Review

Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours

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Background: **Somatostatin receptors have been found on a variety of neuroendocrine tumours, such as carcinoids and paragangliomas, as well as on most pancreatic endocrine and breast tumours. Somatostatin receptor scintigraphy with a radionuclide-labelled somatostatin analogue, [^{111}Indium-diethylenetriaminopenta-acetic acid]octreotide, is a sensitive and specific technique for visualizing *in vivo* the presence of somatostatin receptors on various tumours.**

Methods: **Material was identified from previous review articles, references cited in original papers and a Medline search of the literature. Additional material was obtained from recently published abstracts of meetings.**

Results and conclusion: **Somatostatin receptor imaging of neuroendocrine tumours is essential in the diagnostic evaluation of most of these tumours. The expression of somatostatin receptors *in vivo* not only predicts the outcome of somatostatin analogue treatment but also opens the possibility of new therapeutic strategies. Because better information about spread of the disease can be obtained, more justifiable options for therapy can be proposed.**

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Somatostatin receptor expression

Somatostatin (SS) is a small regulatory peptide; it was isolated in the ovine hypothalamic gland in 1973 as a growth hormone (GH) release inhibiting factor[1]. SS is widely distributed in the human body and is found not only in the hypothalamus but also in various parts of the gastrointestinal tract, indicating that inhibition of GH is not its only function[2]. Apart from its function as a neurotransmitter in the central nervous system, it also has inhibitory effects on the secretion of hormones by the pancreatic islets (insulin, glucagon) and on exocrine pancreatic function. SS also inhibits normal gastrin production, and consequently gastric acid and pepsin production[3]. A number of observations have suggested an antiproliferative effect of SS and its stable analogues[4–6].

Critical to all these actions is the expression of SS receptors (SS-Rs) on the cell membrane. These SS-Rs subserve two functions, first to recognize the ligand and bind it with high affinity and specificity, and second to generate a transmembrane signal that evokes a biological response. Large numbers of SS-Rs are found on most tumours with amine precursor uptake and decarboxylation characteristics and neuroendocrine properties, such as carcinoids, paragangliomas, phaeochromocytomas, medullary thyroid cancers and endocrine pancreatic tumours. In addition, large numbers of binding sites with high affinity for SS are also found on breast and brain tumours, as well as on various cells of the immune system[7–10]. At least five different human SS-R subtypes have been cloned[11]. All subtypes bind SS with high affinity, while their affinities for the SS analogue octreotide differ considerably. Octreotide binds with high affinity to SS-R subtype 2 (sst_2) and sst_5, to a lesser degree sst_3, while no binding to sst_1 and sst_4 occurs. Other SS analogues that are in clinical use, such as BIM 23014 (lanreotide) and RC-160 (vapreotide), as well as the hexapeptide MK678, bind to three of the five SS-R subtypes, also displaying high affinity for sst_2 and sst_5 and moderate affinity for sst_3[12].

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SS-R messenger RNA subtypes are widely expressed in neuroendocrine tumours, but their distribution does not necessarily correlate with SS-R subtype expression. Furthermore SS-R subtypes show a differential subcellular localization in human SS-R-positive tumours[13]. The majority of human endocrine pancreatic tumours, such as gastrinomas, glucagonomas, vipomas and 'non-functioning' islet cell tumours, express sst_2. *In vitro* studies have shown that 72 per cent of insulinomas express SS-Rs. However, these are mainly sst_3 receptors, which have low affinity for octreotide[14,15]. Although SS-Rs have been demonstrated on exocrine pancreatic cells in experimental animals (mainly on acinar cells), neither SS-Rs nor neuroendocrine properties could be confirmed on human exocrine pancreatic adenocarcinomas[16]. Carcinoids, paragangliomas, phaeochromocytomas and medullary thyroid cancers all have a mixed distribution of the SS-R subtypes, but sst_2 is expressed most frequently. The presence of different combinations of SS-R subtypes may explain the variable clinical response to SS analogues and the difference in successful localization by SS-R scintigraphy (SRS) of these tumours. Metastases of SS-R-positive tumours initially express the same SS-R subtype as the primary, but loss of these receptors has been described after dedifferentiation of tumour cells or after chemotherapy[17]. In addition, SS-R overexpression has been identified in peritumoral veins of primary neoplasms and in veins surrounding lymph node, bone and lung metastases[18].

Somatostatin receptor scintigraphy

The optimal management of patients with neuroendocrine tumours requires accurate imaging and staging. For the visualization of SS-R-positive tumours, SRS with [^{111}Indium-diethylenetriaminopenta-acetic acid (^{111}In-DTPA^{0})]octreotide (Octreoscan, Mallinckrodt Medical BV, Petten, The Netherlands) has been used for more than 10 years[19,20]. The efficacy of SRS using this agent in patients with histologically or biochemically proven endocrine pancreatic tumours or carcinoids was evaluated in a European multicentre trial[20]. The highest success rates were observed with glucagonomas (100 per cent), vipomas (88 per cent), gastrinomas (73 per cent), 'non-functioning' islet cell tumours (82 per cent) and carcinoids (87 per cent). Insulinomas were detected in only 46 per cent of cases owing to the low incidence of sst_2 on insulinoma cells. The low sensitivity in this study found for some tumours may be related to important differences in scanning procedures, such as the amount of radioligand administered, the duration of the acquisition and the use of single photon emission computed tomography (SPECT)[21]. With SPECT, in which a rotating camera is used, image reconstructions can be made similar to those of spiral computed tomography (CT). This technique gives additional visual information, especially on tumours in the liver and upper abdomen[22]. Twenty-five per cent more liver metastases are detected with SPECT than with planar SRS.

In a prospective study comparing the sensitivity of SRS with that of CT, magnetic resonance imaging (MRI), ultrasonography and selective angiography in the detection of primary and metastatic gastrinomas, SRS altered clinical management in 47 per cent of instances and had a superior sensitivity and specificity[23] (*Table 1*). Cadiot *et al.*[24] compared the results of SRS with those of conventional imaging techniques, including endoscopic ultrasonography, and with surgical findings in 21 consecutive patients with Zollinger–Ellison syndrome. SRS added complementary information to other imaging techniques, including endoscopic ultrasonography, and improved the preoperative detection of extrapancreatic gastrinomas. By combining SRS with endoscopic ultrasonography they were able to detect 90 per cent of the tumours in the upper duodenopancreatic area. SRS identified metastatic disease in 20–30 per cent of patients after all other imaging techniques had failed[22]. In another study of 160 patients with biologically and/or histologically proven gastroenteropancreatic tumours, including pancreatic islet cell tumours, SRS changed the surgical therapeutic strategy in 40 patients (*Table 2*)[25]. Unsuspected liver tumours were discovered

Table 1 Imaging methods for the detection of liver metastases and extrahepatic metastases in patients with Zollinger–Ellison syndrome

	Positive result (%)	
Procedure	Extrahepatic tumour ($n = 80$)	Liver metastases ($n = 24$)
Ultrasonography	9	46
CT	31	42
MRI	30	71
Angiography	28	62
CIM	48	83
SRS	58	92
SRS + CIM	68	96
SRS only*	20	12
CIM only†	10	4

Results are expressed as the percentage of the 24 patients with proven liver metastases and of the 80 patients with extrahepatic disease. Conventional imaging methods (CIM) included ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and angiography. *Tumour detected only with somatostatin receptor scintigraphy (SRS); †tumour detected only with CIM. From reference 23

only by SRS in seven patients, contralateral liver tumours before hepatectomy in two, and extrahepatic disease in 31. In 48 patients with histologically proven hepatic metastases of neuroendocrine tumours, including carcinoids, the present authors compared conventional imaging methods (CIM) with SRS for the detection of extrahepatic disease. CIM consisted of ultrasonography, CT of the thorax and abdomen and, when indicated, bone scanning. All patients were scanned according to a multiple spot views protocol. A minimal dose of 200 MBq ^{111}In and at least 10 μg of peptide was administered as an intravenous bolus, and acquisition was performed 24 and 48 h thereafter. Acquisition time was 15 min and abdominal SPECT was used systematically with a triple head camera. SRS alone demonstrated 114 extrahepatic lesions in 37 patients, whereas CIM visualized only 50 extrahepatic lesions in 22 patients (*Table 3*).

In patients with paragangliomas, SRS provides optimal information on other potential tumour sites in the body; paragangliomas are often multicentric and asymptomatic[26]. For imaging of adrenal phaeochromocytomas, scintigraphy with radiolabelled metaiodobenzylguanidine (MIBG) is more accurate than SRS, since the majority of benign phaeochromocytomas are localized in the adrenal, a localization that is difficult to distinguish from the kidney with SRS. Furthermore, the majority of these benign lesions do not express SS-Rs. Recently, in a large European multicentre study, the sensitivity of [^{131}I]MIBG in detecting benign phaeochromocytomas was shown to be 81 per cent[27], while the detection rate with SRS is only around 25 per cent. The majority of malignant tumours (80 per cent), in contrast, express appropriate receptors and so SRS could be used to characterize adrenal masses suspected to be malignant[28]. SRS has a limited role in the management of medullary thyroid cancer. It might be useful for the detection of residual and recurrent disease after total thyroidectomy, or in patients who present primarily with metastatic disease in order to study the feasibility of performing peptide receptor radionuclide therapy[29,30]. To optimize the detection of metastases in patients with recurrent medullary cancer, the combination of SRS and ^{99m}Tc-radiolabelled dimercaptosuccinic acid (^{99m}Tc-DMSA) should be considered, as together they have a sensitivity of 84 per cent for the diagnosis of medullary cancer. SRS alone has a sensitivity of 29 per cent and ^{99m}Tc-DMSA alone has a sensitivity of 69 per cent[31].

Finally, the difference in SS-R expression between islet cell tumours, especially 'non-functioning' tumours and pancreatic duct cancers, offers the possibility of differentiating between these tumours before surgery[32]. This is important, as palliative surgery in patients with islet cell tumours is of value not only in relieving clinical symptoms but also in decreasing tumour burden, which might enhance the effect of medical treatment and result in improved clinical status and longer survival.

Table 2 Clinical impact of somatostatin receptor scintigraphy in 160 patients with gastroenteropancreatic tumours

		SRS classification		
Initial classification	Total no.	I	II	III
I No metastases	90	65	7	18
II Liver metastases only	59		46	13
III Extrahepatic metastases	11			11

SRS, somatostatin receptor scintigraphy. From reference 25

Table 3 Detection of extrahepatic metastases: somatostatin receptor scintigraphy *versus* conventional imaging methods

	CIM negative	CIM positive	Total
SRS negative	11		11
SRS positive	15	22	37

Imaging was carried out in 48 patients with histologically proven hepatic metastases of neuroendocrine tumours. The table shows number of patients with extrahepatic disease detected by somatostatin receptor scintigraphy (SRS) with [^{111}Indium-diethylenetriaminopenta-acetic acid]octreotide or by conventional imaging methods (CIM) consisting of computed tomography, ultrasonography and bone scanning. In 15 patients extrahepatic metastases were detected with SRS only. Eleven patients were found to have no extrahepatic disease

Clinical use of somatostatin analogues

Most endocrine pancreatic tumours, with the exception of insulinomas, have a malignant potential and have already metastasized at the time of diagnosis. These tumours are in general slow growing and most of the clinical distress is related to the hypersecretion of hormones, which often incapacitates the patient and causes long and repeated periods of admission to hospital. The clinical use of the SS analogue octreotide in this type of patient is of considerable help in controlling symptomatology. Debilitating diarrhoea, dehydration and hypokalaemia (vipoma) and necrolytic skin lesions (glucagonoma) can be well controlled during continuing treatment with octreotide. There is no doubt that octreotide therapy is of great benefit for most of these patients and improves their quality of life dramatically[33]. In selected patients with peptic ulceration and hyperplasia of fundic argyrophil cells (gastrinoma) or life-threatening attacks of hypoglycaemia (metastatic insulinoma) octreotide may also be of therapeutic benefit[34,35].

Clinical studies in those with hormone-producing islet cell tumours have shown a close parallel between the presence of SS-Rs on the tumours and the *in vivo* and *in vitro* suppressive effects of octreotide on hormone release[36]. This indicates that SRS can predict a possible suppressive effect of octreotide on hormonal hypersecretion by endocrine pancreatic tumours. Although octreotide is able to inhibit gastrin release in Zollinger–Ellison syndrome, proton pump inhibitors are currently the first choice as over 80 per cent of patients are controlled by omeprazole, lansoprazole or pantoprazole. A major problem in the treatment of islet cell tumours and carcinoids with octreotide is that the inhibition of secretion of tumour-related hormones is transient. Most patients finally become insensitive to octreotide treatment, possibly by down-regulation of SS-R expression or outgrowth of SS-R-negative clones[6,37,38]. The beneficial effects on clinical symptomatology in those with metastatic endocrine pancreatic tumour and carcinoids is highly variable. Increasing the dose of octreotide or intermittent administration reverses these problems in most cases. The median duration of improvement of diarrhoea and flushing attacks by octreotide in patients with metastatic carcinoid disease is over 12 months[5].

In some patients with metastatic medullary thyroid cancer, continuous treatment with very high doses of octreotide may bring temporary relief. Long-term therapy with SS analogues for catecholamine-secreting (malignant) paragangliomas and phaeochromocytomas has not shown clinical benefit[39].

The role of octreotide in the treatment of pancreatitis is controversial. A meta-analysis of six studies showed a significant decrease in mortality rate in patients with mild or severe disease (6 per cent octreotide *versus* 14 per cent placebo)[40]. However Uhl *et al.*[41] did not find a significant difference in mortality rate or complications in a large series of 302 patients with acute pancreatitis. The decrease in digestive enzyme secretion and the increase in intestinal water and electrolyte absorption caused by octreotide can be beneficial in the treatment of pancreatic and enterocutaneous fistula[42,43]. In elective surgery for pancreatic carcinoma or chronic pancreatitis, perioperative administration of octreotide has demonstrated its value. In a study of 246 patients who underwent pancreatic surgery, octreotide treatment reduced the incidence of death and complications compared with placebo (3 and 32 *versus* 6 and 55 per cent respectively)[44]. Finally, SS and octreotide infusion reduce portal pressure by decreasing splanchnic blood flow. Although the exact mechanisms of acute haemodynamic changes in patients with portal hypertension are unknown, there is a rationale for the use of SS and its derivatives in the control of acute oesophageal variceal bleeding[45]. Early infusion of SS in cirrhotic patients with acute variceal haemorrhage decreases treatment failure and mortality rates, and reduces active bleeding after sclerotherapy, thereby improving the efficacy of sclerotherapy for acute variceal bleeding episodes[46].

Oncological applications of somatostatin analogues

The observation that SS inhibits the release of various peptide hormones has stimulated interest in its use as an antiproliferative agent. In preclinical studies SS analogues have inhibited the growth of a wide variety of SS-R-positive as well as SS-R-negative tumours *in vivo* and *in vitro*[4,6,47]. An indirect tumour growth inhibition may be achieved via the inhibition of circulating tumour growth promoting hormones (GH, insulin-like growth factor 1, insulin) and inhibition of circulating, paracrine- and/or autocrine-secreted stimulatory growth factors. SS and its analogues can also modulate the activity of immune cells[48] and potentially influence tumour blood supply; Reubi *et al.*[49] demonstrated a high density of SS-Rs on veins in the peritumoral zone of several types of malignant tumour. A potentiation of the antiproliferative effect of octreotide has also been suggested[50], but no beneficial effect of octreotide combined with tamoxifen was found in patients with metastatic breast cancer[51]. Critical to the direct antiproliferative effects of SS analogues is the presence of SS-Rs[52]. Both adenosine 3′,5′-cyclic monophosphate-dependent and -independent effector mechanisms have been suggested[53–56], while stimulation of phosphotyrosine phosphatase activity may play an important role in the inhibition of growth factor-stimulated cell growth[57,58].

The results of clinical trials in patients with gastroenteropancreatic tumours, using SS analogues alone or in combination with interferon-α, are rather disappointing, with a biochemical response in 77 per cent of patients with a median duration of 15 months but without any reduction in tumour size[59,60]. Clinically, octreotide has been the most commonly used SS analogue, yielding biochemical response rates of between 30 and 70 per cent but objective tumour shrinkage in less than 10–15 per cent of patients[5,61–64]. Treatment with standard doses of the SS analogue lanreotide does not appear to be any better than that with standard doses of octreotide. However, tumour biopsies before and during treatment with high doses of lanreotide have indicated apoptosis in responding patients[65,66]. Side-effects of long-term administration of SS analogues are rare. The most relevant side-effect is the development of gallstones, which is believed to derive from the inhibition of gallbladder emptying due to the inhibition of cholecystokinin release[67]. The incidence of developing

cholelithiasis and/or gallbladder sludge is reported to be between 30 and 60 per cent, and seems to be dose dependent[68,69]. Patients require cholecystectomy for either symptomatic disease or acute cholecystitis in 15 per cent of cases; prophylactic cholecystectomy is not indicated, unless it is performed during elective cytoreductive surgery[69]. Octreotide might also influence blood sugar levels in patients with diabetes mellitus.

Radionuclide therapy: preclinical

A new and fascinating application is the use of radiolabelled octreotide and other peptides for peptide receptor radionuclide therapy, henceforth referred to as radionuclide therapy. After systemic injection of [^{111}In-DTPA^{0}]octreotide, the radioligand is internalized and transported into the lysosomes by an SS-R-specific and temperature-dependent process starting with endocytosis[70,71]. The radionuclide as metabolite ^{111}In-DTPA-D-Phe is not capable of passing the lysosomal membrane, resulting in a biological half-life in human tumour tissue of over 700 h[72,73]. ^{111}In not only emits γ rays, which can be visualized during scintigraphy, it also emits internal conversion and Auger electrons which have a short to medium tissue penetration (0·02–10 and 200–550 μm respectively). Therefore, an effect on tumour cell proliferation might be expected, as the radiotoxicity of the radionuclide is very high if the DNA of the cell is within the particle range[74,75].

Three experimental animal studies have demonstrated tumour growth inhibition of solid subcutaneous tumours by radiolabelled SS analogues in animal models[76–78]. The authors investigated the antiproliferative effect of [^{111}In-DTPA^{0}]octreotide on SS-R-positive, CA20948 pancreatic tumour cells in a rat liver metastases model with intraportal tumour cell injections[79]. Treatment with 370 MBq (0·5 μg) [^{111}In-DTPA^{0}]octreotide was given on day 1 and/or day 8. After 21 days the number of tumour colonies was significantly decreased by all treatment regimens compared with that in control animals; treatments on day 1 and 8 proved to be superior to single treatment on either day 1 or day 8 (*Table 4*). In repeated experiments, most treated animals showed no or few tumour colonies, an outcome that was not observed earlier in experiments using high doses of non-radiolabelled octreotide[52]. This tumour growth inhibition was predominantly due to the specific binding of [^{111}In-DTPA^{0}]octreotide to the SS-R and not to a systemic or a secondary mechanism since pretreatment with 1 mg octreotide before radionuclide treatment, resulting in saturation of the SS-Rs, almost completely abolished the effect of [^{111}In-DTPA^{0}]octreotide on SS-R-positive cells. Furthermore, radionuclide therapy had no effect on the growth of SS-R-negative CC531 tumours in the same experiment[79]. During the experiments there was no sign of toxicity in the animals and there was no histological damage to the kidney, which is the first organ to be at risk[80]. It was demonstrated earlier that liver regeneration after 70 per cent partial hepatectomy in this model accelerates tumour growth dramatically[81]. Radionuclide therapy was found completely to annihilate this tumour growth stimulation of SS-R-positive tumour cells rendering only a few tumour colonies. In an experiment without tumour [^{111}In-DTPA^{0}]octreotide did not influence liver regeneration or function, suggesting that radionuclide therapy might also be a safe option for adjuvant treatment after liver resection or arterial embolization. Although treatment with ^{111}In-labelled SS analogues may be a promising option for patients with locally irresectable or disseminated gastroenteropancreatic tumours, more experiments in more advanced stages of tumour development, with different doses of [^{111}In-DTPA^{0}]octreotide and with other radioligands, are necessary.

Another approach in treating tumours expressing SS-R is to substitute the radionuclide with a chemotherapeutic agent. Schally's group has developed a cytotoxic SS analogue containing 2 pyrrolinodoxorubicin (AN-201), which is 500–1000 times more potent *in vitro* than its parent compound[82,83]. By linking AN-201 to RC-121, an SS analogue, a new cytotoxic SS analogue (AN-238) was obtained. Various *in vitro* experiments with AN-238 on human and rat SS-R-positive tumours have shown effective inhibition of tumour growth[84,85].

Table 4 Effect of radionuclide therapy with [^{111}Indium-diethylenetriaminopenta-acetic acid]octreotide on somatostatin receptor-positive liver metastases

	No. of metastases			
Treatment	0	1–20	21–100	> 100
Controls				6
Therapy on day 1		4	1	
Therapy on day 8		3	2	
Therapy on days 1 and 8	3	2		

Values are number of animals with given range of metastases (5–6 animals per group), 21 days after direct injection of somatostatin receptor-positive CA20948 tumour cells into the portal vein. Peptide receptor radionuclide therapy with 370 MBq (0·5 μg) [^{111}Indium-diethylenetriaminopenta-acetic acid (^{111}In-DTPA^{0})]octreotide was given on day 1 or 8 or on days 1 and 8. The effect of all treatment schedules was significantly different ($P < 0·01$) from the effect of 0·5 μg 'cold' [^{111}In-DTPA^{0}]octreotide on day 1 and 8 (controls). Treatment on day 1 and 8 was significantly different from treatment on day 8 alone ($P < 0·05$). No significant difference was found between the effect of treatment on day 8 or day 1. From reference 79

Radionuclide therapy: clinical

A phase 1 study on the side-effects and antiproliferative effect of high, multiple radiotherapeutic doses of [^{111}In-DTPA^{0}]octreotide started in 1995[86]. Thirty end-stage patients with mainly neuroendocrine tumours were included. After scoring tumour radioactivity uptake using scintigrams obtained 24 h after the injection of a diagnostic dose (220 MBq) of [^{111}In-DTPA^{0}]octreotide, treatment was initiated. All patients received doses of 6–7 GBq ^{111}In incorporated in 40–50 μg [^{111}In-DTPA^{0}]octreotide with intervals of at least 2 weeks between administrations. A total of eight injections was aimed at, with a possible extension to 12–14 administrations. Twenty-one patients received a total cumulative dose of at least 20 GBq [^{111}In-DTPA^{0}]octreotide with a maximum of 75 GBq. Of the nine patients treated with a total dose lower than 20 GBq, seven had to stop prematurely because of disease progression despite treatment and two had not finished the first course of four administrations at the time of the interim analysis. With a maximum follow-up of 26 months no major clinical side-effects were observed except for a transient decline in platelet and white blood cell count. Kidney function was influenced only slightly and not to a clinically relevant degree. Although in some patients temporary because of end-stage disease, impressive effects on clinical condition and hormone or tumour marker production were observed after the administration of high doses of [^{111}In-DTPA^{0}]octreotide. Before the start of treatment all 21 patients had progressive disease. In eight patients treatment resulted in stable disease and in six tumour shrinkage was monitored by CT or MRI; in these patients beneficial effects occurred on hormone production and symptoms. There was a tendency towards a better result of radionuclide therapy in those whose tumours had a higher accumulation of the radioligand on the scoring scintigram. *Table 5* summarizes recent results and characteristics of patients treated with radionuclide therapy with a minimum dose of 20 GBq [^{111}In-DTPA^{0}]octreotide[86–91].

Table 5 Results and characteristics of patients treated with radionuclide therapy with a minimal dose of 20 GBq [^{111}In-radiolabelled diethylenetriaminopenta-acetic acid^{0}]octreotide

		Tumour size		
Tumour type	Total no.	Reduction	Stable	Progression
Carcinoid	13	3	8	2
Neuroendocrine tumour	6	2	2	2
Gastrinoma	1		1	
Vipoma	1	1		
Glucagonoma	1	1		
Medullary thyroid cancer	3		1	2
Papillary thyroid cancer	1		1	
Glomus tumour	2	1	1	
Phaeochromocytoma	2		1	1
Astrocytoma	1		1	
Inflammatory breast cancer	1		1	
Total	32	8	17	7

All phase 1 studies. Data are from references 86–89

For radiotherapeutic applications, other radionuclides such as ^{90}Y and ^{177}Lu have also been proposed for coupling to SS analogues. ^{90}Y, with a half-life of 2·7 days, is a pure high β emitter with a tissue range up to 1 cm and ^{177}Lu, with a half-life of 6·7 days, emits γ radiation (suitable for visualization) and intermediate β particles with approximately 1 mm tissue penetration. For tumours with a heterogeneous distribution of SS-Rs, ^{90}Y- and ^{177}Lu-labelled SS analogues might have extra beneficial characteristics because of an effect known as 'cross-fire'. A tumour cell lacking an SS-R might be hit by an electron coming from a neighbouring cell that has internalized the radioligand. This mechanism may lead to a high and more homogeneous radiation dose in larger parts of the tumour. Studies with these radiolabelled SS analogues are ongoing.

Transfection of somatostatin receptors

New developments in molecular biology have made it possible to transfect SS-R-negative tumour cells with an SS-R gene. Susini's group has developed an approach using sst_2 gene transfer for the treatment of pancreatic cancer[92]. By inducing the SS-R on the tumour cells, antitumour effects were obtained which might be attributed to several mechanisms. First, an autocrine negative feedback loop in which transfected tumour cells start to produce SS, which binds in an autocrine manner to the induced SS-R, may provide an inhibitory effect on tumour cell growth. Second, binding of SS to sst_2 may upregulate *p27*, a tumour suppressor gene, which leads to cell cycle arrest in the G0–G1 phase, and subsequently causes apoptosis. Local and distant bystander effects have also been noted[93]. The local bystander effect might be attributed in part to apoptosis. When type sst_2-positive cells undergo apoptosis, these cells release apoptotic vesicles and enzymes, which in turn might kill neighbouring cells. The distant bystander effect may be explained by a paracrine effect. SS can upregulate the expression of sst_1 on parental tumour cells, thereby rendering them sensitive to the antiproliferative effect of SS. All the abovementioned mechanisms may contribute to successful treatment of certain types of cancers with gene therapy.

Another reason why transfection of tumour cells with an SS-R gene may be beneficial involves radionuclide ther-

apy[79]. By inducing the SS-R on SS-R-negative tumours, treatment with radionuclides should be possible. Moreover, transfection of SS-R-positive tumours with an SS-R gene can increase the homogeneity of distribution of tumour cells expressing the SS-R and so increase the efficacy of therapy; the present authors are currently investigating this strategy. By using a plasmid with complementary DNA of the SS-R and G418 genes, which provides protection against the cytotoxic drug geneticin, 10 per cent of SS-R-negative CC531 cells were cotransfected *in vitro*. Thereafter geneticin was added to the cells, such that non-transfected CC531 cells were eliminated, resulting in a tumour cell culture of 100 per cent transfected CC531 cells. To test expression and functional capacity of the transfected receptor, binding and internalization studies were performed. A mean of 12 000 receptors per cell were expressed on the cell membrane, while internalization studies showed a high uptake of radioactive octreotide in transfected cells (66 000 *versus* 1200 c.p.m. in controls; $P < 0{\cdot}01$). This effect could be blocked by 'cold' octreotide, indicating a receptor-specific transport mechanism. To evaluate growth and receptor status *in vivo*, *in vitro* transfected CC531 cells and (normal) CC531 cells were tested in a liver metastasis model by injection into the portal vein of WAG/Rij rats. Transfected CC531 cells had the same growth velocity as (normal) CC531 cells and had a high expression of SS-Rs. In future experiments, radionuclide therapy using β-emitting radionuclides, including ^{90}Y and ^{177}Lu, will be tested on these *in vitro* transfected CC531 cells. Transfecting tumour cells with SS-Rs in combination with radionuclide therapy is a new modality in the treatment of cancer; however, it is experimental and its full potential remains to be elucidated in the near future.

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