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Somatostatin receptor biology in neuroendocrine and pituitary tumours: part 2 – clinical implications

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Introduction

In part 1 of our review on somatostatin (SST) receptor biology in neuroendocrine tumours, the somatostatin receptor (SSTR) as a G-protein coupled receptor (GPCR), and the anti-tumour effects of SST and SSTR post-signalling pathways, were reviewed. To recapitulate, SST is a peptide hormone which acts mainly as an inhibitor in many endocrine systems. SST has five receptor subtypes (SSTR1–5) with SSTR2 as the most commonly expressed form in both normal and tumoral tissues. SST has been widely investigated for its anti-tumoral effects and their mechanisms, and currently there are two SST analogues (lanreotide and octreotide) in clinical use. The anti-proliferative action of SST mainly occurs through phosphotyrosine phosphatases which modulate MAPK and PI3K/Akt pathways. On the other hand, its anti-secretory action occurs through decreased intracellular cAMP, K^+ and Ca^{++} levels. While part 1 of our review has principally focused on the molecular components of SST action, part 2 will cover the clinical implications of these molecular effects, starting from SSTR subtype tissue distribution and SST analogue use in the diagnosis and treatment of neuroendocrine tumours.

SSTR subtype tissue distribution and its relevance to tumour imaging and treatment

Because naturally occurring SSTs (SST-14 and SST-28) have short half-lives in the circulation (1–3 min.), synthetic derivatives have been designed to produce more stable compounds. Among several SST analogues that have been synthesized, octreotide, lanreotide, vapreotide and seglitide bind preferentially to SSTR2 and SSTR5, have moderate affinity for SSTR3 and low affinities for SSTR1 and SSTR4 [1, 2]. Currently, octreotide and lanreotide are in clinical use for the treatment of acromegaly and various GEP-NETS [3]. However, the success of this therapeutic approach has been often hampered by the fact that some patients respond to treatment with SST analogues, whereas some are partial responders, and others do not respond at all, suggesting the potential importance of the expression pattern of the SSTRs in each pathology [4, 5]. There are case reports and studies confirming the existence of different receptor expression patterns [6–8]. In a study by Ueberberg and colleagues, SSTR1–5 expression was analysed by RT-PCR and Southern blotting in normal adrenal tissue and adrenal pheochromocytomas (PHEOs), cortisol-secreting adenomas (CPAs), aldosterone secreting adenomas (APAs) and non-functional adenomas (NFAs) [8]. Expression of all five receptor subtypes was observed in RNA obtained from normal adrenal gland. No SSTR5 expression was found in PHEOs, whereas SSTR1 was present in nearly all of these tumours. Only a few of the CPAs expressed subtypes SSTR1 and SSTR4. Expression of all five subtypes was distributed equally in APAs. No SSTR4 was found in any of the NFAs [8].

In other words, the expression pattern of SSTRs is of crucial importance in terms of using SST in imaging and treatment of NETs. If the corresponding tumour does not express the receptors necessary for inhibiting critical pathways, the given drug, mainly SST analogues, will not have any effect. Moreover, treatment has two components for NETs, namely, anti-secretory and anti-proliferative actions. When the mechanisms of these two actions are

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reconsidered, it is also understandable that not always will these two components go hand in hand in every tumour treated. There are GH-secreting pituitary adenoma cases reported in the literature which are good examples for the dissociation of the anti-proliferative and anti-secretory effects of SST analogues [9].

The clinical implication of the differing tissue and tumour distribution of SSTRs becomes more of an issue when it comes to developing new drugs for these tumours. The SSTR expression pattern shows great heterogeneity between different neuroendocrine tissues and also between the tumours originating from different cells of the same neuroendocrine tissue. Several studies have been performed investigating the SSTR subtype distribution patterns in NETs. As it is not possible to mention all these studies here, a brief overview will be made regarding SSTR subtype expression patterns.

To start with, many studies have explored SSTR subtype expression in pituitary adenomas demonstrating that SSTR2 is the most frequently expressed subtype [10]. Specifically, at both mRNA and protein levels SSTR2, SSTR5 and D2 coexpression has been found in most GH-secreting adenomas [11]. However, some 50% GH-secreting tumours, particularly mixed GH/PRL adenomas, also coexpress SSTR3 and SSTR1 [10, 12–16]. The expression of SSTR2 was found to be positively correlated with the *in vivo* GH suppression induced by octreotide [17, 18]. Conversely, in a study by Plöckinger and colleagues, octreotide-resistance was noted in GH-secreting adenomas to be associated with a selective loss of SSTR2 expression, and these tumours specifically expressed SSTR1 and SSTR5 which could make them good candidates for pasireotide (SOM230, Novartis, Basel, Switzerland) treatment which has high affinity to subtypes SSTR1, SSTR2, SSTR3 and SSTR5 [19]. Additionally, new SSTR2 selective SST analogues, with higher affinity to SSTR2 compared to octreotide and lanreotide, showed a more potent effect on inhibition of GH secretion in primary cultures of GH-secreting pituitary adenomas [11]. On the other hand, in some cell culture studies SSTR5 selective SST analogues were found to be more potent [20]. Moreover, the combined activation of SSTR2 and SSTR5 results in additive inhibitory effects on GH secretion which has led to the synthesis of new bi-selective agonist compounds that bind to both SSTR2 and SSTR5 [21].

The majority of prolactinomas express high numbers of D2R and SSTR1. SSTR5 is also notably present, while SSTR2 is only expressed in a minority of them [10, 12, 22–24]. Although dopamine receptor agonists have successfully been used in these tumours, some patients seem to be resistant or partially responsive to dopamine agonist therapy. In *in vitro* studies, SSTR5 agonist treatment have proven to be useful in prolactinomas; however, the clinical importance of SST analogue treatment remains uncertain as their effects are not additive to the widely used dopamine agonist treatment regimens [11].

Non-functioning pituitary adenomas (NFPAs), including gonadotrophinomas, as well as α-subunit producing tumours, express mainly SSTR3 and at a lesser degree SSTR2 and D2R, while they are seldom associated with SSTR1 [14, 25]. The cumulative reported experience in NFPAs with octreotide administered to 100 NFPA patients for an average of 6 months (1–12 months), has been recently reviewed by Colao *et al.* [26]. Tumour volume decreased in 5%, increased in 12% and remained unchanged in 83% of patients; thus, long-term studies are clearly needed before more definitive conclusions can be drawn. As SSTR3 induces apoptosis by induction of p53 and the pro-apoptotic protein Bax, SSTR3 selective SST analogues are seen as potential candidates in treatment of NFPAs.

Corticotroph adenomas mainly express SSTR5 and D2R, whereas SSTR2, SSTR1 and SSTR3 are expressed at lower levels [12, 27–29]. An additional problem with these tumours is that, in the hypercortisolaemic state, as in Cushing's disease, SSTR2 may be down-regulated on pituitary tumour cells. In patients with ectopic ACTH syndrome, octreotide had no significant effects in reducing ACTH and serum cortisol levels, although the response is variable and may be assessed utilizing an octreotide challenge test [30]. The only available ACTH-producing cell line of corticotroph origin is the murine AtT20 cell line. A number of studies have indicated that in these cells SSTR2 and SSTR5 are principally involved in the regulation of ACTH release and that selective agonists that target these subtypes effectively inhibit ACTH secretion [29]. More recently it was found that SSTR5 in particular played a crucial role in regulating ACTH release in these cells, and that SSTR5-targeting agonists were more effective than SSTR2 agonists in inhibiting ACTH release [29]. An emerging drug in terms of potential applications to corticotroph adenomas is the multisomatostatin receptor analogue pasireotide. This agent exhibits greater SSTR5 binding affinity than SSTR2 and has shown continuing efficacy in high glucocorticoid states *in vitro* [11, 31, 32]. In a recent study, pasireotide was shown to be less potent than octreotide in inducing internalization and the signalling of SSTR2 receptors expressed in HEK cells [33]. In contrast, pasireotide was more potent than octreotide in inducing internalization and signalling of SSTR3 and SSTR5 receptors [33]. In a study by Pöll and colleagues, SST and octreotide was shown to stimulate rapid cointernalization of the rat SSTR2A and ss-arrestin into the same endocytic vesicles [34]. In contrast, pasireotide failed to promote substantial phosphorylation and internalization of the rat SSTR2A. Additionally, in the presence of octreotide or SST, pasireotide showed partial agonist behaviour, inhibiting phosphorylation, and internalization of SSTR2A [34]. Pasireotide-mediated phosphorylation led to the formation of relatively unstable β-arrestin-SSTR2A complexes that dissociated at or near the plasma membrane. Thus, octreotide and pasireotide were found to be equally active in inducing classical G protein-dependent signalling *via* the SSTR2A, yet they promoted strikingly different patterns of SSTR2A phosphorylation [34]. In the first, uncontrolled phase II trial in human, pasireotide caused a reduction in urinary free cortisol levels in 76% of patients with Cushing's disease during a treatment period of 15 days, with direct effects on ACTH release, while normalization of urinary free cortisol occurred only in 17% of patients [35]. As it potently suppresses GH and IGF-I secretion and, furthermore multiple SSTR expression is a feature of carcinoid tumours, pasireotide may have potential efficacy in acromegaly and the carcinoid syndrome as well [36].

Thyroid-stimulating hormone (TSH)-secreting tumours, although very rare, significantly express SSTR1, SSTR2 and SSTR5 [10, 12, 16, 37]. In patients treated with octreotide, TSH level normalization was noted in 80%, whereas significant tumour shrinkage was observed in 50% [11]. Beck-Peccoz and colleagues have reported even better results with more than 90% of patients achieving normalization of free T4 and free T3 [38–40]. In a recent study it was demonstrated that SSTR2 is the SSTR subtype predominantly expressed in a series of TSH-secreting adenomas [41], and the patient with highest expression of SSTR2 showed marked shrinkage of the tumour on octreotide treatment. These data suggest that SSTR2 is involved in the control of TSH secretion and SST analogues form an important treatment modality in these tumours.

Furthermore, as many pituitary adenomas coexpress SSTRs and D2R and ligand induced heterodimerization has been shown between SSTR5/D2 and SSTR2/D2 receptors, chimeric molecules ('dopastatins') targeting both receptors hold great hope as future treatment options [16]. These drugs may be favourable in acromegaly and other pituitary tumours and also gastrointestinal endocrine tumours where tachyphylaxis may limit SST analogue efficacy [16].

When it comes to GEP-NETS, these tumours may be 'functioning' and thus cause a clinical syndrome due to hormonal hypersecretion, or 'non-functioning' when the symptoms are related only to the mass effect of the tumour [11]. Regarding SSTR expression, it has been reported that in the endocrine pancreas SSTR5 and at lower levels SSTR1 are expressed in insulin secreting β-cells, SSTR2 is mainly expressed in glucagon-secreting α-cells and SSTR5 in the SST-releasing δ-cells, while SSTR3 and SSTR4 are poorly expressed [42, 43]. However in a study evaluating SSTR expression in malignant pancreatic endocrine tumours, SSTR2 and SSTR4 was positive in 90% and SSTR1 in 70% of the tumour tissues, whereas SSTR3 and SSTR5 stained positive in only 50% of the tumour tissues [44]. The SSTs were evenly distributed among the different tumour subtypes. However, tumours belonging to the same subgroup of endocrine pancreatic tumours showed a variable expression of receptor subtypes. No differences in receptor-subtype expression pattern were noted either between poorly and well-differentiated tumours, or between primary tumours and metastases [44]. In an immunohistochemical study analysing SSTR expression in GEP-NETS [45], 94% were positive for SSTRs among the tumours analysed. The negative cases were all non-functioning tumours. SSTR2A and SSTR5 were highly expressed (86 and 62%, respectively), and surprisingly found even in poorly differentiated endocrine carcinomas [45]. SSTR expression was less frequent in pancreatic than in gastrointestinal tumours. Well-differentiated neoplasms had a higher density of SSTRs. However, there are also case reports in the literature with functioning NETS and negative SSTR expression [6, 7]. In a case report by Singer and colleagues, ectopic Cushing's syndrome caused by a well-differentiated neuroendocrine carcinoma of the ileum was presented in which immunohistochemical analysis of the primary tumour was positive for SSTR2 as opposed to the metastases [6]. Similarly, in another case report of ectopic Cushing's syndrome caused by a neuroendocrine carcinoma of the mesentery, SSTR1–5 expression was found to be negative in an immunohistochemical analysis of the tumour [7].

In another recent immunohistochemical study, the expression of SSTRs and D2R were investigated in low-, intermediate- and high grade NETs [46]. Both SSTR2 and SSTR5 were found to be expressed in 100% of low-grade, 94% of intermediate-grade and 67% of high-grade NETs [46]. D2R was expressed in 93% of low-grade, 78% of intermediate-grade and 44% of high-grade tumours. Coexpression of all three receptors was recorded in 93% of low-grade tumours. Positive imaging with *Octreoscan* (^{111}In-DTPA-octreotide imaging, see below) correlated with SSTR2 and SSTR5 expression. In a recent analysis investigating SSTR expression in pulmonary NETs ($n = 218$), SSTRs were found to be distributed heterogeneously with a significant progressive decrease from low- to high-grade forms [47]. SSTR2A was strikingly overexpressed in metastatic typical carcinoids as compared with atypical carcinoids and clinically benign typical carcinoids. SSTR tissue immunolocalization correlated with octreotide scintigraphy in 20 of 28 cases. In a study testing the cytotoxicity of novel SST and dopamine chimeric compounds in bronchopulmonary and small intestinal neuroendocrine tumour cell lines, it was revealed that the drug response was very heterogeneous among different tissues, and it was concluded that NETs from different locations arising from different neuroendocrine cells may require cell-specific anti-proliferative agents based on the unique receptor profile of individual lesions [48].

GEP-NETs usually express a high density of SSTRs (this can be expressed as pmol receptors/g tissue), and in SSTR2^{+} and SSTR5^{+} tumours symptoms related to hormone hypersecretion can be controlled by the administration of SST analogues in around 90% of patients [11].

SST analogue treatment has been recently recommended in functioning NETs in European Neuroendocrine Tumour Society Guidelines [49]. Although tumour shrinkage has also been observed in a small number of patients, SST analogue therapy does not offer a curative treatment regimen and the tumour advances in nearly all patients with GEP-NETS [11]. However, based upon phase II experience there is a strong suggestion of a disease stabilizing effect of SST analogues in selected patients [50]. Those patients with a progressive, non-functional GEP-NET, positive octreotide scintigraphy, a low proliferation index and in the absence of surgical options may benefit from a first-line medical therapy with SST analogues. The exploration of the mechanisms of this effect is unclear and hampered by the lack of suitable preclinical models. Very recently, for the first time the clear anti-proliferative effects of octreotide in well-differentiated metastatic midgut NETs have been shown in a placebo-controlled, double-blind, phase IIIB study [51]. In this study by Rinke and colleagues, after 6 months of treatment, stable disease was observed in 66.7% of patients in the slow-release depot octreotide injection group and 37.2% of patients in the placebo group. Functionally active and inactive tumours responded similarly. The most favourable effect was observed in patients with low hepatic tumour load and resected primary tumour. This was one of the first properly controlled large-scale studies clearly showing the anti-proliferative effect of octreotide in NETs.

On the other hand, the recently introduced SST analogue pasireotide was found to be effective in controlling symptoms of diarrhoea and flushing in 25% of patients with metastatic carcinoid tumours inadequately controlled by slow-release depot octreotide injection treatment [52]. Future studies will show whether this analogue also has better anti-proliferative effect, as indicated on phaeochromocytoma cells (see below) [53, 54]. BIM-23A760 is a chimeric molecule, binding to SSTR2, SSTR5 and D2R: this drug, which has shown greater efficacy than the SST analogues used in clinical practice in suppressing GH production from pituitary tumours, is being assessed in patients with NETs [54]. On the other hand, receptor expression alone may not be enough in developing future treatments in NETS as SSTR coupling to a given pathway can be strongly influenced by the ligand used [55]. In a recent study by Cescato and colleagues, pasireotide, which activates SSTR1, SSTR2, SSTR3 and SSTR5 receptors, as mentioned previously, and KE108, which activates all SSTR subtypes were compared in terms of modulated intracellular pathways in two different cell lines, HEK 293 and pancreatic AR42J cells [55]. The results demonstrated that pasireotide and KE108 behave as agonists for the inhibition of adenylyl cyclase but antagonize SST's actions on intracellular calcium and ERK phosphorylation. Thus, pasireotide and KE108 were not SST mimics, and their functional selectivity at SSTR2A receptors should be considered in clinical applications where it might have important consequences for therapy.

Another diagnostic and therapeutic application is imaging of NETs with labelled SST analogues followed by radionuclide therapy. Peptide receptor imaging (PRI) and radionuclide therapy (PRRT) can be combined in a single probe which has been named as 'theranostic' by some authors [56]. The idea that lies behind this approach is the exploitation of the specific receptor binding properties of the peptide ligand by using a radiolabelled ligand to guide the radioactivity to the tumours expressing a particular receptor [56]. The high affinity of the ligand for the receptor facilitates retention of the radiolabel in the tumour. Receptor-binding peptides labelled with γ-radiation emitters for SPECT (indium-111 and technetium-99m) or positron emitters for PET (gallium-68 and fluorine-18) enable visualization of receptor-expressing tissues non-invasively: a technique referred to as PRI [56]. In addition, peptides labelled with β-particle emitters (yttrium-90 and lutetium-177) have the potential to eradicate receptor-expressing tissues: this approach is referred to as PRRT [56]. A peptide analogue labelled with a diagnostic radionuclide is used for imaging to select patients who will benefit from radionuclide therapy. Thereafter, radionuclide therapy is performed with the same or a similar peptide analogue labelled with a therapeutic radionuclide. When a chelator such as DTPA is used, it enables high specific activity complexing of ^{111}In with octreotide, which can be applied for SPECT imaging. Currently, ^{111}In-DTPA-octreotide (^{111}In-pentetreotide) is the most commonly used tracer for imaging of NETs and provides important information on the localization and staging of NETs [57]. The next generation of modified SST analogues includes DOTA,Tyr^3-octreotide (DOTATOC) and DOTA,Tyr^3-octreotate (DOTATATE) [56]. DOTATOC has a higher affinity for SSTR2 and has the chelator DOTA instead of DTPA, which forms thermodynamically and kinetically stable complexes with a variety of radiometals for PRI as well as PRRT: ^{111}In for SPECT, ^{68}Ga for PET, and ^{90}Y and ^{177}Lu for PRRT [56]. DOTATATE is also a third-generation SST analogue which is used for PRI and PRRT. Reubi and colleagues have reported a 9-fold increase in affinity for SSTR2 for DOTA,Tyr^3-octreotate when compared with DOTA,Tyr^3-octreotide, and a 6-to 7-fold increase in affinity for their yttrium-loaded counterparts [58]. SST analogues ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE has been explored in NETs as PRRT for more than a decade and present knowledge and clinical studies indicate that it is possible to deliver high-absorbed doses to tumours which express SSTR2 [59]. In these studies partial and complete objective responses have been detected in up to 30% of patients [59]. Moreover, a consistent survival benefit is reported. Compared to historical controls, there is a benefit in overall survival of several years from time of diagnosis in patients treated with ^{177}Lu-DOTATATE [60]. From animal experiments it can be inferred that ^{90}Y-labelled SST analogues may be more effective for larger tumours, whereas ^{177}Lu-labelled SST analogues may be more effective for smaller tumours, but their combination may be the most effective [60]. Therefore, apart from comparisons between radiolabelled octreotate and octreotide, and between SST analogues labelled with ^{90}Y or ^{177}Lu, PRRT with combinations of ^{90}Y- and ^{177}Lu-labelled analogues should also be evaluated [60]. ^{99m}Tc-labelled SST analogues, such as ^{99m}Tc-hydrazinopyridine-3-carboxylic acid (HYNIC), have also growing importance because of the cost-effectiveness and wide availability of ^{99m}Tc. PET scanning with ^{68}Ga- and ^{18}F-labelled SST analogues will be increasingly applied for detection and follow-up of patients with NETs because of the higher sensitivity of this technique and the reduced time needed for investigation in comparison to SPECT.

Regarding adrenal tissue, in a very recent study SSTR2 expression at the mRNA and protein levels in normal human adrenal tissues, adrenocortical and adrenomedullary tumours, and cell lines was analysed [61]. SSTR2 mRNA expression was detected in normal adrenal cortex, benign and malignant phaeochromocytoma, adrenocortical adenoma and carcinoma, adrenomedullary PC-12 tumour cells and adrenocortical SW-13 tumour cells [61]. The non-cytotoxic SST analogue RC-160 did not have any effect on PC-12 cells. However, the two targeted cytotoxic SST analogues, AN-238, which is a targeted cytotoxic SST analogue consisting of 2-pyrrolinodoxorubicin (AN-201) linked to the octapeptide SST analogue RC-121, and AN-162, which is another cytotoxic SST analogue consisting of doxorubicin conjugated to RC-121, significantly reduced the number of PC-12 cells [61]. In another study, all benign phaeochromocytomas were found be immunohistochemically positive for SSTR3 and the adrenal medulla was predominantly positive for SSTR3 [62]. In a recent study evaluating the effects of the SST analogues octreotide and pasireotide on cell proliferation, apoptosis and catecholamine levels in primary cultured and SSTR-expressing PHEOs cells, significant inhibition of cell growth and apoptosis was noted for both drugs in favour of pasireotide [53]. Regarding imaging, in adrenal phaeochromocytomas, although ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy shows a higher detection rate for benign PHEOs compared to ^{111}In-pentetreotide scintigraphy, in malignant phaeochromocytomas ^{111}In-pentetreotide scintigraphy may reveal ^{123}I-MIBG scintigraphy negative lesions [63]. For scintigraphic detection of head and neck paragangliomas, ^{111}In-octreotide scintigraphy seems superior to ^{123}I-MIBG scintigraphy [64].

In patients with medullary thyroid carcinoma both SST analogues and tumour-targeted radioactive treatment using radiolabelled SST analogues have limited therapeutic value due to minor radioactivity uptake by these tumours in most patients [65]. In pituitary tumours from different origins, ^{111}In-pentetreotide scintigraphy is also of very low value.

Conclusions

The incidence and prevalence of NETs have significantly increased over the last two decades. NETs are heterogeneous tumours and the high variability of SSTR subtype expression reported above may be due in part to the different techniques used in these studies (mainly mRNA analysis by Northern blot, *in situ* hybridization, 'real-time' PCR or protein assays such radioactive-binding studies and immunohistochemistry). There is even considerable heterogeneity in SSTR expression patterns in pituitary tumours. This point poses a problem in treatment of NETs as treatment response is quite unpredictable. On the other hand, for SSTRs, as for GPCRs in general, the possibility of new drugs with different pharmacological profiles at specifically targeted receptor subtypes holds great promise [66]. SSTRs associate with other receptors to form molecular complexes whose binding, pharmacological and signalling properties can diverge substantially from those of the corresponding single receptors [67]. In other words, these receptor interactions may allow the activation of intracellular pathways not regulated by the individual receptors or modify their binding and desensitization responses that may be useful for therapeutic purposes. The currently available data already indicate that the pattern of dimer formation and its dynamic behaviour after ligand binding is subtype specific and can also be species dependent; however, there is still no evidence to explain how these differences influence aspects of SSTR functioning [67]. The precise identification and functional characterization of SSTR homo- and heterodimers constitutes a promising goal that could open new avenues to understand the physiology of SSTRs and their natural and synthetic ligands in health and disease.

The differential intracellular trafficking of SSTRs is likely to be involved in the regulation of long-term responsiveness of individual target cells to stable SST analogues [68]. The SSTR2 receptor appears to be an ideal pharmacological target because the lack of detectable down-regulation may enable target cells to retain their responsiveness during prolonged agonist exposure, and its rapid internalization and recycling may allow the accumulation of considerable amounts of radiolabelled SST analogues in target cells [68]. In contrast, due to its rapid down-regulation, the SSTR3 receptor appears to be a less favourable pharmacological target [68].

It seems that SST analogues will be a cornerstone treatment for NETs in the foreseeable future. Several analogues and chimeric molecules with different signalling properties are being developed, and many are on their way. Better understanding of the effects of these agents and modulated pathways will clarify the putative role SST analogues in the treatment of not only NETs but also in other cancers that are also well known to express SSTRs.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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