Expert Opinion

Somatostatin and somatostatin receptors: implications for neoplastic growth and cancer biology

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Somatostatin agonists (SM-As) are capable of achieving durable symptomatic relief and significant clinical responses in certain tumours. Herein, we review the diverse direct and indirect mechanisms of antineoplastic activity elicited by SM-As as well as the hurdles that complicate their use as monotherapies in a broader range of malignancies. Emphasis is placed on recent clinical attempts to neutralise the IGF-mediated survival factor effects in the bone metastasis microenvironment in advanced prostate cancer. The first clinical trials of this 'anti-survival factor manipulation' strategy utilised the ability of SM-As to suppress the growth hormone-dependent liver-derived IGF-I bioavailability in combination with other drugs, such as dexamethasone, zolendronate and oestrogens, acting systemically and at the bone metastasis microenvironment. These regimens restored androgen ablation responsiveness in stage D3 prostate cancer patients and successfully produced objective clinical responses while only mild toxicities were observed. Furthermore, we focus on the preclinical experimental data of a targeted SM-A coupled to the super-potent doxorubicin derivative AN-201. The resulting conjugate (AN-238) has shown increased antitumour potency with a favourable toxicity profile. The potential use of novel SM-As as anticancer drugs is discussed in relation to data suggesting other direct and indirect treatment approaches pertaining to the somatostatin system.

Keywords: anticancer targets, somatostatin, somatostatin receptor

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1. Introduction

It has been > 35 years since somatostatin (SM) was first described as a hypothalamic hormone that suppresses growth hormone (GH) secretion [1]. The initial localisation of the molecule in the hypothalamus by Pelletier *et al.* in 1977 [2] was subsequently followed by identification of SM in a wide diversity of human tissues [3] serving mainly as the body's universal endocrine 'off-switch'. The SM gene, located on chromosome 3q28, encodes a 116 amino-acid preprohormone (preprosomatostatin) which contains the 92 amino-acid SM prohormone (prosomatostatin) connected to a 24 amino-acid signal peptide. Prosomatostatin is the precursor peptide of the two biologically active SM forms: the predominant form is the 14 amino-acid long somatostatin-14 (SM-14) while the more potent form is the amino-terminus extended somatostatin-28 (SM-28) [4]. The biological roles of the two SM isoforms very strongly overlap and the relative proportions of SM-14 to SM-28 vary between different tissues [3,5].

SM peptides functionally bind to the five known, distinct SM receptor subtypes (sst_{1-5}). Each of the five sst subtypes is encoded by a separate chromosome.

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However, they all display significant structural similarities and belong to the superfamily of GPCRs that is characterised by a core of seven transmembrane α-helices connected by three intra and three extracellular loops. sst_2 Has two splice isoforms: sst_{2A} which has a longer cytoplasmic carboxyl-terminus and seems to be the vastly predominant physiologically active isoform in humans and the shorter sst_{2B} isoform [6-13]. The different sst subtypes can coexist in the same tissue and even on the same cell at different densities. Determining the specific function of each sst has, therefore, been a very daunting task that is still continuing. The recent development of SM agonists (SM-As) and antagonists that bind to only one sst [5,14-16], the generation of specific antibodies against each sst [3,17,18] and sst knockout mouse models [19-22] have profoundly contributed to our knowledge of the distinct sst characteristics. However, explaining the already complex sst signalling properties has become even more challenging by the recent discovery that sst receptors can form heterodimers with dopamine receptors [23], other sst subtypes [24], opioid receptors [25] or EGFRs [26], thus, creating receptor oligomers with unique pharmacological profiles.

2. sst Expression in cancer

The physiologically key roles of SM are performed through the inhibition of different endocrine and exocrine systems and the wide variety of these biological processes indicates the great therapeutic potential of this peptide in diverse clinical conditions [27-30]. It was thus soon realised that a range of different tumours overexpress sst receptors compared to non-transformed tissues. The underlying stimuli that induce this overexpression as well as the biological role served by the increased sst densities on tumour cells have not been conclusively explained. It is possible that the upregulation of SMs and sst receptors serves as a homeostatic, growth inhibitory autocrine/paracrine response to the deregulated tumour cell proliferation. This may also explain the preferential sst overexpression in less aggressive tumour phenotypes that has been reported for a number of cancers [31-33]. However, it should be noted that the opposite observations have also been documented in some malignancies [34] pointing again to the complexity of the sst role in cancer cell biology. It also remains to be determined which specific sst subtypes may have a prognostic utility in each cancer. Nevertheless, it can arguably be asserted that sst receptors and their intracellular signalling pathways should generally be considered as tumour suppressive.

A main physiological function of SM in the human CNS is the control of pituitary hormone secretion. In particular, SM inhibits the secretion of pituitary GH and thyroid-stimulating hormone [3,5]. sst_{2A} And sst_5 are predominantly expressed in pituitary adenomas with sst_5 being mainly expressed in prolactinomas [35] and sst_{2A} being the commonly overexpressed subtype in the GH-secreting pituitary adenomas that cause acromegaly [12,36]. It should be emphasised here that sst expression patterns can vary between otherwise identical tumour types and even within a tumour specimen. For example, a study by Jaquet *et al.* could not detect sst_2 mRNA transcripts in 7% of GH-secreting pituitary adenomas [37] while immunohistochemical visualisation of sst-positive tissues reveals sites of lower expression [38,39]. Complete surgical removal is the first-line treatment of pituitary adenomas. However, SM-As today have significant and well-established therapeutic value in acromegaly patients with unresectable or recurrent GH-secreting pituitary adenomas [36].

SM receptors are also overexpressed in many neuroendocrine tumours including carcinoids of the gastrointestinal (GI) tract, non-carcinoid gastroenteropancreatic tumours (mostly insulinomas, gastrinomas and vasoactive intestinal peptide-secreting tumours), medullary thyroid carcinomas, small cell lung cancer, pheochromocytomas and neuroblastomas [40-45]. While the incidence of these neoplasms is low, it has been steadily increasing in the past years [41,46]. Approximately two-thirds of these neuroendocrine tumours originate in the GI tract [40,41]. The different neuroendocrine tumours exhibit various patterns of sst subtype expression [40-44]. However, sst_{2A} is particularly expressed in ~ 90% of carcinoid tumours and 80% of gastrinomas, vasoactive intestinal peptide-secreting tumours and glucagonomas while it is found in 50 – 70% of insulinoma samples [38,39,47,48]. SM-As currently have an established clinical role particularly in the treatment and diagnosis of metastatic carcinoids and of functional endocrine pancreatic tumours.

The expression of sst receptors has been documented in cell lines and primary tissue samples in a wide variety of non-neuroendocrine solid tumours, including breast, prostate, colon, pancreatic adenocarcinoma, lung, liver, renal, adrenal cortex and thyroid cancers, and may likewise exist in other tumours regulated by growth factor systems [31,49-58]. Furthermore, a potent anticancer activity of SM-As against these neoplasms has been observed in various *in vivo* rodent models, mostly human tumour xenografts in athymic nude mice [49-53,59]. However, the clinical outcomes of SM-As as monotherapies for these malignancies have generally been disappointing, with very few exceptions [60,61]. Thus, there are currently no approved indications for such compounds as a monotherapy for the treatment of non-neuroendocrine solid tumours. On the other hand, a number of novel therapeutic strategies, such as the combination of SM-As with other drugs as part of the anti-survival factor (ASF) therapy, show strong promise both conceptually and experimentally with early clinical data showing a significant treatment effect [62-65]. These approaches are detailed in Section 6.1 of this review.

3. Synthetic SM-As

Following recognition of the clinical relevance of the SM system, it was soon realised that endogenous SM-As are impractical in the clinical setting because of their very short

plasma half-life (1 – 3 min) requiring continuous parenteral infusion for therapeutic purposes. Subsequently, the first synthetic octapeptide SM-As were developed to be more stable and have much longer half-lifes compared to the native peptides. These compounds are generally designed to retain the amino-acid sequence Phe^7, Trp^8, Lys^9,Thr^{10} that is crucial for native SM biological activity (Trp^8 and Lys^9 are the absolute essential residues of this segment while minor substitutions can be used in Phe^7 and Thr^{10}, as is the case for lanreotide and vapreotide) and are intramolecularly stabilised by the incorporation of cyclic or bicyclic structure through a disulfide bond or an amide linkage. Octreotide, the first synthetic SM-A available for clinical use, was thus synthesised in 1979 and has since become the mainstay of SM therapeutics [66] followed in recent years by lanreotide and vapreotide (RC-160) [67-69]. These three clinically approved SM-As bind with the highest affinity to sst_2, high affinity to sst_5 and intermediate affinity to sst_3, while displaying minimal or no affinity for sst_1 and sst_4 (**Table 1**). Furthermore, all three compounds exhibit similar antitumour efficacy effectuated through the same sst subtypes [14,70-73]. In clinical practice, the receptor-subtype specificity of SM-As was considered desirable because, normally, the endogenous SMs are rapidly digested by peptidases thus preventing a prolonged systemic circulation of the hormones that could potentially cause unwanted toxicities through nonspecific sst activation in various end-organs. **Table 1** lists the sst binding affinities, approved clinical indications and common dosing schedules of the three SM-As currently in the market.

Since their initial introduction in the clinic, depot formulations of the octapeptide SM-As have been developed, offering the advantage of sustained drug release. Thus, the octreotide long-acting repeatable compound, manufactured by the incorporation of octreotide into biodegradable polymer microspheres, and the extended-release aqueous formulation of lanreotide (lanreotide Autogel®) require only a single subcutaneous administration every 4 weeks [74-76]. The simplified dosing regimens offered by these compounds considerably improve patient adherence [75,77]. Formulations with further prolonged activity such as a 3-month sustained-release vapreotide [78] are currently undergoing clinical testing.

The three clinically approved octapeptide SM-As have well established and similar safety profiles [36,77,79-81]. The most common abnormalities are GI complaints (diarrhoea, nausea, loose stools and abdominal discomfort), gallstone formation (cholelithiasis) in 10 – 30% of individuals that most of the times remains asymptomatic, as well as glucose metabolism alterations that are usually very mild and of little clinical significance. A few patients may also develop moderate, temporary hair loss. Severe complications such as acute hepatitis and pancreatitis are extremely rare. The predominant side effects are the GI tract symptoms which are mostly mild to moderate and disappear in a few days following drug administration, most likely because of local adaption in the GI tract and exocrine pancreas. Adverse reactions at the injection site such as pain, erythema, itching and local swelling can also occur and are generally transient and mild. In addition, because the template sequence of the octapeptide SM-As is based on the endogenous SM-As [3], these synthetic peptides are very weakly immunogenic and very rarely cause skin rashes and other usually mild allergic reactions [36,77,79,81].

The consistently excellent safety profile of the clinically available analogues emboldened researchers to explore the therapeutic potential of more 'universal' sst ligands. Although there are currently no synthetic SM-As capable of binding to all sst subtypes with high affinity, compounds with broader receptor specificity have been synthesised. Currently, the furthest developed multi-receptor SM-A is pasireotide (SOM230) which binds to sst_1, sst_2, sst_3 and sst_5 with high affinity while exhibiting minimal affinity for sst_4 [82-84]. This cyclohexapeptide also shows very good metabolic stability as well as different sst internalisation and trafficking patterns compared to octreotide, which may result in more prolonged biological effects [84,85]. Furthermore, the broader receptor binding of pasireotide may produce biological activity in octreotide-resistant or refractory tumours as well as in diseases which predominantly express octreotide-insensitive sst subtypes, such as corticotroph tumours [86]. The safety and efficacy of pasireotide in these clinical conditions is currently under evaluation and the initial reports are promising [87-90].

Similar to other GPCRs [91,92], the development of sst antagonists significantly lagged compared to their respective agonists. The first two full sst antagonists were described in 1996 [93] and both selectively antagonised sst_2 with sst_2-ANT [Ac-4-NO_2-Phe-c(*D*-Cys-Tyr-*D*-Trp-Lys-Thr-Cys)-*D*-Tyr-NH2] being the most potent of the two. A number of subtype-selective antagonists have since been developed [16,94] considerably facilitating research on sst biology and with potential applications in sst-targeted tumour therapeutics [15,95]. Peptidic SM-As are rapidly hydrolysed in the GI tract following oral administration and must, therefore, be delivered parenterally. Consequently, efforts are also being made to manufacture non-peptidic orally bioavailable SM-As. A recent review by Wolkenberg and Thut 2008 [96] summarises the current status, potential applications and developmental challenges of these newly emerging compounds.

4. Tachyphylaxis to SM-As

Curiously, while SM-A therapy can achieve successful long-term remissions in acromegaly patients and the potent responses persist even after decades of continuous treatment, the vast majority of patients suffering from other tumour types will eventually escape from the antitumour and palliative effects after several months of treatment [36,97-101]. Dose escalation can restore clinical response but eventually all patients will become refractory to SM-A treatment. The exact pathophysiological events that mediate this acquired resistance (tachyphylaxis) have not been fully explained and may be different to the physiological SM-desensitisation

Table 1. Binding affinities, FDA-approved clinical indications and common dosage of the SM-As currently on the market.

	sst Binding affinities*					Clinical indications	Common dosage
	sst_1	sst_2	sst_3	sst_4	sst_5		
Octreotide	290 – 1140	04 – 2.1	4.4 – 34.5	> 1000	5.6 – 32	Acromegaly; symptomatic palliation of carcinoid syndrome; VIPoma-associated diarrhoea	Octreotide: s.c. 100 – 500 µg 3 × daily Octreotide LAR: i.m. 10, 20 or 30 mg every 28 days
Lanreotide	500 – 2330	0.5 – 1.8	43 – 107	66 – 2100	0.6 – 14	Acromegaly	Lanreotide: i.m. 30 or 60 mg every 10 – 14 days Lanreotide Autogel®: deep s.c. 60, 90 or 120 mg every 28 days
Vapreotide (RC-160)	481 – 1000	5.4	30.9	45 – 351	0.7 – 7.5	GI bleeding due to portal hypertension and oesophageal varices	i.v. Bolus of 50 µg followed by continuous infusion of 50 µg/h for 5 days for the treatment of variceal bleeding

*Binding affinities represent published minimal and maximal values obtained by different groups [14,70-73]. These differences are presumably caused by variations in the experimental conditions. Values are listed in nM and expressed as IC_{50} or K_i.

GI: Gastrointestinal; i.m.: Intramuscular; i.v.: Intravenous; LAR: Long-acting repeatable; s.c.: Subcutaneous; SM-A: Somatostatin agonist; sst: Somatostatin receptor; VIPomas: Vasoactive intestinal peptide-secreting tumours.

processes in normal tissues which occur in a few days or weeks at most [3,102,103]. Hofland and Lamberts 2003 [103] extensively reviewed a number of mechanisms that are potentially involved in SM-A tachyphylaxis, including the downregulation of the cell surface sst receptors that bind to the octapeptide analogues, selection of sst-negative tumour cell clones, desensitisation caused by receptor uncoupling to second messengers as well as gene mutations of sst receptors or of downstream effectors, resulting in reduced functional activity of the receptors. Current experimental data on the internalisation and regulation of sst_2, sst_3 and sst_5 were reviewed by Jacobs and Schulz 2008 [104]. Explanation of these events is further complicated by the divergent interactions of sst subtypes with the different SM-As. A recent study showed that binding of both SM-14 and octreotide to rat sst_{2A} results in internalisation of the receptor–ligand complex into early endosomes followed by degradation of SM-14 but not of octreotide which was subsequently released very slowly in the supernatant as an intact peptide [105]. Interestingly, in both cases, sst_{2A} did not recycle for at least 2 h after stimulation with either SM-14 or octreotide [105]. Another recent report demonstrated that octreotide and pasireotide exhibit markedly different intracellular sst trafficking. Octreotide and SM-14 induced prolonged human sst_{2A} internalisation whereas pasireotide binding formed unstable complexes that resulted both in rapid recycling of sst_{2A} and less potent signalling through this receptor [85].

The biological processes behind the enduring sensitivity of acromegalic adenomas are unknown. It is believed that, contrary to other neoplasms, GH-secreting tumours may upregulate functionally active cell surface sst receptors in response to octapeptide SM-A treatment. These adenomas may also exhibit higher genetic stability compared to other, usually more aggressive, tumour types. Furthermore, receptor heterodimerisation may result in altered desensitisation properties. Heterocomplexes of sst_2 with sst_3 as well as sst_1 with sst_5 show different internalisation and desensitisation patterns compared to the individual receptor subtypes [24,106]. It is interesting to note that gallbladder motility is the only major physiological process that is persistently inhibited by SM-As without a decline in the initial response [99]. It is not known why the gallbladder is resistant to tachyphylaxis. The presence of different sst patterns compared to other tissues may be a key factor contributing to this phenomenon. Rigorous data on these issues are urgently needed because knowledge of such mechanisms may provide important insights on SM-A treatment schedules and dosages as well as suggest novel strategies to overcome tachyphylaxis.

5. Mechanisms of antitumour activity of SM-As

5.1 Direct antitumour activity

Table 2 lists the known, as well as some hypothetical, mechanisms of SM-A-mediated effects in cancer patients. SM can directly bind to sst receptors on the tumour cells and thus stimulate antiproliferative pathways which can lead either to cell cycle arrest or to apoptosis depending on the SM-A, the

Table 2. Mechanisms of SM-A action in cancer.

Direct antitumour activity
Antimitotic (cytostatic) effects by sst_1[114], sst_2[115], sst_4[109] and sst_5[113] signalling
Apoptotic (cytotoxic) effects by sst_2[126] and sst_3[124] signalling
Direct blocking of autocrine/paracrine 'survival factor' secretion by cancer cells [132]
Attenuation of malignant cell 'aggressiveness': restoration of contact inhibition [135]; inhibition of blood vessel adhesion [137]
Indirect antitumour activity
Suppression of the GH/IGF-I axis: inhibition of GH secretion [142]; negative regulation of IGF-I production [131]; increased release of IGFBPs [145]
Reduced levels of other trophic hormones* (e.g., insulin, prolactin, gastrin; see Patel 1999 [3] and Weckbecker *et al*. 2003 [30] for reviews on the negative regulation of hormones by SM-As)
Inhibition of tumour blood flow: reduced perfusion due to vasoconstriction* [152]; blocking of neovessel formation by vascular endothelial cells [159]; reduction of pro-angiogenic factors* [163]; attenuation of monocyte activity in neoangiogenesis [155]
Modulation of host immune response* (see Ferone *et al*. 2004 [164] and Pinter *et al*. 2006 [165] for reviews on the immunomodulatory effects of sst activation)
Other beneficial effects to cancer patients
Palliation of paraneoplasmatic and other manifestations [170]
Analgesic activity [177]

*The clinical relevance of these mechanisms is unknown or controversial.

GH: Growth hormone; IGFBP: IGF-binding protein; SM-A: Somatostatin agonist; sst: Somatostatin receptor.

sst subtype, as well as the activated intracellular cascades that may vary between cells [3,107-109]. sst_{2A} Is the predominantly expressed receptor in many tumours and can induce antimitogenic effects mainly through the sequential activation of kinases and phosphatases typically involving the stimulation of the phosphotyrosine phosphatase SHP-1 [107,110,111]. SHP-1 inhibits the MAPK cascade by directly or indirectly dephosphorylating the MAP kinase ERK1/2. Inhibition of MAPK can also occur by other phosphotyrosine phosphatases, such as DEP-1, in a SHP-1-independent pathway [112], or through different pathways including the sst_5-mediated suppression of cGMP and protein kinase G activity [113]. On the other hand, sst-mediated pathways can also block cell growth by activating ERK1/2 [114,115]. This is in agreement with previously established observations in various cell models that ERK1/2 phosphorylation can have either a growth inhibitory or a stimulatory effect depending on both ERK1/2 activation intensity and duration in a cell- and tissue-specific manner [116,117]. Thus, sst activation can in some cases facilitate cell growth [118]. A notable example of opposite activity by the two sst_2 isotypes is seen in Chinese hamster ovary cells where transfection and subsequent stimulation of rat sst_{2A} induces cell growth arrest mediated by prolonged phosphorylation of another MAPK (p38), while activation of rat sst_{2B} increases Chinese hamster ovary cell proliferation [119]. Recent studies suggest that sst_2 stimulation can also inhibit the PI3K/Akt signalling pathway resulting in increased expression of the tumour suppressor gene Zac1 [120]. Attenuated AKT activity may likewise suppress cancer cell growth by negative regulation of the mammalian target of rapamycin pathway [44,121]. A possible crosstalk may also exist between these signalling cascades and the MAPK/ERK pathways. Such interrelations remain to be explained.

While activated sst_1, sst_2, sst_4 and sst_5 generally produce cytostatic effects through similar interplays of downstream effector pathways, sst_3 mainly induces pro-apoptotic (cytotoxic) signals [107,122,123]. More specifically, sst_3 can initiate intrinsic intracellular apoptotic signalling pathways involving the induction of p53 and the subsequent activation of the pro-apoptotic protein Bax [122,124]. The influence of the cellular context on receptor function was again demonstrated in endothelial cells that exhibited no pro-apoptotic changes following sst_3 activation [125]. It was recently shown that sst_2 can also induce apoptosis through a p53-independent pathway [126,127].

Another effect of SM-As on tumour cell growth involves inhibiting the secretion of autocrine/paracrine effectors of tumour cell survival such as the IGF-I and -2, EGF, IL-6 and the TGF family. It is well established that the increased local bioavailability of these 'survival factors' readily supports the survival and aberrant growth of cancer cells [128,129]. sst Receptors may attenuate the secretion of such survival factors in the tumour microenvironment, thus, establishing an autocrine/paracrine antiproliferative effect. While sst receptors clearly inhibit survival factor secretion from neoplastic cells and their microenvironment, it remains to be determined to what extent they also directly suppress the synthesis of such molecules in the tumour tissues. In the case of IGF-I, SM-As have been shown to suppress both gene expression and secretion [130,131]. All sst subtypes can block the secretory function of cells by inhibiting cAMP production and by triggering K^+ efflux through plasma membrane potassium channels [5,132]. Furthermore, sst_1, sst_2 and sst_5 can retard secretion by inhibiting Ca^{+2} influx through L- and N- type voltage-dependent calcium channels [132-134]. The recently discovered ligand-dependent sst homo and heterodimerisation has significantly expanded the potential mechanisms of direct tumour cell modulation by these receptors [23-25]. For example, heterodimerisation of sst_5 with the dopamine 2 receptor forms a receptor complex with significantly enhanced cAMP inhibitory properties [23]. Similarly, sst_2/mu-opioid receptor

heterodimers are considerably more potent activators of the ERK1/2 pathway following sst_2-selective agonist binding compared to monomeric sst_2 [25]. Such phenomena have for the most part been documented in cell lines and their significance in normal and malignant human tissues remains to be determined and will provide important insights on the complex functional and structural aspects of these receptors.

An important process during malignant transformation is the acquired ability of cancer cells to grow uncontrollably even when in contact with neighbouring cells. It was recently shown that stable transfection of pancreatic cancer cell lines with human sst_{2A} resulted in formation of functional intercellular gap junctions which restored contact inhibition of cell proliferation [135]. Furthermore, during the initial stages of metastatic development, the malignant cells must enter the lymphatic and systemic circulation by detaching from adjacent cells and then attaching to and disrupting the endothelial basement membrane [128,136]. It has been shown that SM can reduce adhesion of carcinosarcoma cells to the blood vessels and thus attenuate the metastatic potential of these tumours [137].

5.2 Indirect antitumour activity

SM-As exert indirect antitumour actions by binding to normal host cells which in turn activate various processes that benefit the host against the neoplasm through a variety of different mechanisms (**Table 2**). It is well established that the GH/IGF-I axis can play a crucial role in the biological behaviour of many tumours [128,136,138,139]. Liver cells respond to GH stimuli by increasing IGF-I production which then enters the systemic circulation. IGF-I receptors are expressed in various types of neoplasms and can initiate tumour cell mitogenesis in response to IGFs in the tumour microenvironment [128,136,138,140,141]. SM-As can significantly reduce serum IGF-I by directly suppressing IGF-I gene expression [130,131], inhibiting pituitary GH secretion [142] or suppressing serum insulin levels (**Figure 1**) [131]. The GH/IGF-I axis suppression achieved by SM-As has shown considerable clinical effectiveness in the treatment of GH-secreting pituitary adenomas [36,77]. These analogues may further inhibit tumour growth by blocking the release of other trophic hormones such as insulin, prolactin, gastrin and the vasoactive intestinal peptide but the clinical significance of these pathways is unknown. Furthermore, SM-A therapy may also inhibit production of survival factors, including IGF-I, from non-transformed stromal and other cells in the tumour microenvironment, as well as increase the expression and secretion of IGF-binding proteins (IGFBPs) which bind to IGFs with higher affinity compared to the IGF-I receptor and thereby reduce extracellular IGF bioavailability [143-145]. Further clinical implications of these processes are discussed in Section 6.1.

During the initial stages of tumourigenesis, nutrients can be supplied by simple diffusion into the tumour mass. As the neoplasm expands beyond a few cubic millimetre volume, there is an increased demand for oxygenation, nutrient perfusion and waste product removal that can only be assuaged by an extensive neovasculature network established through the synthesis and secretion of pro-angiogenic factors, including VEGF-A, basic fibroblast growth factor, platelet-derived growth factor and IL-8. These growth factors regulate a complex cascade of events starting with the aggressive stimulation of the normally quiescent vascular endothelium and culminating in neovessel formation [136,146-149]. This process, termed 'neoangiogenesis', has received extensive attention in recent years by the cancer research community and a number of drugs targeting neoangiogenesis have recently gained approval in a number of indications including metastatic renal cell carcinoma, colorectal, lung and breast cancers [150]. SM-As may inhibit tumour blood flow through four different mechanisms: i) reduction of tumour blood flow by vessel constriction; ii) decreased proliferation, adhesion, chemotactic migration and invasion of vascular endothelial cells; iii) suppression of pro-angiogenic factors; and iv) inhibition of monocyte infiltration and attenuation of monocyte-derived pro-angiogenic signals.

The known vasoconstrictive properties of SM-As suggest that they may interfere with tumour blood perfusion by inducing vasoconstriction. Thus, in a study of experimental hepatic metastases, a significant inhibition of tumour growth was attributed to reduced hepatic arterial flow due to octreotide infusion [151]. However, other experimental studies in rat liver tumours did not confirm these data [152-154].

A large number of studies in diverse cell culture systems and rodent models have demonstrated the antiproliferative effects of SM-As on the vascular endothelium [125,155-158]. Experimental data using octreotide indicate that at least sst_{2A} and sst_5 are overexpressed on the neoangiogenic endothelium and can inhibit endothelial cell proliferation [159,160]. However, further research using pasireotide has also implicated other sst subtypes in this mechanism [161]. Importantly, it seems that the functional expression of sst subtypes in tumour neovessels is independent of sst expression in the tumour itself. Thus, growth of tumour xenografts from the sst-negative Kaposi sarcoma cell line KSImm was significantly inhibited by SM administration and this purely indirect antitumour effect was mediated, at least in large part, by an antiangiogenic mechanism [155]. sst Receptors can also inhibit endothelial cell migration and invasion by interfering with intracellular actin dynamics and actin stress fiber formation [162]. *In vitro* assays in VEGF stimulated HUVECs have shown that octreotide can inhibit HUVEC invasion and migration [159]. Perhaps unsurprisingly, the antisecretory properties of sst receptors have been shown to suppress serum levels of pro-angiogenic factors such as VEGF and basic fibroblast growth factor in cancer patients treated with octreotide [163]. However, the prevalence and clinical relevance of these effects will have to be corroborated by further studies in cancer patients.

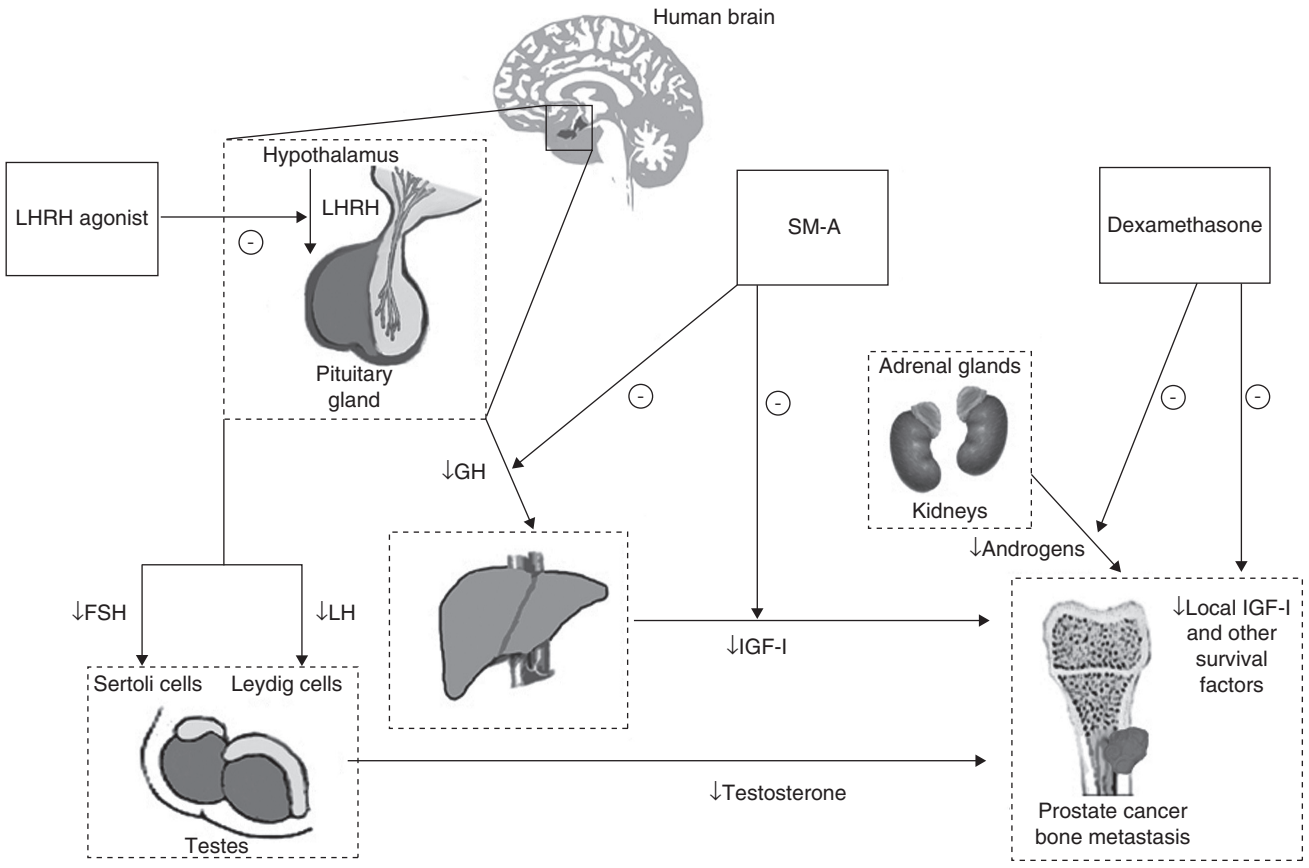

Figure 1. The anti-survival manipulation strategy in stage D3 prostate cancer patients with bone metastasis. Androgen ablation is achieved by administration of an LHRH analogue resulting in pituitary LHRH receptor downregulation, desensitisation and subsequent inhibition of LH- and FSH-release reducing testosterone to levels comparable to orchiectomy. Treatment with SM-A suppresses GH-dependent hepatic secretion of IGF-I into the circulation. Dexamethasone administration blocks the local uPA/plasmin mediated increase of IGF-I bioavailability (hydrolysis of IGFBPs) and attenuates other survival factor pathways by restricting the activation of latent TGF-β1 and limiting the expression of IL-6 and PTHrP in the bone metastasis microenvironment. This inhibition of survival factor signalling can reinstate cancer cell susceptibility to androgen deprivation [62-65,128,195,196,203]. Dexamethasone can also block the secretion of adrenal androgens, by downregulating pituitary ACTH, which may result in a modified CAB effect. However, the fact that the ASF protocol reintroduced objective clinical responses in patients previously refractory to CAB (LHRH analogue/orchiectomy + antiandrogen) indicates that this is not the major contribution of dexamethasone in ASF but may nevertheless have a supporting role in disease control.
ACTH: Adrenocorticotropic hormone; ASF: Anti-survival factor; CAB: Combined androgen blockade; FSH: Follicle-stimulating hormone; GH: Growth hormone; IGFBP: IGF-binding protein; LH: Luteinising hormone; LHRH: Luteinising hormone-releasing hormone; PTHrP: Parathyroid hormone-related peptide; SM-A: Somatostatin agonist; uPA: Urokinase-type plasminogen activator.

There is a wide expression of sst subtypes throughout the immune system and extensive evidence denote a number of diverse potential immunomodulatory effects by activated receptors [164,165]. However, there are very limited data on how sst-mediated signalling on the immune system might affect neoplastic growth. With regards to neoangiogenesis, it has been shown that SM can inhibit monocyte chemotactic migration [155,166] and it is well known that monocyte recruitment to tumour sites can facilitate neovessel growth through the release of pro-angiogenic factors [167]. Another beneficial sst-mediated anticancer immune effect may be the stimulation of the reticuloendothelial system shown in a rat model of fibrosarcoma or colonic adenocarcinoma growth in the regenerating liver following partial hepatectomy [152]. On the other hand, while it is generally suggested that the immunomodulatory effects of SM-As will be beneficial to cancer patients, there are some data to the contrary. SM-As have been shown to inhibit human NK cell activity [168] and to reduce proliferation of a variety of lymphoid cells as well as suppress immunoglobulin production [164]. NK cells in particular are a major component of the host's immune defence to malignancies and their suppression may actually facilitate cancer growth. It must be noted, however, that another study reported significant enhancement of NK activity against the human leukaemia cell line K562 by lymphocytes obtained from healthy donors and pre-exposed to SM-14 [169]. Further research is, therefore, required to explain the immunomodulatory effects of SM-As in cancer

patients. Even if SM-As do exhibit immunosuppressive effects, they are quite weak as indicated by decades of treatment experience with such compounds that have shown no clinically relevant immunosuppression. However, the effects may be more prominent when ultra-high doses of SM-As are tested in trials or when less sst-selective compounds are used. If such processes are shown to indeed be of relevance to cancer patients, then a number of optimisations in the dosing regimens, combination with immunostimulatory compounds or modification of the compounds themselves may take a fuller advantage of the antineoplastic effects of SM-As.

5.3 Other beneficial effects for the cancer patient

SM-As have broader favourable effects in patients suffering from malignancies (**Table 2**). SM and its synthetic octapeptide analogues are clinically used for the palliation of carcinoid syndrome symptoms such as diarrhoea, dehydration, flushing attacks, hypokalaemia, carcinoid heart disease with right heart failure as well as bronchial constriction which can lead to pulmonary hypertension. These paraneoplastic effects are due to the hypersecretion of vasoactive substances such as 5-HT/serotonin, histamine, tachykinins and prostaglandins which can sometimes be life-threating, especially when patients manifest the so-called 'carcinoid crisis' characterised by extensive flushing, hypotension and, occasionally, shock [170-172]. Furthermore, functional endocrine tumours of the GI tract release hormones including gastrin, vasoactive intestinal peptide, insulin and glucagon that can result in peptic ulceration, hypoglycaemic attacks and necrotic skin lesions in addition to diarrhoea and hypokalaemia. SM-As can alleviate these symptoms by suppressing the release of such substances and by decreasing gut motility and intestinal fluid production [28,101,173].

SM-As also exhibit analgesic activity and patients with bone metastasis have experienced alleviation of bone pain following treatment with these drugs [62,174]. A number of case studies indicate that SM-As may have potent analgesic activity even in opioid-insensitive cancer pain, thus, justifying the use of such compounds especially when all else fails [170,175-177]. These palliative effects substantially improve the quality of life of cancer patients and may even indirectly prolong survival because a general improvement in these patients' well-being may enhance their prognosis. Indeed, in a recent study of 3704 cancer patients it was found that baseline quality of life was an independent and strong predictor of overall survival [178].

6. Applications of SM-As in cancer treatment and diagnosis

SM-As are the most widely used peptides for the treatment of acromegaly and neuroendocrine tumours. Octreotide and lanreotide can achieve rapid and long-term control of hormonal hypersecretion in ~ 50 – 70% of acromegalic patients while the rest will require another treatment [36,97,98]. SM-As have an increasingly important role in the management of endocrine tumours, mainly those originating from the gut or pancreas. About 70 – 90% of patients with such malignancies will achieve significant symptomatic relief following SM-A therapy and in some cases cancer remission will also be obtained although complete regression is very rarely achieved [99-101]. Radiolabelled SM-As have also become important diagnostic tools particularly in patients with suspected or recurrent neuroendocrine malignancies. The first clinically approved radiolabelled SM-A was [^{111}In-DTPA-*D*-Phe^1]-octreotide (octreoscan) [179,180], which has since become a valuable tool in the staging and follow-up of sst_2 and sst_5 positive neuroendocrine tumours. Tumour tissue sample analysis from patients injected with octreoscan showed that receptor binding of the radiolabelled SM-A is followed by internalisation and translocation of the Indium-111 (^{111}In) radionuclide to the perinuclear area [181]. Positive octreoscan imaging strongly correlates with sst expression in *in vitro* assays of excised tumour specimens pointing to the reliability of this compound as a non-invasive *in vivo* indicator of sst_2 and sst_5 expression [38,182]. The main advantages of radiolabelled SM-A imaging is that it allows detection, localisation and staging of sst-expressing neuroendocrine tumours with very good sensitivity and positive predictive value compared to other imaging techniques and may also predict response to SM-A therapy or sst-targeted radionuclide therapy and chemotherapy [179,180,183,184]. It must be noted that radiolabelled SM-As exhibit diverse sst affinity profiles (**Table 3**) [185-187] depending on the peptide, the organic chelator used to conjugate the radioisotope to the peptide complex or even the conjugated radioactive metal itself. This may indicate significant variability in the diagnostic sensitivity and clinical indications of each distinct compound depending on the sst expression profile of the tumour.

6.1 SM-As in the ASF manipulation strategy against tumour cells

As detailed in Section 5 of the present manuscript, SM-As can inhibit a number of 'survival factors' that accumulate in the tumour metastasis microenvironment and support malignant tissue growth. Particularly in bone-tropic cancers, including those of prostate origin, it is known that micrometastatic loci in the bone are supported by growth/survival factors that are present in the local skeletal tissue and facilitate cancer cell expansion into clinically evident macrometastasis while also participating in the development of hormonal and chemotherapy refractoriness [128,143,188-191]. This suggests that antimetastatic strategies should not only focus on directly attacking cancer cells (anticancer therapy) but also on targeting the several potential survival factors as well as their anti-apoptotic signalling pathways (neutralisation of the survival factors in host tissue microenvironment/ASF therapy). It is, therefore, crucial to identify and inhibit the major survival factor pathways that can protect metastatic cancer cells from conventional treatments.

Table 3. Binding affinities of commonly used radiolabelled and chelated SM-As*.

	sst_1	sst_2	sst_3	sst_4	sst_5	Ref.
[^{111}In-DTPA-*D*-Phe^1]-octreotide	> 10,000	22	182	> 1000	237	[185]
(octreoscan)‡	> 1000	1.5	32	> 1000	1.1	[186]
	> 1000	1.5	15	> 1000	0.5	[187]
[Y-DOTA-*D*-Phe^1-Tyr^3]-octreotide‡	> 10,000	11	389	> 10,000	114	[185]
[Y-DOTA-*D*-Phe^1]-octreotide‡	> 10,000	20	27	> 10,000	57	[185]
[Y-DOTA-*D*-Phe^1-Tyr^3]-octreotate‡	> 10,000	1.6	> 1000	523	187	[185]
[Ga-DOTA-*D*-Phe^1-Tyr^3]-octreotate‡	> 10,000	0.2	> 1000	300	377	[185]
[DOTA-*D*-Phe^1-Tyr^3]-octreotate‡	> 10,000	1.5	> 1000	453	547	[185]
[^{111}In-DOTA]-lanreotide	215	4.3	5.1	3.8	10	[186]
[Y-DOTA]-lanreotide‡	> 10,000	23	290	> 10.000	16	[185]
^{99}mTc-depreotide (NeoSpect)	> 1000	2.5	1.5	> 1000	2	[187]

*Binding affinities represent published medial or median values obtained by different groups. These differences are presumably caused by variations in the experimental conditions. Values are listed in nM and expressed as IC_{50}[185] or K_d[186,187].

‡Reubi *et al*. [185] used non-radioactive metals in their binding experiments, which are expected to behave similarly to their respective radioactive isotopes.

SM-A: Somatostatin agonist; sst: Somatostatin receptor.

This approach was used to develop a novel treatment strategy under the term 'anti-survival factor therapy' (ASF), namely the combination of SM-A with dexamethasone (**Figure 1**) [189,192-194]. The clinical applicability of this concept was first tested by targeting mainly IGF-I bioavailability. A large number of experimental data have indicated that IGF-I is a major nodal point for several anti-apoptotic and tumour growth processes that may also potentiate cancer cell resistance to hormonal manipulations and/or chemotherapy [189,195]. The ASF strategy aims to maintain, enhance or even restore the susceptibility of metastatic cells to conventional therapeutic modalities. Therefore, ASF manipulation therapy should be performed in combination with a pro-apoptotic regimen (anticancer therapy) such as androgen ablation therapy or chemotherapy in the clinical setting of advanced prostate cancer. Androgen ablation has been the mainstay of metastatic prostate cancer therapy for > 60 years and a number of different strategies have been used to achieve clinically significant androgen deprivation. These include bilateral orchiectomy, oral estrogen administration, treatment with luteinising hormone-releasing hormone (LHRH) agonists (with or without co-administration of antiandrogens) or the more recently approved LHRH antagonists [91,192,196-198].

Essentially, androgens signalling through the androgen receptors on prostate cancer cells can be considered as highly potent 'primary' survival factors for these tumours. Following androgen ablation, a number of 'secondary' but crucial anti-apoptotic pathways, including the IGF-I, IL-6, TGF-β1 and parathyroid hormone-related peptide (PTHrP) cascades, take a more active role in protecting the prostate cancer cells from apoptosis and may restore in part the transcriptional activity of the androgen receptors, thus, compensating for the lack of androgens during androgen ablation manipulations [189,199,200].

The vast majority of circulating IGF-I is produced by the liver following stimulation of hepatic cells by systemic GH. Furthermore, the increased concentration of IGF-I in the sites of skeletal metastasis is also due to osteoblast/tumour cell-derived production of this survival factor. Local processes in the bone metastasis microenvironmnet, such as the tumour cell-derived urokinase-type plasminogen activator (uPA)/plasmin-mediated hydrolysis of IGFBPs, further increase local IGF-I bioavailability. Moreover, experimental data have indicated that glucocorticoid receptor activation by potent agonists such as dexamethasone can downregulate IGF-I release at the sites of bone metastasis and inhibit uPA-mediated release of IGF-I, activate latent TGF-β1, as well as the IL-6 and PTHrP expression by prostate cancer cells [192,196,201,202].

The ASF concept was first tested utilising drugs that are currently accessible for clinical use and are known to exhibit low-grade toxicity. Long-acting SM-As were thus chosen to suppress the GH-dependent hepatic IGF-I production. Dexamethasone, an analogue with 30 times higher glycocorticoid activity than cortisol and no mineralocorticoid properties, was selected to inhibit locally the uPA/plasmin/IGFBP-mediated increase of IGF-I release [194]. This ASF therapy design specifically aimed to restore objective responses in androgen ablation refractory (stage D3) patients (**Figure 1**). Initial case-series studies of this protocol showed significant improvement in patient performance status as well as biochemical responses, as determined by ≥ 50% reduction of prostate specific antigen (PSA) levels from baseline, in > 70% of patients with only mild side effects observed [63,203].

These encouraging results prompted a randomised Phase II clinical trial comparing an ASF protocol (lanreotide 30 mg intramuscularly every 14 days and dexamethasone 4 mg orally tapered to 0.5 – 1 mg daily plus androgen ablation by orchiectomy or triptorelin 3.75 mg intramuscularly every 28 days) with cytotoxic salvage chemotherapy (estramustine 140 mg orally three times daily and etoposide 100 mg orally

on days 1 – 21) in stage D3 prostate cancer patients [62]. Both treatments showed similar efficacy with regard to overall survival, biochemical and partial clinical response, performance status and pain scores. However, ASF therapy offered the advantage of a substantially better toxicity profile. Patients in the chemotherapy arm demonstrated significantly more frequent cytopenias, whereas only mild glucose deregulation was more common in the ASF group [62]. In addition, analysis of prostate cancer patients who did respond versus those who did not respond to ASF manipulation, based on the detection of sst_2 and sst_5 receptors by octreoscan, has revealed that the presence or absence of clinical response to ASF manipulation was independent of sst_2 and sst_5 presence. These sst subtypes are considered to be the main antitumour effectuators of the octapeptide SM-As used in the ASF trials. On the other hand, clinical response did correlate with the reduction of plasma IGF-I levels during ASF manipulation [204]. These data suggest that the activity of SM-A in this ASF strategy was through a serum IGF-I-dependent mechanism (indirect antitumour effect). This ASF protocol has also shown efficacy in stage D3 patients under androgen ablation when combined with zolendronate [64].

The South European Uro/Oncological Group conducted a multi-centre, randomised Phase II trial designed to evaluate the efficacy of androgen depletion using triptorelin plus dexamethasone treatment with or without lanreotide/Autogel administration. Published data indicated a longer biochemical response duration and time to PSA progression in the lanreotide arm [205]. These data support the notion that combination of dexamethasone with SM-A is essential for an effective ASF manipulation. Recently, a preliminary study reported that a higher dose of lanreotide in combination with dexamethasone and androgen ablation resulted in a ≥ 50% decrease of PSA levels and improvement of bone pain in 7 (46.7%) out of 15 patients [65]. In addition, Sciarra's group tested a similar approach using oestrogens to achieve both biochemical castration and direct cytotoxicity combined with GH-dependent liver-derived IGF-I inhibition by lanreotide in a pilot study of 10 stage D3 prostate cancer patients [206]. Nine patients showed a ≥ 50% PSA decrease from baseline and significantly improved performance status and bone pain were documented in all patients while only mild toxicity effects were reported.

6.2 sst-Targeted cancer therapy

The expanding knowledge in molecular cancer biology has provided new tools for making cancer therapy more directed and specific. The excellent and specific images provided by radiolabelled SM-As substantiated the ability of these peptides to selectively concentrate in tumors expressing particular sst subtypes as listed in **Table 3**. Thus, various potent radiotherapeutic metals such as Yttrium-90 (^{90}Y) and Lutetium-177 (^{177}Lu) have been coupled with SM-As and are currently being tested in patients with sst-positive cancers [207,208]. Few major clinical side effects have been reported and encouraging objective responses have so far been noted especially in patients treated with ^{177}Lu-octreotate ([^{177}Lu-DOTA-*D*-Phe^1-Tyr^3]-octreotate) [209]. As shown in **Table 3**, the introduction of radiolabelled metals such as Yttrium and Gallium to the chelated SM-A [DOTA-*D*-Phe^1-Tyr^3]-octreotate slightly alters its sst binding profile. Accordingly, it can be conjectured that ^{177}Lu-octreotate exhibits unique sst binding properties without, however, any significant change on the rank order of affinity for each subtype. Therefore, ^{177}Lu-octreotate can be considered as a predominantly sst_2-targeted radiotherapeutic. The present review focuses on the concept of sst-targeted chemotherapy and the currently available preclinical data on this strategy.

The concept behind targeted cytotoxic SM-As is to conjugate a chemotherapeutic agent to an SM-A which will then selectively bind to sst-positive cancer cells. Internalisation of the compound will then result in accumulation of the chemotherapeutic drug inside the malignant cells resulting in enhanced antitumour efficacy as well as a favourable toxicity profile compared to 'straight' chemotherapy. Out of a number of such agents that were developed for initial testing, the cytotoxic SM-A, AN-238, was ultimately selected for evaluation on several experimental models [210,211]. AN-238 is based on the octapeptide SM analogue RC-121 which binds to sst_2 and sst_5 with high affinity and to sst_3 with moderate affinity. AN-238 is synthesised using glutaric acid as a flexible linker that forms an amide bond with RC-121 and an ester bond with the chemotherapeutic compound AN-201. The highly cytotoxic AN-201 is a derivative of the commonly used chemotherapeutic doxorubicin and shows 500 – 1000 times stronger potency *in vitro* compared to the parent compound [212]. All rapidly proliferating cells are especially susceptible to AN-201 and the major toxicity effect of this agent is myelosuppression due to preferential killing of rapidly dividing haematopoietic progenitors. AN-238 largely retains the sst binding properties of the octapeptide carrier component as well as the cytotoxic activity of the superactive doxorubicin derivative [210]. AN-238 binding to sst subtypes apparently results in active internalisation of the cytotoxic radical which then induces apoptosis in rapidly proliferating cells by interacting with cytoplasmic and nuclear components [211]. Further research is required to explain the internalisation events and subcellular compartmentalisation of AN-238 following receptor binding in sst-positive cancer cells.

Although cytotoxic SM-As have not yet been tested in humans, the efficient localisation of tumour nodules throughout the human body by radiolabelled SM-A scintigraphy is a strong testament to the targeting potency of the SM system. Furthermore, there is a wealth of experimental data showing strong anticancer activity of AN-238 in a very diverse range of malignancies including melanomas, lymphomas, prostate, renal cell, breast, brain, lung, pancreatic, GI, ovarian, endometrial, neuroendocrine and liver cancers [211,213-217]. Preclinical results in these tumours, some of which are doxorubicin-resistant,

consistently demonstrate a markedly stronger antitumour effect and a significantly better toxicity profile of AN-238 treatment compared to AN-201. sst Targeting specificity has invariably been confirmed both *in vitro* and *in vivo* by pretreatment with the parent SM-A, RC-121, which significantly decreases the antitumour effect and aggravates the toxicity of AN-238. Notably, AN-238 can overcome the intrinsic chemoresistance of some cancers due to loss of p53 function and seems to also significantly decelerate the development of multiple drug chemoresistance compared to AN-201. More specifically, it has been demonstrated in a number of cancer cell models that treatment with AN-238 can inhibit, through an unknown mechanism, the expression of membrane transporters that mediate efflux of chemotherapeutic drugs [211,213,214,218].

These established experimental data and theoretical background are crucial in formulating conjectures and proposals regarding the potential clinical applications of cytotoxic SM-As in humans. No sst-specific toxicities by AN-238 have been observed in the preclinical models, presumably because the relatively low doses administered cannot induce sufficient sst-mediated signalling of the carrier peptide. On the other hand, the ester bond linking the glutaric acid spacer to the AN-201 can be hydrolysed by serum carboxylesterase enzymes which may lead to systemic toxicity by AN-201 released in the circulation. However, the reported AN-238 toxicity has been consistently low in numerous preclinical studies in rodents [211,213-217]. Moreover, the half-life of the ester bond has been determined by *in vitro* assays to be only ~ 20 min in nude mouse and ~ 60 min in Copenhagen rat sera compared to ~ 120 min in human serum [211,219]. AN-238 may thus show a more beneficial toxicity profile in patients compared to the animal models. In the clinical setting, some toxicity should be anticipated in the rapidly-proliferating cells of the bone marrow and the GI tract. On the other hand, no significant harm to the pituitary is expected because of the slow turnover ratio of pituitary cells. Furthermore, AN-238 is a lipophylic compound that is expected to be preferentially eliminated through the hepatobiliary tract with no significant renal accumulation and toxicity. All things considered, targeted cytotoxic SM-As are expected to show a markedly reduced systemic toxicity compared to non-targeted chemotherapy.

Targeted peptide therapy is restricted to those cells expressing the targeted receptors. However, there is significant heterogeneity of sst density between and within individual tumours, with some cancer cells expressing little or no sst receptors. Therefore, careful determination and characterisation of sst subtype expression patterns is required before and during clinical application of the cytotoxic analogue. This can be achieved either by direct tissue biopsies or by non-invasive radiolabelled SM-A imaging. It should be noted that AN-238 has shown potent activity in a variety of experimental tumour types, including tumours that express low levels of sst_2 and sst_5. Therefore, it is likely that AN-238 may produce significant clinical responses in tumours that are refractory to 'straight' SM-As. AN-238 has also shown significant growth inhibitory effects in sst-negative tumour xenografts by targeting tumour neovasculature [220]. Furthermore, the conjugated cytotoxic AN-201 is released inside the targeted cells by carboxylesterase enzymes, which are also found in the tumour microenvironment. Consequently, AN-238 hydrolysis in the extracellular space may cause bystander killing of adjacent cancer cells, including those that may be sst-negative [211]. It is of note that AN-238 did not downregulate the expression of tumour cell sst receptors in a number of models tested [217,221] indicating that long-term administration of this treatment is feasible. The low systemic toxicity of the targeted therapy would allow dose escalation resulting in improved outcomes. Furthermore, AN-238 administration could be combined with other, targeted or non-targeted, treatment strategies to achieve complete destruction of the sst-negative malignant tissue sites. Clinical testing of this compound is, therefore, warranted. **Table 4** shows a comparison between AN-238 and other sst-based agents.

7. Expert opinion and conclusion

The clinical effects of SM-As in patients with neoplastic disease are mediated by a wide repertoire of biological processes which showcase both the broad potential of such therapies in different clinical indications as well as the complexities that may significantly compromise their clinical efficacy. SM-As exert their antineoplastic action by eliciting direct cytostatic and cytotoxic responses on tumour cells and by indirect antitumour effects including the suppression of various growth factors that drive tumour growth and the inhibition of tumour blood flow (**Table 2**). Although many of the data on these mechanisms are based on experimental models and the clinical relevance of some sst functions is presently unknown, knowledge of these pathways may prove invaluable in designing treatment approaches that can optimally harness the antitumour properties of sst receptors.

Compared to other antineoplastic therapies currently in use, SM-As have a very favourable toxicity profile even at very high doses and also offer the advantage of convenient dosing schedules that can be performed entirely in the outpatient setting. Because of the mild side effects, it is very difficult to establish dosage limits of SM-A therapy based on maximum tolerated toxicity. Some studies have reported results that suggest a dose-related antitumour response in neuroendocrine cancers, which may justify the use of ultrahigh SM-A in certain cases [101,222-224]. Therefore, there is an urgent need to develop formally structured dosage regimens to optimise the efficacy of SM therapeutics. However, neuroendocrine tumours are relatively rare, heterogenous cancers and it is extremely difficult to set up and accomplish adequately powered multi-centred randomised clinical trials focusing on a specific neuroendocrine tumour type.

Novel chimeric compounds have recently been developed targeting other receptors, such as dopamine receptors, in

Table 4. Comparison between 'straight' SM-As, radiolabelled SM-As, the chemotherapeutic agent doxorubicin and the targeted cytotoxic SM-A AN-238.

	SM-As	Radiolabelled SM-As	Doxorubicin	AN-238
Mechanism of action	Direct and indirect antineoplastic effects through sst stimulation	sst-Targeted medical imaging of energy emitted by conjugated radioisotopes using scintigraphy or PET scan Cancer cell death through sst-targeted internalisation of high-energy radioisotopes (^{111}In, ^{90}Y, ^{177}Lu)	Cytostatic effect by DNA intercalation; generation of ROS	sst-Targeted internalisation of conjugated AN-201 (similar action to doxorubicin but 500 – 1000 times more potent)
Side effects	Mild GI tract complaints; minor glucose deregulation; generally asymptomatic cholelithisiasis	In therapeutic applications: mild GI tract and other toxicities due to carrier peptide activity; rare serious renal toxicity and myelosuppression	Acute nausea and vomiting occur frequently and can be severe; rare irreversible myocardial toxicity; frequent complete alopecia (reversible); leukopenia	Low toxicity in all preclinical models tested; side effects anticipated in the bone marrow and the GI tract but expected to be considerably milder compared to non-targeted chemotherapy
Clinical applications and efficacy	Treatment of some pituitary and neuroendocrine tumours; little clinical relevance as monotherapy against other solid tumours but may be used effectively in combination regimens currently under evaluation in clinical trials; recently developed novel analogues may broaden applicability	Imaging allows detection, localisation and staging of sst-expressing neuroendocrine tumours with very good sensitivity and positive predictive value Initial trials of targeted therapy against neuroendocrine tumours are very promising particularly in patients treated with ^{177}Lu-octreotate; Experimental data suggest potential applicability in other cancers expressing low receptor levels	Commonly used for the treatment of various malignancies	Potent preclinical antitumour activity in several different malignancies, including those expressing low receptor levels; efficacy in doxorubicin resistant models; may overcome intrinsic chemoresistance of some tumours

GI: Gastrointestinal; PET: Positron emission tomography; ROS: Reactive oxygen species; SM-A: Somatostatin agonist; sst: Somatostatin receptor.

addition to SM receptors [225]. The precise place of these molecules in the clinic remains to be determined but they may become very useful additions to the clinician's toolbox, particularly in cases refractory to the traditional SM-As. Chimeric ligands exhibit very potent activity in experimental tumour models which may be at least in part attributed to heterodimerisation of the targeted receptors. It is thus crucial to characterise the effects and the signalling pathways activated by such dimers to better delineate their potential clinical applications and anticipate potential toxicities of the chimeric ligands.

Clinical applications of ASF protocols have produced objective clinical responses with only mild side effects in androgen ablation refractory patients. A randomised Phase II trial demonstrated that ASF manipulation has a favourable toxicity profile compared to cytotoxic salvage chemotherapy. To this day, clinical testing of ASF has focused on IGF-I inhibition using established and well-characterised drugs, including SM-As which play a prominent role in liver-dependent IGF-I suppression. However, the ASF paradigm is not limited to blocking IGF-I. A variety of different survival factor signalling pathways may need to be targeted to minimise the host tissue's non-desirable protection of metastatic tumour cells. Future research efforts should further explain the role of survival factors in metastatic disease. Novel drugs inhibiting crucial survival factor processes will also be invaluable additions to the growing anticancer armamentarium. In this respect, new SM-As currently in the pipeline may also exhibit unique properties that could greatly expedite ASF manipulations.

Radiolabelled SM-As have become increasingly important in the management of neuroendocrine tumours. Such compounds may also have therapeutic antitumour potential as targeted radiopharmaceuticals. SM-As can also be used as peptide carriers that can selectively deliver chemotherapeutic compounds to cancer cells and thereby markedly increase

the therapeutic index of these cytotoxic agents. The strong therapeutic efficacy and the excellent toxicity profile of targeted cytotoxic SM-As established in numerous preclinical studies justify clinical assessment of these compounds.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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