Somatostatin – receptor mediated diagnosis and treatment in gastrointestinal neuroendocrine tumours (GEP-NET's)

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Introduction

Neuroendocrine tumours constitute a group of tumours that originate from neuroendocrine cells throughout the body. That includes endocrine tumours of the thymus, lung, pancreas and gastrointestinal tract. Neuroendocrine gastrointestinal tumours have classically been divided into carcinoid tumours and endocrine pancreatic tumours. Many of these tumours produce hormones that can induce clinical symptoms in the patient [1]. Since these hormones are stored in secretory granules containing chromogranin A, a common feature for patients with neuroendocrine tumours is elevated levels of chromogranin A in plasma. Measurement of this hormone is a very sensitive marker for neuroendocrine tumours [2].

Patients with endocrine pancreatic tumours (EPT) can develop different syndromes according to the hormone produced. These syndromes include the Zollinger-Ellison syndrome for patients producing gastrin, the Verner-Morrison syndrome for patients with vasoactive intestinal peptide (VIP) production, the insulinoma syndrome due to excess of insulin/ /proinsulin and the glucagonoma syndrome for patients with high glucagon production respectively. A subgroup of endocrine pancreatic tumours (30-40%) does not produce any hormone that give rise to clinical symptoms and these tumours are called non-functioning endocrine pancreatic tumours.

Patients with gastrointestinal endocrine tumours have traditionally been divided into foregut (gastric, duodenal), midgut (ileal, jejunal, appendicial) and hindgut carcinoids (colonic and rectal). For patients with midgut carcinoid tumours the carcinoid syndrome becomes overt when the patient develops liver metastases. The carcinoid syndrome consists of flushes, diarrhea, the carcinoid heart disease and sometimes bronchial constriction. These tumours produce serotonin and tachykinins and the most frequently measured tumour marker is the urinary 5-HIAA (5-hydroxyindoleacetic acid) which is a degradation product of serotonin. Patients with foregut carcinoid tumours may produce several different hormones including gastrin, ACTH (adrenocorticotropin releasing hormone), ghrelin and somatostatin, and therefore the symptoms may vary considerably in these patients.

Recently a new classification has been proposed by WHO. The tumours are divided into well differentiated neuroendocrine tumours, well differentiated neuroendocrine carcinoma, tumours with uncertain behavior and low differentiated carcinoma. Proliferation index (Ki-67, MIB-1), angioinvasion and mitoses are important factors in the classification [3]. This classification is now being introduced into the clinic.

Somatostatin and somatostatin analogs

Somatostatin is a peptide hormone that was first isolated in 1973 [4]. The primary function attributed to this hormone was the inhibition of growth hormone release. Subsequently several other functions of somatostatin have been identified such as a general inhibitory effect on hormone release from endocrine cells, inhibition of secretion from the exocrine pancreas, reduction of gastrointestinal motility and a neurotransmitter function and immunoregulatory [5]. Already in 1978 the first report discussing the use of natural somatostatin for the treatment of a patient with a carcinoid tumour in order to reduce hormone related symptoms was published [6]. However, the use of natural somatostatin for long-term treatment is difficult since the half-life of this hormone is only 90 seconds necessitating continuous intravenous infusion. In the early 1980s the first long-acting

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somatostatin analog, octreotide, was introduced for clinical use. Octreotide is an octapeptide with a half-life in the circulation of about 115 minutes after subcutaneous injection [7]. The initial clinical applications were acromegaly and hormone producing tumours of the gastrointestinal tract [8]. Beside octreotide, another somatostatin analog is now available, lanreotide [9]. Both these somatostatin analogs have the same receptor binding profile with a high affinity for somatostatin receptor subtypes 2 and 5.

The primary effect of the somatostatin analog treatment is to inhibit the secretion of excessive hormones produced by the tumour cells and thereby significantly reduce hormone related symptoms. In patients with carcinoid crises or the VIPoma syndrome, treatment with a somatostatin analog may be life-saving. This relief of symptoms is usually concomitant with reduced hormone levels detected in plasma and urine. In different studies, significantly reduced hormone levels are found in 50-70% of patients treated with somatostatin analogs. In most patients an improvement of quality-of-life can be seen following treatment with somatostatin analogs. Today long acting formulations of both octreotide (Sandostatin LAR®) and lanreotide exist (Somatuline Autogel®) [10].

In *in vitro* experiments somatostatin analogs have been shown to inhibit proliferation of many different tumour cell lines. It has been demonstrated a stabilization of tumour growth in 30-50% of patients possibly by reduction of growth promoting factors and inhibition of angiogenesis [11]. However, only very few patients (2-5%) respond by reduction in tumour size (50%) during treatment with somatostatin analogs [11].

New somatostatin analogs with different receptor subtype binding profiles and biological actions have been reported. It has been argued that analogs with specificity for new subsets of receptors or single somatostatin receptor subtypes may prove valuable for treatment of both malignant and non-malignant diseases. However, until now, only three analogs with very similar binding and biological profiles have been tested in clinical trials (octreotide, lanreotide and vapreotide). A new somatostatin analog is being introduced with a more universal binding profile than the previously available analogs. This new analog, SOM230, binds with high affinity to somatostatin receptors 1, 2, 3 and 5 [12] and effectively inhibits secretion of growth hormone from primary cultures of rat pituitary cells. The *in vivo* effect of growth hormone suppression in rats is also very high. In long-term studies, the reduction in IGF-1 levels in plasma was 75% in rats treated with SOM230 and 28% in animals treated with octreotide. The inhibitory effect on growth hormone secretion seems to be rather specific since insulin and glucagon levels were reduced only at high doses of SOM230. These results could also be confirmed in primates [13]. SOM230 is now applied in phase II trials in midgut carcinoids. In an early trial with patients with midgut carcinoid refractory to octreotide LAR, 30% responded to SOM230 at doses of 900 μg bid [14].

Somatostatin receptors

Somatostatin acts through specific receptors expressed on the plasma membrane. Five different subtypes have been cloned and they belong to the seven-transmembrane receptor superfamily [15-17]. The receptors are G protein-coupled but several other second messenger systems are also used for intracellular signal transduction. The somatostatin receptors are expressed in a tissue specific manner [18]. All somatostatin receptor subtypes can be found in the brain and in the endocrine cells of the pancreas. In the endocrine pancreatic cells the receptor expression shows considerable variability [19]. In the endocrine cells of the pancreatic islets somatostatin receptor subtypes 1, 3 and 4 are almost always expressed in all four cell types, while somatostatin receptor subtype 2 is found in most alpha cells and beta cells, but only in about half of the delta and very few PP (pancreatic polypeptide) cells. Somatostatin receptor subtype 5 is found in all beta cells and delta cells but almost never in alpha cells or PP cells. This expression pattern differs from the expression found in endocrine cells scattered throughout the exocrine pancreas and also from endocrine cells found in the ductal epithelium. In these locations fewer receptor subtypes can be identified although all receptor subtypes are present in some cells.

Somatostatin receptor subtype 2 is found in the gastrointestinal tract together with subtype 1 and 5. The receptor subtype most rarely expressed is subtype 4 that can be found in the lung, however, very little research has been directed towards this receptor and future studies may show other locations for this receptor as well. It has been shown that somatostatin receptor subtype 2 is the subtype mainly responsible for the inhibitory effect on hormone release from endocrine cells [18]. This action involves inhibition of cAMP formation and also a reduction in intracellular calcium levels leading to inhibition of hormone secretion. Patel et al. showed that somatostatin receptor subtype 3 might be involved in apoptosis [20]. In a recent paper another group has been able to couple induction of apoptosis to somatostatin receptor subtype 2 as well [21]. The increase of apoptosis was shown in a cell line, LH-60, that has a deletion of the p53 gene. Thus, in these cells the induction of apoptosis has to be independent of p53 accumulation.

Receptor subtypes 1, 2 and 5 may mediate a growth-inhibiting signal at least *in vitro* [22,23]. It has been shown that SHP-1 protein plays an important role in somatostatin mediated cell growth arrest signaled through receptor subtype 2 [24]. The activity of SHP-1 is stimulated by somatostatin receptor subtype 2 and the activated SHP-1 inhibits the cell proliferation by accumulation of hypophosphorylated retinoblastoma protein leading to growth arrest.

The possibility of G protein-coupled receptor to form dimers has been proposed previously. Somatostatin receptors have been shown to form dimers, both between different somatostatin receptor subtypes [25] and also with dopamine receptors [26]. The exact physiological function of this dimerization is not clear, but in experimental systems it has been shown that somatostatin receptor subtype 5 can form dimers with receptor subtype 1 but not with somatostatin receptor subtype 4. Thus, there seem to be some restriction as to the dimers that can be formed. This phenomenon was studied in transfected CHO-cells and it was shown that somatostatin receptor subtype 5 could be found as a monomer which was considered to be inactive and as a homodimer or a heterodimer with somatostatin receptor subtype 1 after stimulation of a ligand binding to the receptor

Table 1. **Expression of somatostatin receptor subtypes in neuroendocrine tumours examined by immunohistochemistry and RT-PCR**

	Sst1	Sst2	Sst3	Sst4	Sst5
Endocrine pancreatic tumours					
Papotti et al. [28]	30/33*	37/48	30/48	8/33*	29/48
Kulaksiz et al. [29]	21/69	54/69	54/69	ND	53/69
Oda et al. [31]	6/7	6/7	6/7	ND	ND
Midgut carcinoid tumour					
Papotti et al. [28]	12/13*	21/26	17/26	3/13*	21/26
Kulaksiz et al. [29]	13/35	30/35	26/35	ND	29/35

ND: not done; * indicates use of RT-PCR method

[25]. It was also shown that somatostatin receptor subtype 1 was internalized only as a heterodimer, and this might explain why normal endocrine cells adapt to somatostatin analogue treatment and maintain a normal responsiveness in cells that express all five receptor subtypes.

Somatostatin receptor expression in neuroendocrine tumours

The expression of somatostatin receptors in neuroendocrine tumours was first shown by Reubi in 1987 by autoradiography using somatostatin labeled with radioactive iodine [27]. After the somatostatin receptor became cloned, in situ hybridization and RT-PCR took the place of autoradiography. During the past few years polyclonal antibodies specific for the five different somatostatin receptor subtypes have been developed and there are now some reports of the somatostatin receptor expression in neuroendocrine tumours based on immunohistochemical staining. See *Tab. 1* for a summary of results concerning somatostatin receptor expression in different neuroendocrine tumours.

There are some papers reporting on the expression of somatostatin receptors in endocrine pancreatic tumours. Papotti et al. [28] have investigated the expression of somatostatin receptor subtypes by RT-PCR (all subtypes) and immunohistochemistry (subtypes 2, 3 and 5). They found that most tumours expressed somatostatin receptors subtype 1, 2, 3 and 5. However, only a minority of tumours expressed receptor subtype 4. They reported that all patients included with gastrinomas and glucagonomas expressed somatostatin receptor subtype 2 while all somatostatinomas expressed receptor subtype 5. The expression in insulinomas was, however, variable.

Another group has also reported on the expression of somatostatin receptors 1, 2, 3 and 5 in endocrine pancreatic tumours [29]. They found a high expression of receptor subtypes 2, 3 and 5 while the expression of subtype 1 was intermediate. They did not investigate the somatostatin receptor subtype 4 expression. For details see *Tab. 1*.

In carcinoid tumours, the expression of somatostatin receptor subtype 2 has been correlated to responsiveness to treatment with somatostatin analogs [30]. In a recent publication the predictive value of somatostatin receptor expression was investigated in patients with endocrine pancreatic tumours [31]. Tumour specimens from seven patients with endocrine pancreatic tumours were stained for somatostatin receptor subtypes 1, 2 and 3. The only patient responding to octreotide injection was a patient with an insulinoma who had a very strong expression of somatostatin receptor subtype 2. In this patient octreotide could reduce the hypoglycemias. In this report most patients expressed all three subtypes that were examined, but the expression was often rather weak.

Both Papotti and Kulaksiz have reported on the expression of somatostatin receptors in carcinoid tumours as well [28,29]. The results are similar to the results for endocrine pancreatic tumours with a high expression for subtypes 2, 3 and 5 reported by both authors. Papotti reported a high expression also for receptor subtype 1 while this was low in the paper by Kulaksiz. Somatostatin receptor subtype 4 was only investigated by RT-PCR in Papottis' work and showed a low expression. A considerable variation in the receptor expression was not only seen between patients, but also within the same patient's tumour tissue sample.

Imaging

Somatostatin analogs can be labeled with radioactive isotopes, injected intravenously and the distribution of tracer can subsequently be detected with a gamma camera. Octreoscan is the most frequently used method, and today this investigation is included in the basic work-up of patients with neuroendocrine tumours [32]. The investigation will give information both about the receptor status of the tumour and also of the tumour spread. This information is used when decisions are made about the treatment of the patients. Patients with somatostatin receptor expressing tumours usually respond to treatment with somatostatin analogs, while those that lack such expression usually fail to respond with a decrease in hormone levels [32].

The use of somatostatin receptor scintigraphy for radio nuclear imaging of neuroendocrine tumours has been compared with other diagnostic methods. A comparison was made between ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) and ^{111}In-pentetreotide in 54 patients with different neuroendocrine tumours [34]. The difference in sensitivity in detecting metastases seen on computerized tomography or magnetic resonance tomography was investigated. It was shown that ^{111}In-pentetreotide was more sensitive than ^{123}I-MIBG with a detection rate of 67% vs 50% for carcinoid tumours and 91% vs 9% for endocrine pancreatic tumours. These differences may in part be explained by the fact that the two different methods reflect different biological features and in some patients they might be complementary to each other. For patients with midgut carcinoid tumours and endocrine pancreatic tumours both spread of disease and somatostatin receptor status might be of importance and therefore an ^{111}In-pentetreotide scintigraphy should be performed.

In another investigation, fluorodeoxyglucose (FDG) positron emission tomography (PET) and somatostatin receptor scintigraphy were compared in patients most of whom had carcinoid tumours [35]. In this study FDG PET was performed

in 17 patients and somatostatin receptor scintigraphy in 16 patients. Most patients had typical carcinoid tumours with a low proliferation rate. FDG PET correctly confirmed 4/7 primary tumours and 8/11 metastatic lesions, while somatostatin receptor scintigraphy identified 6/7 primary tumours and 10/11 metastases. There was no correlation between the tracer uptake in tumour lesions and histological features such as proliferation rate measured by Ki-67 or p53 expression. It was concluded that somatostatin receptor scintigraphy should be performed in most patients and that FDG PET should be used in patients that are negative at somatostatin receptor scintigraphy. In a most recent study PET with C^{11}-5HTP had significantly higher sensitivity than Octreoscan® in patients with neuroendocrine GEP-NET's [36].

Treatment with somatostatin analogs

Midgut carcinoid tumours

A large number of clinical trials with octreotide in midgut carcinoid tumours have been published [37-39]. The reported subjective and histochemical response rate has been between 40% and 60% when the tumor responses have been less than 5%. In patients with midgut carcinoid tumours the use of somatostatin analogs has been considered to be first line treatment in the presence of a carcinoid syndrome. In some studies the somatostatin analog is combined with alpha-interferon [40]. Aparicio et al. recently discussed the use of somatostatin analogs in neuroendocrine tumours [41]. They used somatostatin analogs (octreotide 100 μg thrice daily and/or lanreotide 30 mg every 14 days) in 35 patients with progressive disease, 12 midgut carcinoid patients, 13 patients with endocrine pancreatic tumours, 5 with primary tumours in the lung and 5 patients with other locations of the primary tumour. A partial reduction in tumour size was observed in one patient, while the tumour growth was stabilized in 20 other patients. The authors also divided the patients into those with tumours with a high proliferation rate and those with a low proliferation rate. They found a significantly lower response rate in patients with rapidly progressing tumours (4/12) as compared to patients with slowly growing tumours (13/17), $p<0.02$. The median duration of treatment in this study was 7 months. The dose of somatostatin analog might be critical. Ultra high doses of somatostatin analogs have demonstrated significant clinical benefit in patients resistant to standard doses of octreotide or lanreotide [42,43]. Guidelines for the use of octreotide in clinical practice have recently been published [44].

Endocrine pancreatic tumours

The use of somatostatin analogs in the treatment of endocrine pancreatic tumours is well established. Single treatment with somatostatin analogs produces good symptomatic and biochemical responses, but the effect on tumour size is disappointing with only about 5% objective responses. The use of a combination of somatostatin analogs and alpha-interferon has been proposed as a possible strategy to control both hormone symptoms and tumour growth. Such a combination was reported on by Frank et al. [45]. In their study 21 patients with progressing tumours were included. One patient had a decrease in tumour size while 60% of the patients remained stable for a median of 12 months. However, their material was a mixed material with several different tumour groups and they used response criteria that are not commonly accepted, designating a reduction in tumour size by >30% as an objective response. Therefore, results from this study are difficult to compare with results from other groups.

Another study investigating the potential of this combination to control both symptoms and tumour growth has been presented [46]. Only patients with malignant endocrine pancreatic tumours were included. A total of 16 patients were treated with a combination of a somatostatin analog (octreotide or somatuline) and alpha-interferon (interferon-alpha2b, lymphoblastoid interferon or human leukocyte interferon). During treatment with this combination 3 patients (19%) showed a reduction in tumour size by >50% for about 2 years (19-25 months). Eleven patients showed stabilization of tumour size for 13 months (4-32 months) while 2 patients continued to progress. In 62.5% (10 of 16) of the patients a biochemical response was detected for a median of 22 months (range 10-32 months). Five patients remained stable for 9 months (4-20 months) and only one patient progressed. From this study it seems that the combination can be used with good results in patients with endocrine pancreatic tumours and can be considered as an alternative for patients who do not want to receive chemotherapy as first line treatment.

In another study 15 patients with malignant gastrinomas were treated with octreotide [47]. All patients had liver metastases and were in a progressive state. The patients were treated with octreotide 200 μg twice daily and were eventually switched over to long-acting release octreotide 20-30 mg every month. After 3 months of treatment 7 patients (47%) had stabilization of their previously progressive disease and one patient had a reduction in tumour size (6%). The mean duration of response was 25 months (range 5.5-54.1 months) and six of the eight responders were still responding at the time of last follow-up. This response could not be correlated to pre-study clinical parameters such as tumour extent, gastrin levels or acid secretory rates. Patients with slow-growing tumours tended to have a higher response rate. During follow-up only 25% of patients responding to somatostatin analog treatment died as compared to 71% of the non-responders. The authors claimed that octreotide is an effective antitumour treatment and might be considered early in the treatment of patients with endocrine pancreatic tumours.

Tumour targeting

During the last few years the same substances that are used for somatostatin receptor scintigraphy have been used for high-dose radioactive tumour targeting therapy. There have been some reports on small clinical trials with good results both on hormone levels and on tumour size [48,49]. The toxicity is mainly limited to impairment of kidney function and bone marrow suppression with a decrease in platelets and white blood cells.

In a phase II study, 41 patients with neuroendocrine gastroenteropancreatic and bronchial carcinoid tumours were included [50]. Thirty-four patients had progressive disease.

They were treated with four courses of ^{90}Y-DOTATOC up to a total dose of 6000 MBq/m^2. Complete remission was found in 1 patient while 9 of 41 showed a partial response. A minor response was observed in 5 patients and 6 patients progressed. The rest of the patients remained stable. The median duration of response was not reached after 26 months of follow-up and the two-year survival was 76%. A reduction in morphine dependent tumour-associated pain was observed and 83% of patients with a carcinoid syndrome had a reduction in symptoms. Side-effects included grade III pancytopenia in 5% and vomiting in 23% of patients.

In another study the same group reported on a similar study including 39 patients with neuroendocrine tumours, treated with 7.4 GBq/m^2 of ^{90}Y-DOTATOC [51]. The response rates were within the same range with only 3 patients progressing and 2 patients showing a complete remission. Bone marrow suppression was seen in the same range as in the previous study. However, in this study one patient developed grade 2 renal insufficiency.

^{111}In-pentetreotide can also be used to treat patients with neuroendocrine tumours. In a small study, 27 patients with advanced gastroenteropancreatic tumours who had failed all forms of conventional therapy were treated with at least 2 monthly injections of 180 mCi ^{111}In-pentetreotide [52]. A total of 16 patients were considered to have clinical benefit from the treatment. A radiological response was found in 2 patients and tumour necrosis in 7 patients. Tumour markers decreased by >50% in 81% of the patients. An inclusion criterion for entering this study was that patients should have less than 6 months expected survival. The median survival after treatment was 18 months (range 3-54 months) and the treatment was well tolerated. Thus, the authors argued that treatment with ^{111}In-pentetreotide might prolong the survival in these severely ill patients.

The adverse reactions to tumour targeting treatment with radioactive somatostatin analogues mainly affects bone marrow and kidney function. In a report concerning a patient with midgut carcinoid tumours treated with ^{90}Y-DOTATOC, a severe deterioration of kidney function occurred 15 months after treatment was discontinued [53]. The patient had received 4 doses of ^{90}Y-DOTATOC reaching a cumulative dose of 9.62 MBq. Injections were administrated every 6th week. In an attempt to prevent renal toxicity, the patient received an amino acid solution, Hartmann-Hepa 8%, together with the fourth treatment cycle. Before and during treatment the patient had normal levels of serum creatinine and urea nitrogen. After 15 months a progressive deterioration of renal function was observed leading to end-stage renal disease. The patient was treated with intermittent haemodialysis when creatinine clearance declined to less than 10 ml/min. A contributing factor to this renal failure might be that the patient did not receive treatment with amino acids until the last treatment period.

In nuclear medicine, cationic amino acids are used in order to prevent renal damage from high doses of radioactive isotopes. The hypothesis is that positively charged amino acids bind to the negatively charged sites in the renal tubular cells and hence decrease the tubular reabsorption and further degradation of the injected conjugate. It has been shown that infusion of arginine and lysine can reduce the kidney uptake of ^{111}In-pentetreotide and radiolabeled Fab-fragments both in experimental models and in patients [54,55].

In another report, 5 patients treated with ^{90}Y-DOTATOC developed renal failure [56]. In three of these patients a kidney biopsy could be performed showing a thrombotic microangiopathy. This pathological-anatomical diagnosis is the same as the picture seen in patients receiving external radiotherapy. In these patients the renal failure became overt only 3 months after the last injection of ^{90}Y-DOTATOC. This severe adverse reaction indicates that further studies are needed to understand how kidney protection should be administrated and the level and frequency of doses of ^{90}Y-DOTATOC that should be used.

New isotopes will be tested in the future in order to treat patients with somatostatin receptor expressing tumours. One such new isotope is 177-lutetium (^{177}Lu), a beta- and gamma-emitting radionuclide. An advantage of this radionuclide as compared to 90-yttrium is that it has a shorter penetration in tissue, making it more suitable for treatment of small tumours. The somatostatin analog DOTA-0-Tyr3-octreotate binds with a very high affinity to somatostatin receptor subtype 2 and can be labeled with ^{177}Lu. In animal experiments with a rat model, ^{177}Lu-octreotate had a favorable impact on survival. In a study comparing the uptake of the two different radioactive compounds, ^{90}Y-DOTATOC and ^{177}Lu-octreotate, performed in six patients with somatostatin receptor expressing tumours, the uptake in spleen, liver and kidney was equal, while the tumour uptake was three to fourfold higher in four of five patients from ^{177}Lu-octreotate [57]. Also in this study, infusion of amino acids reduced the kidney radiation dose by almost 50%. Thus, a higher absorbed dose can be obtained in most tumours without increase in doses absorbed by potentially dose-limiting organs. In a recent paper by Kwekkeboom and co-workers, the results of treatment of 131 patients with neuroendocrine tumours, treated with cumulative doses up to 600-800 m Ci of ^{177}Lu-Octreotate. Complete remission was obtained in 2%, partial remission in 26%, minor responses in 19%, stable disease in 35% and progression in 18%. Hematology toxicity occurred in less than 2% and renal insufficiency in one patient and hepatorenal syndrome in another [58].

Future aspects

SOM230 is a new somatostatin analog with high affinity for somatostatin receptor subtype 1, 2, 3 and 5 that has entered early clinical studies and results will soon be available. Much effort is also being placed into development of methods to investigate the expression of the different somatostatin receptors in normal and malignant tissue. Several groups have developed receptor subtype specific antibodies that can be used in immunohistochemistry and hopefully these will soon be included in the diagnostic work-up. The use of different radioactively labeled somatostatin analogs is also a subject which draws much attention at the moment and new trials with new analogs and new isotopes will be initiated very soon. In the future mixtures of isotopes might be used in order to treat both very small and

medium sized metastases at the same time. Radio sensitizers that may improve the effect of radioactive targeting therapy are also being developed.

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