[40,41,43-46,53,57,58] Most studies using SPECT tracers did not report side effects like hypoglycemia, nausea, or vomiting.[28,29,48,52] However, in two studies where a SPECT tracer was administered, a substantial number of side effects (nausea and vomiting) were observed.[45,46] Clinical studies with exendin-based PET tracers led to only few cases of vomiting while more cases of nausea were reported.[40,41,43-46,53,57,58] Despite that the effect of exendin-4 is self-limiting,[56] there is still a substantial risk of hypoglycemia because of insulin release by functional insulinomas. In various studies, hypoglycemia was countered by glucose infusion or prevented by prophylactic glucose infusion. Blood glucose monitoring of patients is therefore essential once the tracer has been administered. The available data show that the occurrence of side effects was lower in studies with PET imaging compared with SPECT imaging, but this can depend on factors such as peptide dose and glucose infusion. For an overview of the clinical studies and tracers, see Tables 2 and 4.

Furthermore, studies have compared the use of exendin-4 with the receptor antagonist, exendin(9-39). Waser and Reubi showed excellent binding affinities in a Rip1Tag2 mouse model for both the agonist and antagonist.[59] Interestingly, Brom et al found that receptor affinity on INS-1 cells was high for both the agonist and antagonist, but the antagonist did not show internalization, and the tumor uptake was low.[60] The discrepancy between the studies can be explained by the receptor density, where the Rip1Tag2 mouse model has a higher number of receptors that can be bound by the antagonist. The number of bound receptors was not significantly different for the agonist and antagonist in case of the INS-1 cells.[60] Furthermore, when comparing the number of receptors for INS-1 cells and human insulinoma tissue, a substantial lower receptor density for human functioning insulinomas can be observed.[16,60] In case of a lower number of receptors, which is the situation in vivo, the agonist performs much better than the antagonist. Therefore, only the agonist is suitable for in vivo targeting of the GLP-1R.

Finally, several studies report on the use of radioiodinated antagonist-based tracers. [^{125}I]I-BH-exendin(9-39) exhibited high uptake in murine pancreas,[61] and the antagonist [Lys^{27}(^{125}I)I-BH-exendin(9-39)NH$_2$ demonstrated tumor uptake that was comparable with the agonists but with a substantially reduced kidney uptake.[51] In contrast, the antagonist [Nle^{14},[^{125}I]I-Tyr^{40}-NH$_2$]exendin(9-39) showed lower affinity and lower internalization than the more favorable agonist [Nle^{14},[^{125}I]I-Tyr^{40}-NH$_2$]exendin-4.[50]

3.4 | Fluorescence imaging for intraoperative detection of insulinoma

Because of the large penetration depth of γ-photons, whole-body imaging with SPECT and PET gives preoperative information on tumor size and location. Intraoperatively, gamma probes can be used for radioguided detection of tumors, as has been proven successful for [^{111}In]In-DOTA-exendin-4 for up to 14 days after tracer injection.[47] Fluorescence imaging probes provide images with better spatial resolution, and could therefore be used for more precise intraoperative delineation of the tumor, and fluorescence-guided surgery (FGS). Hypothetically, this will prevent unnecessary damage of pancreatic tissue, reduce the time that patients are under anesthesia, and related comorbidity. Various fluorescent exendin tracers have been developed,[62-66] with the primary goal of pancreatic beta cell visualization and quantification, although these are not used clinically so far. For in vivo imaging, fluorophores in the far-red wavelength (800 nm) are most suitable, since there is reduced autofluorescence of tissue at this wavelength, and because there is higher tissue penetration of 800-nm light. A frequently used dye for fluorescence guiding purposes is IRDye800CW, which has been conjugated to multiple targeting moieties and is increasingly used for clinical FGS in various solid tumor types.[67-69] We have developed a clinical grade exendin-4-IRDye800CW conjugate and shown

feasibility of insulinoma targeting and imaging in mice with subcutaneous GLP-1R overexpressing Chinese hamster lung cell tumors.[70] We intent to start clinical trials in which this tracer is employed for FGS of insulinoma. To combine high resolution, high sensitivity, and deep tissue penetration, dual-labeled targeting moieties with a radionuclide and fluorophore have been developed for other theranostic applications in oncology. One example is the carbonic anhydrase IX targeting probe [^{111}In]In-DTPA-G250-IRDye800CW for which fluorescence imaging was proven to be safe and suitable for intraoperative guidance of renal cell cancer resection in the clinic.[69] To the best of our knowledge, only Brand et al developed a dual-labeled exendin-4 tracer (fluorescein and ^{64}Cu).[71] With this tracer, small insulinoma xenografts were visualized with PET, and with fluorescence, individual pancreatic islets could be detected. Especially when conjugated with far-red fluorophores such as IRDye800CW, similar dual-modal tracers could be used for preoperative detection and intraoperative surgical guidance, ensuring complete resection of the insulinoma while preserving healthy pancreatic tissue.

4 | THERAPY WITH EXENDIN-4–BASED TRACERS

4.1 | Peptide receptor radionuclide therapy

Importantly, since for benign insulinoma surgical resection remains the therapy of choice, only patients with metastasized malignant insulinoma are eligible for (SSTR directed) PRRT. However, some effort has also been taken to develop exendin-4–based tracers for PRRT. As described above, ^{111}In-labeled exendin-4 analogs are predominantly used for imaging of γ-radiation, but indium-111 also emits low energy Auger electrons, which have a tissue penetration of only 0.02 µM to 10 µM. They exert their cytotoxic potential when in close proximity to the DNA after internalization. Auger electron emitting [Lys[40](Ahx-DTPA-[^{111}In]In)NH$_2$-exendin-4 efficiently repressed insulinoma growth in the Rip1Tag2 mouse model, but administration of high doses resulted in significant renal radiation damage and chronic renal failure.[72] Since all exendin-4–based tracers show high kidney uptake, kidney toxicity is a serious concern and precludes PRRT from clinical application at the moment.

4.2 | Kidney dosimetry and methods to reduce kidney uptake of exendin-4–based tracers

Some dosimetry studies have been performed with exendin-4–based tracers. Absorbed kidney doses that were found in case of exendin-4–based imaging tracers ranged from 0.1 to 4.5 mGy/MBq; these data were mostly derived from animal studies.[27,35,73,74] Furthermore, two studies investigated the potential of PRRT with ^{177}Lu-labeled exendin-4 using dosimetric calculations either extrapolated from biodistribution data of ^{177}Lu-labeled exendin-4 in rats or with a macro- and small-scale-dosimetry model[75] applied to ^{111}In-labeled exendin-4 SPECT/CT scans in humans.[73,76]

Estimated activities that could be administered without exceeding the maximum allowed absorbed kidney dose of 23 Gy were 3.8 GBq and 1.0 to 1.8 GBq, respectively. Concomitant absorbed insulinoma doses of 30 to 128 mGy/MBq were found, and these doses can lead to tumor shrinkage as was seen for pancreatic NETs after ^{177}Lu-labeled DOTATATE treatment.[77] Furthermore, the dose to the islets remained below 5 Gy, a dose which is considered a low risk of developing diabetes.[78] However, the absorbed kidney doses would allow for only one therapeutic cycle, in contrast to treatment with ^{177}Lu-labeled somatostatin analogs in which two to six cycles of 7.4 GBq are possible.[77] Higher injected doses and thus improved feasibility of PRRT with ^{177}Lu-labeled exendin-4 could be achieved by successfully lowering the renal accumulation.

Commonly used methods to reduce kidney uptake of peptide-based tracers are competitive inhibition of reabsorption by coinfusion of positively charged amino acids, trypsinized albumin, or the plasma expander gelofusine. Coinfusion of the combination of poly-glutamic acid and gelofusine has reduced renal uptake of ^{111}In-labeled exendin-4 by 48% in preclinical models.[79] Poly-glutamic acid is however not clinically available while gelofusine can be used in the clinical setting. In healthy volunteers, coinfusion of gelofusine showed a reduction of 18% in renal accumulation of ^{111}In-labeled exendin-4, without lowering tracer uptake in the pancreas.[76] Dosimetric calculations indicated that coinfusion with gelofusine increased the estimated allowable injected dose of ^{177}Lu-labeled exendin-4 with more than 20%, which would lead to higher absorbed insulinoma doses.

Other strategies to reduce renal uptake are introduction of a cleavable linker to allow renal excretion of the radionuclides,[80] inhibition of neutral endopeptidases to increase metabolic stability of the peptide in the circulation,[79,81-84] and incorporation of highly lipophilic groups[34] (efficacies of these strategies are summarized in Table 5). Furthermore, groups have conjugated exendin to PEG,[85-87] albumin,[88] an albumin binding domain,[89] a nonglycosylated human Fc fragment,[90] or nanoparticles[91-93] to increase circulation time. Since these strategies potentially increase uptake of the exendin-4 conjugates in other organs such as the liver, biodistribution and potency for imaging should be assessed for every compound.

TABLE 5 Strategies to lower kidney uptake of exendin-4–based tracers and their efficacy as described in various studies

Strategy	Outcome
Cleavable linker	• No significant change in kidney retention in comparison with [^{111}In]In-Ex4NOD40. It was assumed that the peptides were not cleaved before reabsorption in vivo.[80]
Inhibition of neutral endopeptidases	• Polygelines Haemaccel and gelofusine both increased urinary secretion of protein β_2-microglobulin, most likely explained by competitive inhibition of tubular protein reabsorption.[81] • Gelofusine and poly-glutamic acid (PGA) reduced kidney uptake by 18.7% and 29.4%, respectively. Gelofusine and PGA combined decreased kidney uptake by 47.9%.[79] • Gelofusine, albumin fragments, and lysine decreased renal uptake by 52%, 25%, and 15%, respectively.[82] • Albumin-derived peptide lowered renal uptake by 26% while gelofusine led to a reduction of 16%.[84]
Incorporation of highly lipophilic groups	• Kidney uptake was considerably lower compared with radiometal-labeled compounds and ranged from 30 to 50 %ID/g.[34]

Clinical applicability of exendin-4–based PRRT thus depends on multiple factors. First, renal accumulation should be largely reduced using improved or novel strategies to allow for higher insulinoma doses and possibly enable multiple therapy cycles. Another important factor using exendin-4 for PRRT is achieving a high specific activity, which enables the injection of therapeutic activity doses while keeping peptide doses sufficiently low. Low specific activities require the administration of higher peptide doses and could increase the risk of side effects. Preferably, peptide doses should be comparable with doses applied in imaging; nevertheless, the risk of side effects should be evaluated carefully.

4.3 | Photodynamic therapy

To avoid kidney toxicity, photodynamic therapy (PDT) might be an alternative tumor-ablative intervention. PDT involves administration of a photosensitizer (PS), followed by specific illumination of the tumor with light of a specific wavelength, often in the near infrared (NIR) range.[94] The activated PS will be converted from the ground singlet energy state into the excited singlet state. The PS can then decay back to the ground state, thereby emitting fluorescence, or it can undergo intersystem crossing and go to an excited triplet state. In this state, it can react directly with a substrate, which then reacts with oxygen to produce oxygenated products, or it can react directly with oxygen to form $^1O_2$.[94] Products of these two reactions are responsible for cell killing.[95] A large number of PSs have been developed and tested for treatment of cancer.[96] First generation porphyrin-based PSs were effectively used for treatment of various cancers, such as melanoma[97]; however, they were also taken up in normal tissue and skin, leading to severe skin phototoxicity. Hypericin is a second-generation PS that was shown to effectively internalize and accumulate in RINm5F insulinoma cells, and upon illumination, it induced apoptosis[98]; however, no experiments in in vivo models have been described so far.

By conjugating a PS to a tumor targeting molecule, it is possible to induce very specific cell death of target-expressing cells, a concept referred to as targeted photodynamic therapy (tPDT)[99] (Figure 1). This strategy will decrease side effects caused by accumulation of PSs in normal tissues. The technique is increasingly applied in various types of cancer, and a first clinical trial with cetuximab conjugated to the PS IRDye700DX in head-and-neck cancer patients is currently performed (ClinicalTrials.gov identifier NCT02422979). IRDye700DX is a frequently used PS in tPDT applications, mainly because of its high quantum yield, favorable excitation characteristics, and hydrophilicity of the molecule. Exendin-based tPDT could be a future application for ablation of small tumors in the pancreas, thereby reducing morbidity caused by unneeded radical resections. Furthermore, inoperable tumors that are in the near vicinity of, eg, the pancreatic duct could be removed without damaging these vital structures. These procedures could be performed laparoscopically since lasers for PDT are clinically available. We have developed an exendin-4-IRDye700DX conjugate, which causes very efficient and specific cell death of GLP-1R expressing cells in vitro and in vivo.[100]

5 | FUTURE OUTLOOK ON THE USE OF EXENDIN-4 IN INSULINOMA THERANOSTICS

SPECT and PET imaging with exendin-4 analogs provide means for delineation and localization of insulinoma lesions. Compared with SPECT, PET imaging is preferable because of increased spatial resolution and therefore better tumor delineation. Currently, gallium-68 is the most universally available and affordable positron emitter, offering easy labeling via a chelator. The sensitivity of [^{68}Ga]Ga-DOTA-exendin-4 PET/CT has proven to be superior to the sensitivity of [^{111}In]In-DTPA-exendin-4 SPECT/CT or MRI.[46] When NODAGA is used instead of DOTA, a higher
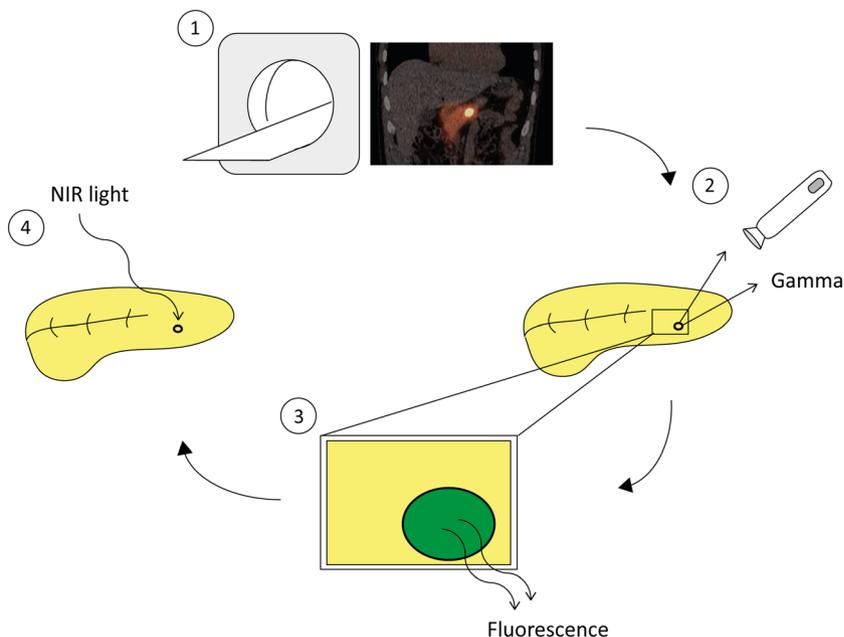
FIGURE 2 Multimodal exendin for theranostics of insulinoma. Radiolabeled exendin-4 can be used for SPECT or PET imaging to locate the lesion (1), however to detect the lesion intraoperatively a gamma probe (2) and fluorescence imaging (3) can be used. Furthermore the lesion can then be treated with NIR light to eradicate GLP-1R expressing cells (4).

specific activity can be obtained, allowing administration of lower peptide doses and thus minimizing risk of side effects due to receptor activation.[101,102] Therefore, we are currently performing a prospective multicenter study comparing [^{68}Ga]Ga-NODAGA-exendin PET/CT with MRI and [^{68}Ga]Ga-DOTA-TATE PET/CT (ClinicalTrials.gov identifier NCT03189953).[101,102]

Upon localization of an insulinoma, surgical resection is the treatment of choice; however, this is not always possible because of risk of complications or inoperability of patients. Therefore, imaging methods could merge into theranostics when exendin-4 is also used as a tracer for PRRT or tPDT. Currently, radiotoxicity in other tissues that take up or excrete the exendin-4–based tracers limits application of PRRT.[73] tPDT could be used for specific elimination of tumor cells, without causing damage to other tissues. Importantly, compared with benign insulinomas, malignant insulinomas are known to have increased expression of SSTR and limited expression of GLP-1R. Therefore, assessment of expression of these targets by nuclear imaging would be essential before applying tracer-based therapy.

To conclude, because of superior sensitivity when compared with conventional imaging methods, we believe that exendin-4–based PET/CT imaging should be considered as a primary method in patients with biochemical signs of insulinoma, enabling a one-stop shop procedure for detection and localization of insulinoma. Surgery will remain the therapy of choice for benign insulinoma, since high kidney uptake precludes the use of exendin-4–based tracers for PRRT. However, exendin-4–based tracers conjugated to fluorescent molecules may enable FGS or specific elimination of

insulinomas with tPDT, without causing kidney damage (Figure 2).

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Maarten Brom studied Life Sciences at the Hogeschool Utrecht and Molecular Life Sciences at HAN University, Nijmegen. After graduating in 2006, he started his PhD project in 2007 at the department of Radiology and Nuclear medicine of the Radboudumc Nijmegen, involving development of radiotracers for determination of beta-cell mass. He continued working on these projects, and on clinical implementation of exendin-based tracers as a post-doc researcher and group leader. Currently he works as a project manager at Tracer Europe BV, Groningen.

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