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Evolution of Neuroendocrine Tumor Therapy

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On April 2, 1986, a symposium comprised of multidisciplinary preclinical and clinical scientists and physicians was convened and the proceedings published.[1] It addressed neuroendocrine disorders of the gastroenteropancreatic (GEP) systems and introduced preclinical and clinical applications of the somatostatin peptide analogue SMS 201–995 (octreotide [Sandostatin]). Three years later, in 1989, octreotide was the first Food and Drug Administration (FDA)-approved drug for the symptomatic control of carcinoid syndrome and the watery diarrhea syndrome of the pancreatic neuroendocrine tumor (NET), VIPoma.[2] Now 30 years later, octreotide, and the recently FDA-approved agent lanreotide, continue as first-line therapies for all symptomatic NETs. Furthermore, the isotopie radiolabeling of octreotide specifically targets somatostatin receptors overexpressed on NETs and has heralded yet another FDA-approved diagnostic-therapeutic strategy termed theranostics, which allows an octreotide derivative to act as a radiodiagnostic molecular imaging agent and a radiotherapeutic product for the treatment of malignant endocrine tumors.[3,4]

To better understand the context of these developments, and the pivotal role native somatostatin and its long-acting analogues play in normal peptide regulation and neuropeptide excess associated with NETs, we delineate and define distinct eras in the history and discovery of gastrointestinal (GI) endocrinology. The major periods of gut endocrinology include: the physiology ("juice") era, the clinical era, the peptide chemistry era, and the peptide diagnostic and therapeutic era.[5]

Building on the historical milestones recently addressed in reviews by O'Dorisio[5] and Oberg,[6] we address and expand on the two reviews where appropriate. Regarding ^{177}Lu-DOTA(tyr)-octreotate and ^{90}Y-DOTA-(tyr)-octreotide therapy in childhood and adult NETs, we highlight the collaboration between academia and industry in basic science and the clinical research that advanced LUTATHERA (Lu-177-dota-tate) to FDA approval as standard of care therapy for low-grade NETs.[4] Examples of new radioisotopes and therapy compounds currently in development for diagnosis and therapy for high-grade NETs are also discussed.

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DISCLOSURES

None.

Endocrinology began in 1902 with the physiology era, with the discovery of the "blood-borne chemical messenger" secretin by Bayliss and Starling.[7] They demonstrated that HCI placed into canine duodenum resulted in the secretion of alkaline pancreatic juice. They called this substance "secretin" and later coined the term "hormone" derived from the Greek military word *Opuaw*, which means "I arouse/excite to activity."[5]

In 1905, Edkins,[8] a prominent physiologist, described a potent gastric acid secretagogue subsequently termed "gastrin." It was not until 1961 that Gregory and Tracy[9] identified the multigastrin forms confirming its biologic properties described by Edkins. Physiologists Ivy and Eldberg[10] described their observation on hormone-mediated gallbladder contraction. They noted that the extract from dog proximal small intestine when injected intravenously into another dog was associated with gallbladder contraction. A second pair of physiologists, Harper and Raper,[11] found that dog small intestine extract was associated with gallbladder contraction and pancreatic juice release and termed it "pancreozymin." For a time, the abbreviation CCK/PZ was used. It was ultimately determined that pancreozymin was indeed cholecys-tokinin (CCK). This highlights the insensitivity of the bioassay techniques at the time, and the tremendous impact that radioimmunoassay (RIA) was to have on the neuroendocrine field.

A few years before the discovery of CCK, Banting and Best[12] were able to stabilize sheep insulin and achieve glucose homeostasis in pancreatectomized dogs. Shortly after insulin stabilization, a patient with insulin-dependent diabetes mellitus was successfully treated with the extracted sheep insulin. This and other key insulin milestones were reviewed by the endocrinologist Forsham[13] in 1982. In the United States, large-scale insulin production was achieved thanks to the strong collaboration between academia and industry (Eli Lilly) and NOVO-Nordisk in Europe. Diabetes mellitus represented a peptide-deficient state of the enteropancreatic axis as opposed to the excess peptide hormone production by functional NETs.

During the era of physiologic discovery, morphologists, anatomists, and pathologists were working to identify the GEP cells responsible for the secretion of these newly identified peptide hormone substances. Table 1 lists the key investigators who helped define the neuroendocrine cells of the GEP axis.[5,6]

By 1950 it was clear that, within the GEP system, there were many unexplained control systems and a larger number of different neuroendocrine cells and their secreting products and actions that were yet to be recognized. A prominent gastrophysiologist, Grossman,[22] worked diligently to assign hormone and neuroenne action to the previously described substances, such as CCK and secretin. Until that time, the extracted peptide material was crude and only partially purified. This affected bioassay interpretation and assignment of the actual neuropeptides responsible for the observed actions. One example was the identification of incretin, a substance residing in the small intestine, released by a glucose load and affecting additional insulin secretion in a hormonal fashion. Moore[23] is credited with the first physiologic observation of a small intestinal extract that lowered blood sugars in the presence of an increased glucose load into the duodenum. It is now accepted that

incretin is caused, in part, by the two GI peptides glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1.[24]

The peptide chemistry era was ushered in with two remarkable discoveries in the 1950s and 1960s. The first was the development of column chromatography, which used cross-linked dextran gel for gel filtration of substances based on particle size and cross-linking and molecular weight.[25] The resin columns used different size beads, which excluded extracts of different molecular weights and purification. The purification of gastrin from Zollinger-Ellison tumors by Gregory and Tracy in 1961 was an excellent example of the purification by column chromatography.[5] Furthermore, Jorpes and Mutt from the Karolinska Institute in Stockholm, Sweden, purified several GI peptides extracted from porcine intestine using large-diameter columns.[26,27] It has been estimated that the combined efforts of Gregory, Jorpes, and Mutt led to the purification of more than 14 GI neuropeptides that included GIP, vaso-active intestinal peptide (VIP), pancreastatin, and neuropeptide Y, and peptide tyrosine.

The second critical discovery was the development of RIA by Yalow and Berson in 1959.[28,29] With highly purified GI peptides being rapidly produced, RIA used highly pure peptide standards in competitive protein binding curves with a short wavelength isotope, iodine 125- Kev 30, offering for the first time high peptide sensitivity and specificity measurements. Shortly after the initial description of RIA, McGuigan[30] published the gastrin RIA. With the development of high-titer peptide antibodies for RIA, antibodies directed against peptide-secreting neuroendocrine cells using the immunohistochemical (IHC) methodology was simultaneously developed. Two active investigators in neuroendocrine clinical research in the mid-1970s were the endocrinologist S.R. Bloom and pathologist J.M. Polak. Together they identified by RIA and IHC many GI neuroendocrine secreting cells,[31–33] and made a great contribution to GI neuroen-docrinology by the mid-1970s. The United States had also developed RIAs for the newly identified neuropeptides. The Mayo Clinic developed commercial neuropeptide RIAs under the supervision of V.L.W. Go. Also, The Ohio State University/University Reference Laboratory performed CLIA-certified GI neuropeptide RIAs under the supervision of S. Cataland and T.M. O'Dorisio. The most durable commercial neuropeptide RIA laboratory in the United States is the Inter Science Institute, which will soon celebrate 50 years of performing peptide RIAs.[34]

In 1977, R. Yalow received the Nobel prize in physiology and medicine "for the development of RIA of peptide hormones." S. Berson had passed away and was not eligible posthumously. Dr Yalow shared the Nobel Prize that year with R. Guillemen and A. Schally "for their discoveries concerning the peptide hormone production of the brain." Dr Guillemin and his colleagues had discovered somato-statin.[35] Arimura and colleagues[36,37] established an acetone extraction RIA to measure plasma somato-statin plasma in 1978. The impact that RIA had on GI peptide discovery is depicted in Fig. 1.

With the discovery of new peptides/hormones during this period between 1960 and 2000, it would be only a matter of time before the development and utility of some of these peptides became clinically relevant (the peptide therapy era). The clinical era, albeit, at a much slower pace, progressed in parallel with the discovery of GI hormones beginning in 1902.

The pathologist S. Oberndorfer is credited with the description of small bowel tumors, which he termed "karzinoide," meaning carcinoma-like. His publication in 1907[38] and description was the first to distinguish the slower growing tumors from true carcinomas. It was not until 1928 that he revised the initial description of benign tumors to more accurately reflect their malignant and metastatic potential.[39] In his section on carcinoid tumors, Oberg[6] cites a case report by Ransom[40] from 1890 of a woman with probable malignant carcinoid tumors who flushed after eating. Oberg[6] suggested this could be the first description of carcinoid syndrome. Lembeck,[41] in 1953, confirmed that serotonin was present in an ileal carcinoid tumor, specifically within the enterochromaffin cells. The problem of being able to determine carcinoid tumors as functional serotonin-secreting tumors in the past has been caused by the difficulty in measuring the plasma serotonin, which has a short half-life of 35 seconds. This is been overcome with the addition of ascorbic acid to a whole-blood sample.

It has now been shown that ileal carcinoid tumors are the second-most frequent leading tumor of the GI tract. Moreover, they have a higher incidence than esophageal and gastric carcinomas combined.[42] An insulin-secreting pancreatic NET was first described by Wilder and colleagues[43] in 1927. It was a case that used a bioassay whereby they could demonstrate that the liver metastasis contained bioactive insulin. Whipple and Frantz[44] published a large series of islet cell tumors associated with hypoglycemia. They also described what came to be known as Whipple triad: documented low blood sugar associated with symptoms of hypoglycemia, improved with glucose replacement.

In 1955, Zollinger and Ellison[45] described two patients with abdominal pain, diarrhea (because of excess gastric acid secretion), and atypical bleeding ulcerations of the small bowel associated with NETs of the pancreas. Shortly after the initial description, the syndrome was named ulcerogenic syndrome and/or Zollinger-Ellison syndrome. One of the first two patients initially reported was a 17-year-old woman at the time of diagnosis. A few years following her subtotal gastrectomy, it was noted she was a member of a multiple endocrine neoplasia (MEN) syndrome type 1 (MEN-1) kindred, and one of the authors (T.M.O.) helped care for this patient for almost 20 years. Her weight had remained quite stable even in the presence of liver metastasis and subtotal gastrectomy. It was determined by RIA that her tumor secreted gastrin and somatostatin, and that the somatostatin acted, in part, as an antagonist to gastrin secretion on her liver tumors via a peptide-peptide interaction. She was never begun on octreotide, but her liver lesions remained stable until the time of her death at age 65. A similar case of a gastrinoma secreting somatostatin was discussed by O'Dorisio and colleagues in 1987.[46]

Gregory and coworkers[47] identified gastrin from patients with Zollinger-Ellison syndrome, including one patient from the original Zollinger-Ellison publication. Using classic bioassay, they injected gastrinoma tumor extract intravenously into two dogs and showed profound gastric acid output. Their work validated Edkins[8] physiologic observation in 1905 using canine stomach mucosa extracts.

In 1958, internist J.V. Verner and pathologist A.B. Morrison described two patients with fulminant secretory diarrhea, hypokalemia, achlorhydria (most often hypochlorhydria), and pancreatic NETs. The patient also had metabolic acidosis caused by bicarbonate loss in the

diarrhea.[48] Although initially termed "watery diarrhea, hypokalemia, achlorhydria," it came to be called watery diarrhea syndrome. Because the neuromo-dulator VIP shares amino acid homology with secretin and GIP, both neuropeptides were thought to be the modulating peptide excess in the watery diarrhea syndrome. It was not until the purification of VIP by S. Said and V. Mutt and the development of the VIP RIA that the actual pathohumoral state of VIP and watery diarrhea syndrome was established.[49,50]

Although glucagonoma syndrome was first described in 1942, McGavran and co-workers[51] reported a case of a patient with glucagonoma syndrome with elevated plasma glucagon levels, diabetes mellitus (type II), severe dermopathy, and a pancreatic NET in 1966. The immunoreactive-like glucagon RIA was performed by R.H. Unger and proved to be one of the best glucagon polyclonal antibodies (Unger 30K) for glucagon RIA in the United States. The association of the often-lethal thromboem-bolism in the glucagonoma syndrome was reported by Mallinson and coworkers in 1974.[52]

Somatostatinoma began to be described in the late 1970s. They are rare and are more often peripancreatic than pancreatic in location. These are considered asymptomatic but are associated with gallbladder disease (because of antagonism of CCK), diabetes mellitus (type II), and subclinical fat malabsorption (because of antagonism of pancreatic enzyme release).[53]

Although only 20% of pancreatic NETs are functional, these tumors of the GEP system predominantly secrete their excess peptides/amines in an endocrine manner. They may also secrete peptides or amines alien to their cell of origin in a paraendocrine (paracrine) fashion.[46,54] Because of the ability to measure plasma neuropeptides by specific and sensitive RIA, and recognizing their physiologic and pathophysiologic actions, we can ascribe peptide/amine function to GEP NETs based on their syndrome/symptoms. Although it is currently accepted that GEP NETs derive from neuroendocrine cells/tissue, the amine precursor uptake decarboxylase hypothesis of Pearse[55,56] remains appealing. His concept considered that the diffuse endocrine system is of neural crest origin. It was supported by the finding that neuron-specific enolase is present in all parts of the neuroendocrine cell system.[57] Unfortunately, we have come to appreciate the inadequate specificity of neuron-specific enolase antibodies, which may have impacted on Pearse's conclusion that the origin of neuroendocrine cells are derived from neural crest tissue. Later worked by Andrews and colleagues[58] was an endodermal origin of neuroendocrine cells, and not necessarily neural crest origin. The amine precursor uptake decarboxylase concept, however, remains a convenient and practical framework to describe and study NETs.

Most enteropancreatic NETs are considered sporadic. However, inherited syndromes associated with pancreatic and thyroid NETs exist, and their genetics has been determined. These include MEN1 and MEN2 syndromes, von Hippel-Lindau disease, neurofibromatosis-1, and tuberous sclerosis. Although the inherited NET-associated syndromes are rare, we have clinically observed MEN1 and MEN2 more often in our NET clinics than von Hippel-Lindau disease or tuberous sclerosis. This may be caused, in part, by the functional nature of the pancreatic NETs in MEN1, and the diagnosis and management of pheochromocytoma in MEN2 syndromes. Norton and coworkers[59] published a review of

the genetics and clinical management of MEN1 and MEN2 in 2015. Table 2 represents the major NETs of the GEP system and their MEN associations.

Clinically affected MEN1 patients most often present initially with hypercalcemia and elevated parathyroid hormone or a history of parathyroid surgery and evidence of four gland parathyroid hyperplasia. The most common pituitary tumor, when present, is a prolactinoma, but can also be a growth hormone- or corticotropin-secreting tumor. The pancreatic NET, when it occurs, is most commonly an insulinoma or gastrinoma, but rare glucagonomas or VIPoma can also be seen in other members of MEN1 kindreds. The pancreatic NETs are most often multiple adenomas, one or two of which may grow while the other adenomas remain stable. Correcting the hypercalcemia when present before working up a functional PNET is recommended. Whereas carcinoid tumor can co-occur in MEN1 and MEN2 syndromes, the pulmonary carcinoid tumor seems more prevalent in MEN1 patients, in our experience.

Regarding MEN2 syndrome, the most frequent component of MEN2 almost always involves medullary thyroid carcinoma (MTC) from the neuroendocrine C-cells (parafollicular cells) of the thyroid gland. MTC is always present in MEN2 and constitutes the primary diagnosis. Parathyroid hyperplasia can also be present in MEN2A but is not as clinically frequent as seen in MEN1 patients. The third gland involved in MEN2 is the adrenal medulla, which gives rise to pheochromocytomas. Patients may present first with symptoms of pheochromocytoma and thereafter an MTC is discovered. Both MTC and pheochromocytoma are often bilateral. MEN2B is much less common (5%) than MEN2A, which accounts for 95% of MEN2 patients. MEN2B is clinically more aggressive, also consists of pheochromocytomas, but does not have parathyroid hyperplasia; it is also associated with a marfanoid body habitus and ganglioneuromas of the GI tract.[59] Carcinoembryonic antigen with serial measurements of calcitonin is helpful in detecting early aggressivity and metastasis of MEN2-associated MTC.

The final portion of this review addresses selected aspects of the various peptide therapies that currently exist in the United States. The following schema represents a partial approach to the various therapeutic modalities (Fig. 2).

As noted, the arrows are two-way, and designed to represent that electing one therapy does not eliminate its option at a different phase of treatment. It is important to demonstrate that any of the therapeutic options can be repeated. Most of the listed options are discussed by other authors in this issue. This review briefly address surgery/debulking and somatostatin and ianreotide therapy, and discusses the most recent FDA-approved peptide receptor radionuclide therapy (PRRT).

SURGERY/CYTOREDUCTION

It is historically and presently accepted that the first best therapy in the management of NET is surgery, whenever possible. Less well-established is the overall survival (OS) improvement when the primary tumor is removed versus being unable to remove the primary tumor. This is caused, in part, by the reality that all surgical studies of this nature are

retrospective and the assignment of patients to no surgery is inherently unethical. That said, there are publications that strongly suggest benefits in progression-free survival (PFS) and OS when the primary tumor and hepatic metastasis debulking is possible.[60–63] At the University of Iowa, our endocrine surgeon (editor of the present monograph) is aggressive in removing primary PNETS and SBNETs, with liver tumor debulking (and liver sparing) when safe surgery and low patient risk are possible[63]

OCTREOTIDE/LANREOTIDE

Octreotide and Ianreotide remain as first-line management and therapy for functional and nonfunctional NETs. They are remarkable for their durability over decades and merit discussion. Octreotide (Sandostatin) and, somewhat later, Ianreotide (Somatu-line) were both developed as analogues (more properly, congeners) of the active ringed portion of native somatostatin-14.[64–66] Their other natural form is somatostatin-28, representing an extension of somatostatin-14 away from its active eight amino acid ring.[67] As noted from Fig. 1, somatostatin has been shown to have all four regulatory functions: (1) endocrine, (2) paracrine, (3) neurocrine, and (4) autocrine.[67] Shortly after its initial discovery and publication in 1973 by Brazeau and colleagues,[35] Sandoz (now Novartis) focused their medicinal chemists to synthesize a longer acting fragment of the eight amino acid ring of the native somatostatin to be used clinically. Almost 9 years later, octreotide (SMS 201–995, Sandostatin) was synthesized by Bauer and colleagues.[64] Shown next is the amino acid structure of Sandostatin-native somatostatin-14 and the eight amino acid synthetic structures of octreotide and lanreotide both containing the D-isomers of the naturally occurring amino acids and the bioactive ringed portion. D-isomers prevent enzyme degradation, as compared with the naturally occurring L-form amino acids in somatostatin-14. Also documented in Fig. 3 showing the 1 to 14 somatostatin and octreotide and lanreotide is the purported amino acid, lysine, within the ringed portion considered to be the primary peptide binding site of somatostatin, octreotide, and lanreotide to the somatostatin receptor subtype 2 (sstr2A), the most prevalent receptor of the five somatostatin receptor subtypes on neuroendocrine cells and their NETs (see Fig. 3).[67]

It is important to appreciate that for 10 years following the discovery of native somatostatin, there was a large number of publications reporting somatostatin's mechanisms of action and regulatory role in mammalian physiology[68–70] and its regulatory role in NETs. Based on the information available on native somatostatin, and the wide-spread clinical use of octreotide, somewhat later the use of lanreotide was a reasonable and rational extension. Both analogues had a much longer plasma half-life than the naturally occurring somatostatin, and a much more potent and durable action on NETs.[71–74] During the late 1980s, while octreotide and lanreotide were being used on a compassionate use basis to treat NETs and growth-hormone-secreting pituitary tumors causing acromegaly, there were efforts to characterize the various receptors on NETs. Reubi and coworkers[75] mapped somatostatin receptor subtypes using autoradiographic techniques that included the use of ^{125}Iodine isotope labeled to the tyrosine substituted for phenylalanine in octreotide at position 3. Patel and Srikant[76] demonstrated peptide analogue subtype selectivity using five clonal human somatostatin subtype receptors (hsstr1–5). During the same year, Bruns and colleagues[77] discussed the molecular pharmacology of somatostatin-receptor subtypes. This was made

possible for sstr2A by highly specific IHC with a commercially available polyclonal antibody, UMB-1 (Biotrend, Epitomics, Inc). Characterization of the UMB-1 antibody was published in 2012 by Korner and coworkers.[78] As noted in our therapeutic schema, all patients coming to our NET clinics for the first time will have their tumor tissue stained (when available) for sstr2A. Qian and colleagues[79] published a study examining the presence of somatostatin subtype receptors 1 to 5 and OS and PFS in patients with metastatic NETs. They concluded that patients with NETs that express sstr2A (but not sstrl, sstr3, sstr4, or sstr5) have a longer OS. They determined that tumors with sstr2A IHC that are treated with somatostatin analogues have a longer PFS.[79]

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY AND THERANOSTICS

The remarkably persistent standard of care use of somatostatin analogues, especially octreotide, would almost naturally lead to PRRT of GEP NETs. We discuss the history of theranostics, from the FDA-approved diagnostic ^{68}Ga-DOTATATE PET scan (NET-SPOT) and its therapeutic partner, ^{177}Lu-DOTATATE PRRT, and allude to novel tumor targets that may lead to FDA approval in the near future.

Fig. 4 shows a timeline establishing the similar role that octreotide has had since its synthesis and clinical use in 1982 on PRRT.[80] It depicts close interaction between discovery by academic centers and industry leading to clinical use of modified octreotide as a recently FDA-approved effective and rational therapy for NETS.[81]

An excellent review of PRRT development was recently published by Levine and Krenning.[82] Noted in Fig. 4, targeted radiotherapy began with the work of S. Hertz using ^{131}Iodine treatment of severe hyperthyroidism.[83] Although his work had been done well before the 1946 *JAMA* publication,[83] World War II interrupted Dr Hertz' investigative efforts. During the 1940s, Dr Hertz recognized that thyroid targeting with ^{131}Iodine made it possible to successfully treat patients with thyroid cancer. The Society of Nuclear Medicine and Molecular Imaging established a yearly Sol Hertz Award in 2016, recognizing "individuals who have made outstanding contributions to radionuclide therapy."

The first use of the term "peptide receptor" concept probably derives from the work by the Erasmus University group, headed by Krenning[84] and Maecke and colleagues.[85] There are early publications by Krenning and colleagues[84] that not only address the peptide receptor acronym, but also demonstrate proof of concept using ^{111}In-octreotide as an imaging and therapeutic agent given to a single patient. Mueller-Brand with Maecke and their colleagues reported on the "powerful new tool," DOTA-TOC (a chelator attached to [tyr3]-octreotide), for sstr2A in metastatic NET subjects. This was the first use of β emitting energy, ^{90}Yttrium, coupled with the DOTA chelator.[86]

Krenning and his group at Erasmus pursued diagnostic imaging with ^{123}Iodine-labeled Tyr3-octreotide achieving successful scintigraphic imaging.[87] By 1990, they had successfully developed ^{111}Indium-labeled DTPA (chelator) attached to pentetreotide (OctreoScan) and reported their 1000-patient experience in 1993.[88] The Octreoscan was ultimately used for diagnostic entry criteria in the registered NETTER-1 trial for PRRT[4] coupled with therapy

using ^{177}Lu-DOTATATE. Since 2001, the improved diagnostic scan for detection of somatostatin receptor positivity was developed using the ^{68}Ga-DOTA-somatostatin analogue, thereby increasing the sensitivity and specificity by using PET instead of single-photon emission computed tomography (SPECT). In 2007, Baum and colleagues published their work on the highly sensitive and specific ^{68}Ga-DOTA-(tyr3)-octreotide (TOC) and DOTA-(tyr3-octreotide, substituted threonine for threoninolol-octreotide [TATE]) PET imaging.[89] It was, however, the use of the diagnostic OctreoScan with ^{177}Lu-DOTATATE that led to the first FDA-approved, European Medicines Agency-approved radiopharmaceutical for PRR.[81]

Noted in Fig. 5, the term "theranostics" was coined by Rosch and Baum in 2011.[90] The theranostics concept is the use of the identical linker molecule (peptide in this case) with the chelator "cage" for ^{68}Ga for diagnosis, and the ^{177}Lu/^{90}Y for therapy. A good description of PRRT and of theranostics is depicted in Fig. 5.[85]

On the top right-hand panel is the DOTA-chelator with its "cage" containing the therapeutic radiometal, 90Y. The top middle panel is the DOTA chelator attached to (tyr3)-octreotide (TOC) and considered to be the vector binding to the tumor's sstr2A. The top left panel is the tumor membrane with the sstr2A dangling externally above the membrane. For a single receptor (sstr2A) binding to a single ligand (tyr3)-octreotide, four properties are necessary[85]: (1) high sstr2A expression on the NET, (2) the native peptide (somatostatin) sequence being known, (3) high affinity/specificity/avidity for the target (sstr2A), and (4) the analogues (vector, ligand) are synthetically feasible (50 amino acid residues or less).

The next major breakthrough in theranostics is likely to be the introduction of new radioisotopes and new targeting agents in addition to DOTATOC and DOTATATE. ^{177}Lutetium and ^{90}Yttrium are primarily β emitters with path lengths greater than the average diameter of a single cell, thus generating "cross-fire" effects of cytotoxicity to adjacent cells and normal tissues, a Particle energy emitters, such as ^{225}Ac (astatine) and ^{212}Pb (lead) coupled to a high-affinity somatostatin analogue, are likely to deliver a higher energy dose to a single cell with little or no cross-fire when targeted to tumors expressing high levels of sstr2A. Recent *in vitro* experiments in cell lines expressing sstr2 have shown a six-fold increase in radiation dose/cell from ^{213}Bi-DOTATOC compared with ^{177}Lu-DOTATATE.[91] Importantly, these results substantiate emerging evidence that α emitters may be more effective for PRRT because of preferred dose deposition within the cell nucleus (Table 3).[92]

The contribution of internalization to targeting efficiency was then investigated within the geometry of cells by modifying the uptake of α or β emitting radionucleotides from complete membrane bound (0% internalized) to fully internalized (100%). The up-take values arising with 100% internalization were approximately 1.5-fold higher for the entire cell, and 2- to 3-fold higher for the nucleus when compared with binding to the cell membrane, α Emitters deposit significantly higher doses for the tumor metastasis of various sizes relative to β emitters representing 60 to 140 times higher doses for ^{212}Pb and ^{213}Bi, and 190 to 620 times higher doses for ^{225}Ac when compared with the β emitter, ^{177}Lu

(Azure). Importantly, these results substantiate emerging evidence that a emitters may be more effective for PRRT because of preferred dose deposition within the cell nucleus.

Most NETs are low grade 1 and 2 with Ki-67 less than 20%. Grade 3 NETS and neuroendocrine carcinomas (NECs) have less response to either ^{177}Lu- or ^{90}Y-DOTA-TOC or DOTATATE. These high-grade tumors have a Ki-67 of 55% to 90% and often lack the sstr2A expression, leading investigators to try to identify theranostics targets for grade 3 NETS and NECs. CXCR4 is a chemokine receptor that like sstr2A is a G-protein-coupled receptor expressed on the cell surface and internalized on binding of a high-affinity ligand.[93] We and others have identified CXCR4 expression on NEC, multiple myeloma, and leukemia.[94–98] The ligand for CXCR4 is a small peptide SDF-1, also known as CXCLI2. Pentixafor is a CXCR4 antagonist that can be complexed to the DOTA chelator. ^{GA}68-Pentixifor and ^{177}Lu-Pentixifor are, thus, a theranostic pair. ^{177}Lu can be used for SPECT imaging and diagnosis: however, ^{68}Ga-Pentixifor is improved as a PET imaging agent with a sensitivity of 3 to 5 mm as compared with 10 to 15 m sensitivity for SPECT. ^{177}Lu-Pentixather has shown promise as a radiother-apeutic drug in early studies for patients with multiple myeloma and leukemia,[94] but CXCR4 is expressed on hematopoietic progenitors and stromal cells, leading to concern for bone marrow toxicity. A recent preclinical study has demonstrated that bone marrow from mice treated with ^{177}Lu-Pentixather is able to serve as a graft in lethally irradiated animals, providing support for the use of ^{177}Lu-Pentixather in aggressive malignancies with dosimetry of bone marrow dose to prevent toxicity.[99] Patients with multiple myeloma or leukemia treated with ^{177}Lu-Pentixather routinely receive autologous hematopoietic stem cell rescue.

177LU-PSMA-617 has primarily been tested in Germany under compassionate use circumstances and relapsed metastatic castrate-resistant prostate cancer and has only recently been introduced into US clinical trials. A retrospective analysis of 145 patients treated in 12 European centers demonstrated greater than 50% decrease in prostate-specific antigen levels in most patients.[100] Hematologic toxicity was low even in these heavily pretreated patients; dry mouth related to high uptake of the ^{177}Lu-PMSA-617 in salivary glands was the primary toxicity along with fatigue and nausea.[101] These preliminary results support the conduct of controlled phase 2 trials that are currently ongoing in Europe and the United States.

Although most theranostic compounds are peptide agonists targeting G-protein-coupled receptors, several antagonist molecules are in preclinical and early clinical use. One example is a peptide ligand, 68Ga-DOTA-bombesin (neoBOMB), targeting the gastrin-releasing peptide receptor known to be expressed in prostate cancer cells.[102] This gastrin-releasing peptide receptor antagonist has shown promising results in animal models and its first PET imaging in humans has been recently reported. Similarly, an antagonist at the somatostatin receptor has been introduced as a theranostic pair in NETs. ^{68}Ga/^{177}Lu-DOTA-JR-11 seems to bind to many more sites/cells than either DOTATOC or DOTATATE in low-grade NETs. It is in early phase trials with little information on safety or efficacy available at this time.

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KEY POINTS

- Although most theranostic compounds are peptide agonists targeting G-protein-coupled receptors, several antagonist molecules are in preclinical and early clinical use.
- One example is a peptide ligand, 68Ga-DOTA-bombesin (neoBOMB) targeting the gastrin releasing peptide (GRP) receptor known to be expressed in prostate cancer cells.
- This GRPR antagonist has shown promising results in animal models and its first PET imaging in humans has been recently reported.
- Similarly, an antagonist at the somatostatin receptor has been introduced as a theranostic pair in neuroendocrine tumors.

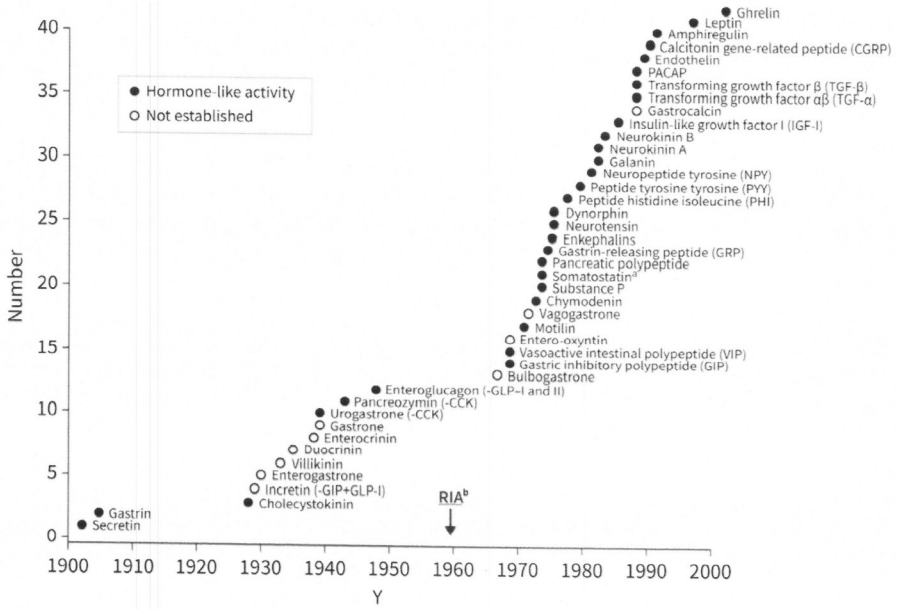

Fig. 1.

Peptides identified in the mammalian gastroenteropancreatic system. [a] Somatostatin has all regulatory actions: endocrine, paracrine, neuroendocrine, autocrine. [b] RIA (radioimmunoassay) first described in 1959.[28,29]

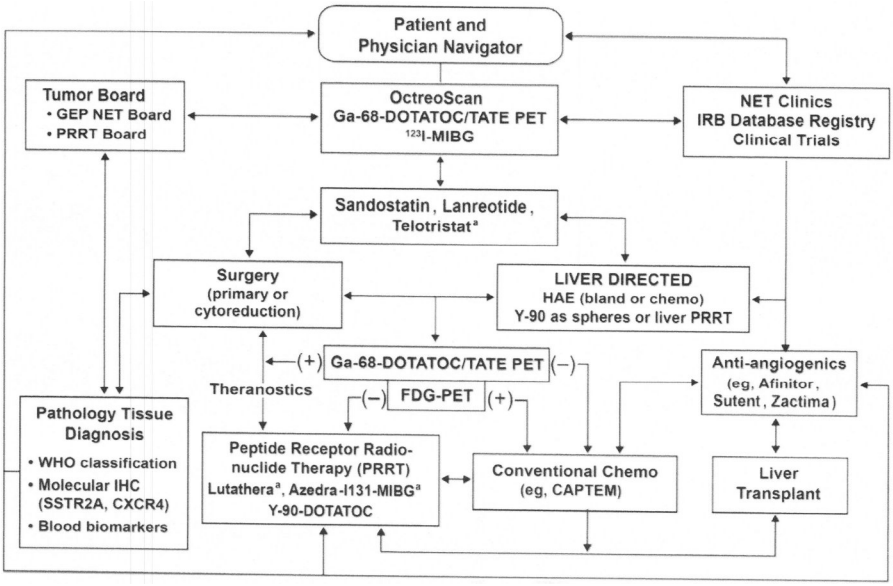

Fig. 2.

Carcinoid and neuroendocrine tumors: cancer management and treatment options of care. [a] Most recently FDA approved. FDG, fluorodeoxyglucose; WHO, World Health Organization. (*Courtesy of* Iowa NET Team, Iowa City, IA.)

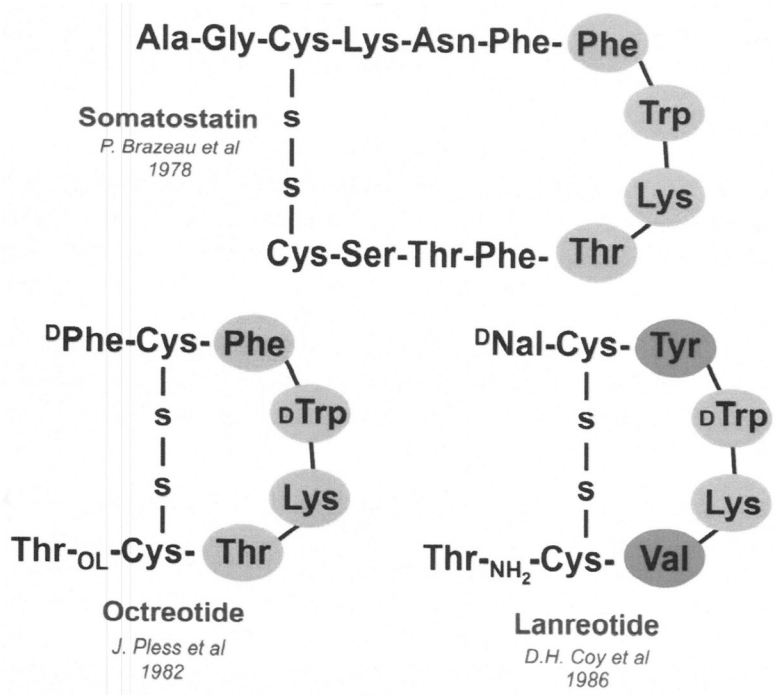

Fig. 3.
Somatostatin and its congeners.

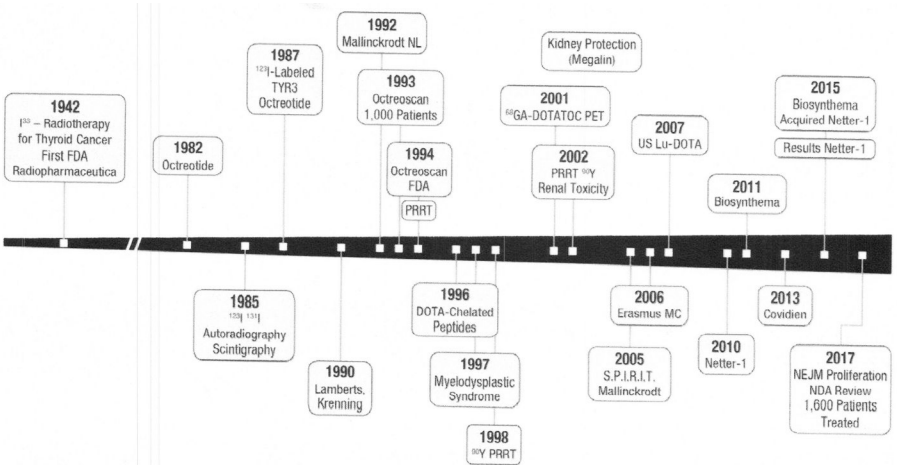

Fig. 4.

A timeline of octreotide culminating in development of PRRT and theranostics.

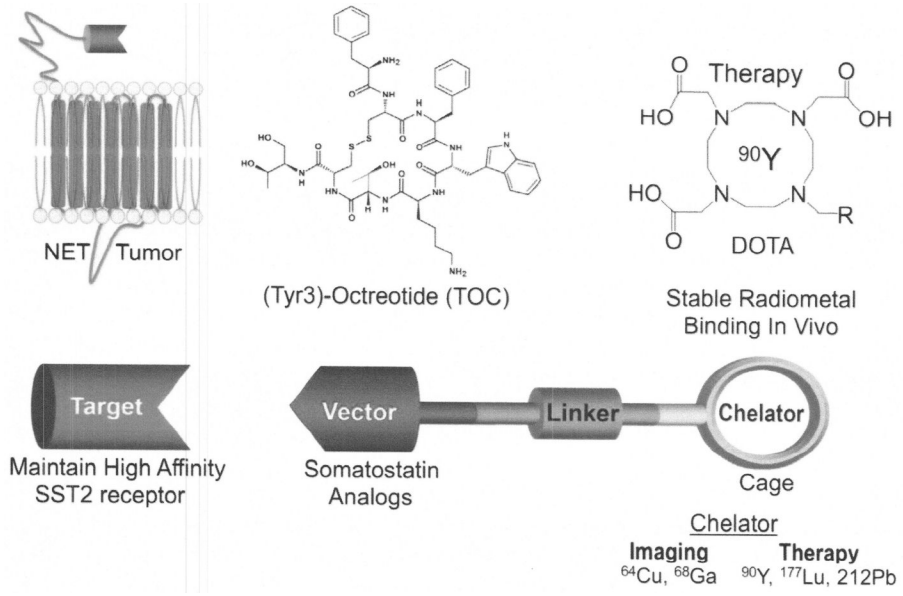

Fig. 5.

Targeted molecular imaging and therapy (PRRT) and theranostics concept. Theranostics is the use of diagnostic radionuclides (^{68}Cu, ^{68}Ga) and therapeutic radionuclides (^{90}Y, ^{177}Lu, ^{212}Pb) labeled to the same somatostatin congener (TOC or TATE).[90] (*Courtesy of H. Maecke, University Hospital, Basel, CH.*)

Table 1

Investigators who helped describe and identify the amine/peptide-secreting cells of the GEP system

Investigator (s)	Year	Observation	References #
P. Langerhans	1870s	Cell clusters on acinar cells	Langerhans and Moorison,[14] 1869
E. Laguesse	1890s	Islets of Langerhans	Langerhans and Moorison,[14] 1869
R. P. Heidenhain	1870	EC EC-like: histamine secretion	Heidenhain,[15]1870
A. Nikolas	1891	EC cells, Gl tract	Nikolas,[16] 1891
N. Kulchitsky	1897	EC cells/crypts of Lieberkühn	Kulchitsky,[17] 1897
M. Ciaccio	1906	EC cells in human Gl tract	Ciaccio,[18] 1906
A. Gosset and P. Masson	1914	Diffuse endocrine system	Gosset and Masson,[19] 1914
F. Feyter	1938	Helle zellen, clear cells; neuroendocrine	Feyter,[20] 1938
F. Feyter	1953	Coined paracrine and neurocrine	Feyter,[21] 1953

Abbreviation: EC, enterochromaffin.

Data from O'Dorisio TM. Gut endocrinology: clinical and therapeutic impact. Am J Med. 1986;81(6B):1–7 and Öberg K. The Genesis of the Neuroendocrine Tumors Concept: From Oberndorfer to 2018. Endocrinol Metab Clin North Am. 2018;47(3):711–731.

Table 2

Major neuroendocrine tumors of the GEP system and their associations with multiple endocrine neoplasias

Peptide/Amine	Syndrome/Symptom	Apudoma/NET	MEN1 or MEN2[a]
Gastrin	Zollinger-Ellison diarrhea, atypical Gl ulcers	Gastrinoma	1
Insulinoma	Hypoglycemia, symptomatic	Insulinoma	1
VIP	Watery diarrhea syndrome	VIPoma	1 (rare)
Glucagon	Dermatosis, diabetes, thromboembolism	Glucagonoma	1 (rare)
Somatostatin	Diabetes, fat malabsorption, cholelithiasis	Somatostatinoma	1 (rare) 2 (very rare)
Pancreatic polypeptide	Asymptomatic	PP-oma	1
Calcitonin	Asymptomatic/diarrhea, flushing	Medullary thyroid carcinoma	2
Norepinephrine/epinephrine	Hypertension, tachycardia, pallor	Pheochromocytoma	2
Serotonin, substance P, neurotensin	Flushing, diarrhea, cool perspiration	Carcinoid	1 (lung carcinoid) 2 (ileal carcinoid)

[a]MEN1, autosomal-dominant; gene resides on chromosome 11q13; 610 aa nuclear protein "MENIN" Tumor Suppressor. MEN2, autosomal-dominant, gene on chromosome 10q; a receptor tyrosine kinase protooncogene[6,59].

Modified from O'Dorisio TM, Vinik Al. Pancreatic polypeptide in missed hormone-producing tumors of the gastrointestinal tract. In Cohen S, Soloway RD (Eds) Contemporary issues in gastroenterology. Edinburgh: Churchill-Livingston 1984;5:117–128; with permission.

Table 3

Radionuclides currently in use for theranostics

Radioisotope (Emission)	Average Path Length (mm)	Mean Particle Energy (MeV)
^{225}Ac (α)	<0.1	5.59
^{212}Pb (α)	<0.1	6.0–8.8[a]
^{177}Lu (β)	1.7	0.134
^{90}Yt (β)	0.05–12	0.933

[a]^{212}Pb decays to ^{212}Bi (36%) and ^{212}Po (64%) with respective α energies.