CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Somatostatin receptors as a new active targeting sites for nanoparticles
Authors	Abdellatif, Ahmed A. H.;Aldalaen, Sa'ed M.;Faisal, Waleed;Tawfeek, Hesham M.
Publication date	2018
Original Citation	Abdellatif, A. A. H., Aldalaen, S. e. M., Faisal, W. and Tawfeek, H. M. (2018) 'Somatostatin receptors as a new active targeting sites for nanoparticles', Saudi Pharmaceutical Journal, 26(7), pp. 1051-1059. doi: 10.1016/j.jsps.2018.05.014
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://www.sciencedirect.com/science/article/pii/S1319016418301154 - 10.1016/j.jsps.2018.05.014
Rights	© 2018, Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) - http://creativecommons.org/licenses/by-nc-nd/4.0/
Download date	2026-10-06 06:39:58
Item downloaded from	https://hdl.handle.net/10468/6920

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Saudi Pharmaceutical Journal 26 (2018) 1051–1059

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Review

Somatostatin receptors as a new active targeting sites for nanoparticles

Ahmed A.H. Abdellatif [a,b], Sa'ed M. Aldalaen [c], Waleed Faisal [e,f], Hesham M. Tawfeek [c,d,*]

[a] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut 71524, Egypt
[b] Department of Pharmaceutics, Faculty of Pharmacy, Qassim University, Buraydah, 51452 Al-Qassim, Kingdom of Saudi Arabia
[c] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Mutah University, Mutah, Al-Karak 61710, Jordan
[d] Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt
[e] Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Minia, Egypt
[f] School of Pharmacy, University of College Cork, Cork, Ireland

ARTICLE INFO

Article history:
Received 25 February 2018
Accepted 22 May 2018
Available online 31 May 2018

Keywords:
Active targeting
Somatostatin analogues
Somatostatin receptors
Nanoparticles
Cellular uptake

ABSTRACT

The delivery of nanoparticles through receptor-mediated cell interactions has nowadays a major attention in the area of drug targeting applications. This specific kind of targeting is mediated by localized receptors impeded into the target site with subsequent drugs internalization. Hence, this type of interaction would diminish side effects and enhance drug delivery efficacy to the target site. Somatostatin receptors (SSTRs) are one type of G protein-coupled receptors, which could be active targeted for various purposes. There are five SSTRs types (SSTR1-5) which are localized at various organs in the body and spread into different tissues. SSTRs could be considered as a promising target to various nanoparticles which is facilitated when nanoparticles are modified through specific ligand or coating to allow better binding. This review discusses the exploration of SSTRs for active targeting of nanoparticles with certain emphasize on their interaction at the cellular level.
© 2018 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

1. Introduction . . . 1052
2. G protein-coupled receptors . . . 1052
   2.1. Somatostatin receptors . . . 1054
   2.2. Somatostatin and its analogs . . . 1054
   2.3. Octreotide (OCT) . . . 1055
   2.4. Challenges in nanomedicine formulation for receptor targeting . . . 1055
3. Cellular uptake of nanoparticles . . . 1056
4. Diagnostic purposes of SST . . . 1057
5. Conclusions . . . 1057
Conflict of interest . . . 1057
Acknowledgments . . . 1057
References . . . 1057

* Corresponding author at: Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Mutah University, Mutah, Al-Karak 61710, Jordan; Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt.
E-mail addresses: htawfeek@mutah.edu.jo, heshamtawfeek@aun.edu.eg (H.M. Tawfeek).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2018.05.014
1319-0164/© 2018 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The nanoparticles represent good model candidates in the field of drug delivery applications. This could be due to many reasons such as they could be prepared in an ideal size suitable for cell internalization and active targeting, facilitated conjugation with various biomaterials and other molecules without changing the biological activity of the conjugated compounds. However, there are some issues should be considered to deliver these nanoparticles to their active sites such as resistance against photobleaching (Chen et al., 2009), enhanced stability presented on an acceptable blood circulation time (Ballou et al., 2005). As well as surface modification to enhance their binding to certain receptors (Abdellatif et al., 2016).

Metallic nanoparticles e.g., gold nanoparticles, (AuNPs), and silver nanoparticles (AgNPs), and quantum dots, Qdots encapsulated, adsorbed or conjugated to different types of drugs could be easily targeted to specific sites in the human body (Akhter et al., 2011). These nanoparticles could be prepared and stabilized using different types of polymers and linkers such as an 11-mercaptoundecanoic acid (11-MUA) and polyethylene glycol (Abdellatif et al., 2016; Alibakhshi et al., 2017). Moreover, the development of metallic nanoparticles is fast and multidirectional, and the developed prospective metallic nanoparticle highlights their effectiveness as a new field for forthcoming cancer therapeutics modalities (Ahmad et al., 2010). Furthermore, they could be conjugated with somatostatin (SST) or its analogs such as octreotide, OCT, as SSTRs agonist, or SSTRs antagonist ligand for active targeting (Surujpaul et al., 2008; Elbakry et al., 2009; Alibakhshi et al., 2017).

Addition of PEG to different types of nanomaterials will improve the biological and physiochemical activities as well as enhancing the circulation time in blood allowing them to reach the specific target sites (Na and DeLuca, 2005; Park and Na, 2008; Abdellatif, 2015). PEG also sheath the nanoparticles with a hydrophilic layer which prevents the opsonization process and resist the non-specific phagocytosis (Zhang et al., 2011; Tawfeek, 2013). Moreover, the PEGylation of nanoparticles preserved and stabilize the final formulated of nanoparticles (Na et al., 2003; Na and DeLuca, 2005; Abdellatif, 2015).

Drug targeting enhance effectiveness, declines adverse effects, and limits systemic drug exposures. The active targeting is usually chosen to bind surface molecules or receptors that are over-expressed in tissues, surface cells or at subcellular level (Abdellatif, 2015; Abdellatif et al., 2016; Ramzy et al., 2017). In addition, active targeting avoids the non-specific internalization through the cell membrane, which affects the targeting efficiency of nanoparticles. This may be enhanced by changing the physiochemical properties such as the density of ligand, and the dimensions of the formulated nanoparticles or to the choice of the involved targeting ligand *in vitro* as well as *in vivo* (Abdellatif, 2015; Alibakhshi et al., 2017; Ramzy et al., 2017).

A great advantage of Qdots over organic fluorophores is that Qdots are resistant to photobleaching (Chen et al., 2009), have long circulation time and are stable in the blood circulation for several months (Ballou et al., 2005). Nevertheless, limited cytotoxicity results from their Cd content (Chen et al., 2012; Ye et al., 2012). In addition, Qdots carrying PEG-amine showed low cytotoxicity when applied to cell culture (Zhang et al., 2006).

Lower acute toxicity has been observed for Qdots *in vivo*, when rhesus macaques were injected with phospholipid micelle-encapsulated CdSe/CdS/ZnS Qdots, the clearance of Qdots was very slow (Ye et al., 2012). Injection of Qdots into tumor-bearing nude mice indicated that they could be used as fluorescent probes for *in vivo* imaging to study the bio-distribution of nanocarriers and their intracellular pathways. Furthermore, Qdots-loaded micelles accumulated in the tumor tissue in a passive way (Cao et al., 2012).

Tumor cells can be killed by excitation of internalized AuNPs (Kang et al., 2010). Ligands-decorated AuNPs can also target special receptors in the human body, i.e. AuNPs capped with peptide Cys-Leu-Pro-Phe-Phe-Asp (CLPFFD) interacted with the transferrin receptor present in the microvascular endothelial cells of the blood-brain barrier (Prades et al., 2012). Furthermore, AuNPs were delivered to ovarian cancer cells that express the epidermal growth factor receptor and the folate receptor than the other single-receptor-targeting systems (SRTS) (Bhattacharyya et al., 2011).

Many studies showed that nanoparticles linked specific ligands or monoclonal antibodies could be targeted to surface receptors over-expressed by cancer cells, such as the SSTRs, the folate receptor, and transferrin receptors, can increase cellular internalization of any drug through endocytosis process and improve the effectiveness of systemic anticancer therapy. Furthermore, nanoparticles coated cell-penetrating peptides and protein-transduction domains, such as oligoarginine and TAT facilitated the uptake of these nanoparticles which cannot successfully enter cancer cells (Abdellatif et al., 2016).

This review points out the active targeting of nanoparticles compared to the passive targeting approaches. In passive targeting, the medication's achievement is directly related to the time at which the active entity still present in circulation. This approach could be manipulated via covering nanoparticles with some kind of coating. Numerous materials can accomplish this task, with some of them being polyethylene glycol (PEG). By addition PEG to the external surface of nanoparticles, it is becoming hydrophilic. Hence, permitting water molecules to bind with the oxygen molecules on PEG via hydrogen bonding. The product of this kind of hydrogen bonding is considered to form a film of the hydrated layer across NP, stealth nanoparticles, which builds the substance antiphagocytic. Hence, the drug-coated nanoparticle is able to stay in circulation for a longer period. However, this kind of mechanism needs tight control of nanoparticles size and distribution. PEGylated nanoparticles could be also used for active specific targeting after being conjugated with a suitable targeting moiety. Nevertheless, the nanoparticles will be in much bigger size, which prevents the non-specific binding through the cell membrane. Actually, nanoparticles within 10 and 100 nm in size are postulated to be present in circulation for a longer time (Sonia et al., 2017).

Nowadays, there is a numerous trials for combing several characters in one materials to form what is called the multifunctional nanomaterials. They could be used for diagnosis, specific targeting drug therapy as well as monitoring therapeutic response. Despite the several advantages of these nanomaterials, toxicity is still an issue and a big challenge, which needs lot of efforts to overcome (Rahman et al., 2012a, 2012b, 2012c).

In this review, a promising receptor site for active targeting of nanoparticles and the interaction of nanoparticles conjugated with specific targeting peptides, i.e. SST and OCT with these receptors have been addressed. In addition, challenges regarding the delivery of these nanoparticles linked peptides and their cellular uptake into different cell lines have been also discussed.

2. G protein-coupled receptors

G protein-coupled receptors (GPCRs) are the biggest family of seven transmembrane domain receptors in mammalian species and are responsible for communication between a cell and its environment (Pierce et al., 2002). They play the main role in many diseases such as cancer and are also the target of numerous drugs such as somatostatin and integrin receptors (Auld et al., 2002).

Different kinds of molecules can activate GPCRs, such as ions, amino acids (i.e. Glutamate, Ca^{2+}) and GABA. Many peptides and large molecule proteins, i.e. chemokine, angiotensin, thrombin, and others, can also activate GPCRs. Biogenic amines i.e. noradrenaline, 5HT, histamine, acetylcholine also can interact with GPCRs. GPCRs can be activated with low nanomolar concentrations followed by rapid tissue intracellular responses to regulate cell function and to exhibit a cell response (Fig. 1a) (Kobilka, 2007). These receptors control many physiological processes in the mammalian species e.g., immune system, central nervous system regulation, all hormones, and enzymes released and/or inhibited from endocrine or exocrine glands (i.e. SSTRs), sympathetic and parasympathetic regulations, and smell senses (Fig. 1b) (Hazell et al., 2012).

The GPCRs carboxyl terminal is located in the cytosol. It plays a specific role in G-protein coupling whereas the N-terminal amino group is localized in the extracellular space (Oliveira et al., 1993). So, these receptors are regulated by many different ligands. Upon ligand binding to GPCRs, they undergo different types of changes. This interaction catalyzes the GDP-GTP exchange on the Gα proteins, then Gα is dissociated from Gβγ subunits. Both αGTP sub-units and Gβγ sub-units complexes then stimulate other intracellular proteins (Neves et al., 2002). The usual pathway of $G_{\alpha s}$ is to activate adenylate cyclase which catalyzes the conversion of ATP to cyclic-AMP. The high concentration of cAMP may then increase the Ca^{2+} release from endoplasmic reticulum (Fig. 1c) (Wettschureck and Offermanns, 2005).

Conversely, stimulation of the $G_{\alpha i/o}$ type inhibits adenylate cyclase to synthesize cAMP. Briefly, the role of GPCR coupled to $G_{\alpha i/o}$ counteract the actions of a GPCR coupled to $G_{\alpha s}$, and vice versa (Neves et al., 2002). Interaction of $G_{\alpha q}$ activates PLC. A phospholipid then cleaved from PLC. DAG and IP3 cleaved from PIP2. IP3 released into the cytosol. IP3 then diffuses through the cytosol to bind to IP3 receptors, particularly calcium channels in ER. These channels allow the release of Ca^{2+} into the cytosol and lead to an increase of intracellular Ca^{2+}. Many of GPCRs that couple to $G_{\alpha 12/13}$ also couple to other classes, often $G_{\alpha q/11}$ (Neves et al., 2002). The pathway of G_{12} and G_{13} is still unclear; it could be a direct interaction with a GTPase-activating protein for Ras, or Brukoń tyrosine kinase. GTPase can bind to GTP, and Rho activates other proteins which are responsible for cytoskeleton regulation such as Rho kinase, (Fig. 1c) (Jiang et al., 1998; Shi et al., 2001). GPCRs can be known as an excellent target for many drugs. Recent studies have reported that many GPCRs, such as chemokine

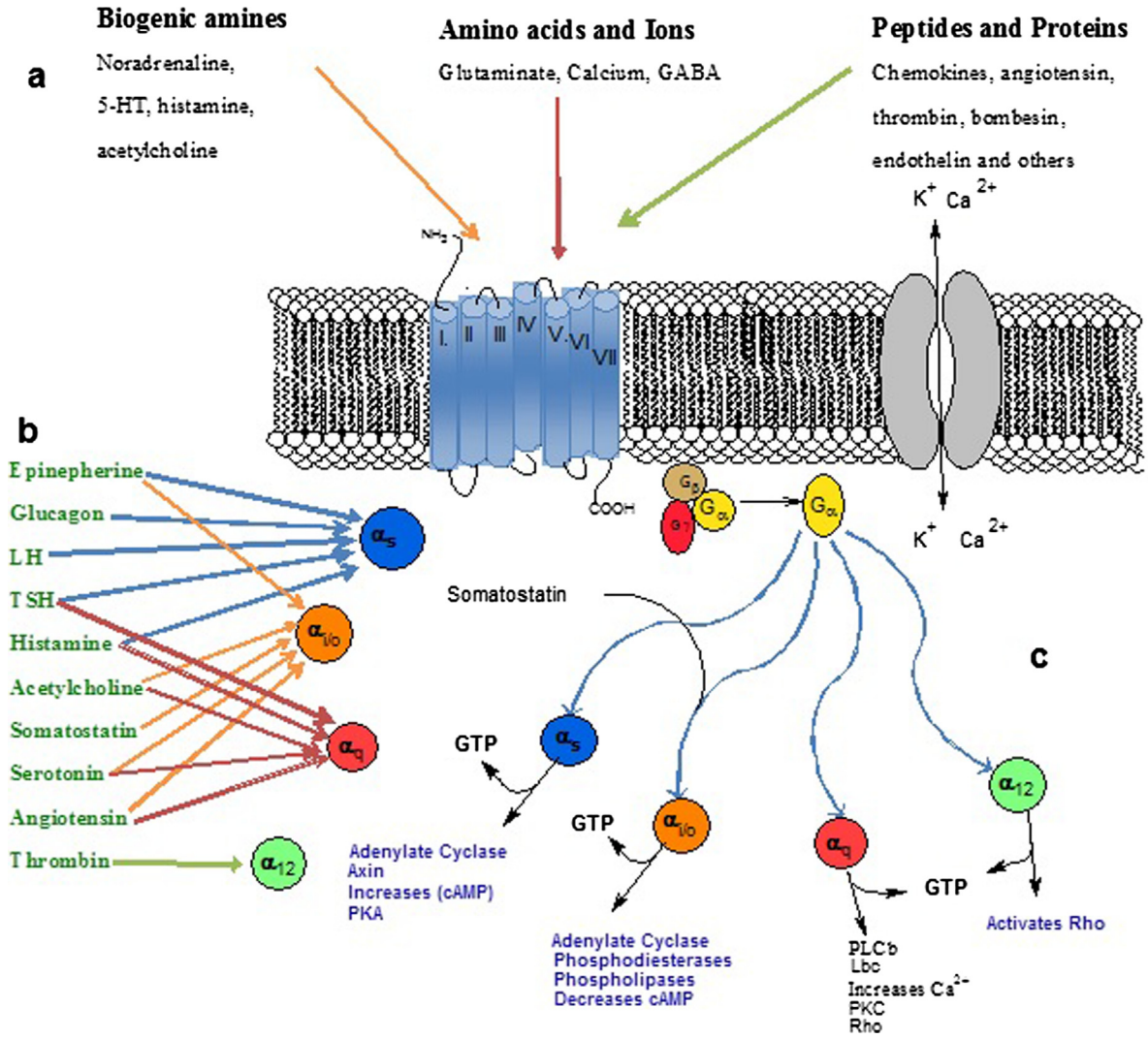

Fig. 1. Schematic drawing of the molecular interactions of G-protein coupled receptors and the actions of small and large molecules on GPCRs, a & b) Regulation of systemic functions by signaling through G protein pathways, c). GPCRs interact with heterotrimeric G proteins (α, β and γ subunits). Agonist binding triggers change in the receptor that catalysis the dissociation of GDP from the subunit followed by GTP-binding to Gα and the dissociation of Gα from Gβγ subunits. Schematic drawing modified from (Neves et al., 2002; Dorsam and Gutkind, 2007).

receptors (Singh et al., 2010; Nimmagadda, 2012), endothelin receptors (Jia et al., 2008; Liakou et al., 2012), TSH receptor (Antonelli et al., 2008; Torosian et al., 2010), LH receptors (Szepeshazi et al., 2007), lysophosphatidic acid receptors (Dorsam and Gutkind, 2007), SSTRs (Msaouel et al., 2009; Luboldt et al., 2010; Oddstig et al., 2011; Sun and Coy, 2011; Treglia et al., 2012), estrogen receptors (Deroo and Korach, 2006), are expressed in cancers (Dorsam and Gutkind, 2007).

2.1. Somatostatin receptors

SSTRs are members of the GPCRs superfamily (Hoyer et al., 1995; Patel, 1999). There are classified to five different subtypes of ($SSTR_{1-5}$), furthermore, $SSTR_2$ have been classified into two different subtypes, $SSTR_{2A}$ and $SSTR_{2B}$ (Taniyama et al., 2005; Rufini et al., 2006). The five receptor subtypes bind with the natural SST and its analogs at low nanomolar concentration and produce defined biological effects in normal and diseased cells (Patel, 1999). The blocking of receptors with antagonist suppresses the interaction of the peptide agonist (Long, 1988). It was reported that SSTRs are expressed in numerous normal and diseased cells, such as the pituitary gland, salivary glands, cerebellum, monocytes, parathyroid, thyroid, activated lymph nodes, vessels, lymphocytes, macrophages, spleen, duodenum, gastric mucosa, ileum, colon, pancreas, blood, bronchial gland, testes, ovary, and myocardium (Abdellatif et al., 2016). $SSTR_{2A}$ expressed in the brain, pituitary gland, islet of Langerhans, stomach, and kidney (Reubi et al., 2001; Taniyama et al., 2005). SSTRs are also expressed in many tumor cells i.e., small cell lung cancer (Virgolini et al., 2002; Rivera et al., 2005; Weiner and Thakur, 2005), neuroendocrine tumors (Appetecchia and Baldelli, 2010), breast cancer, prostate cancer (Sharma and Srikant, 1998), colorectal carcinoma (Reynaert et al., 2004; Ahmad et al., 2013). $SSTR_2$ is expressed in glucagonoma (Zacharias et al., 2005), metastatic lymph nodes (Behr et al., 1997), insulinoma (Wente et al., 2005; Zacharias et al., 2005; Roosterman et al., 2008), normal adrenal gland, pheochromocytoma (Kubota et al., 1994). The majority of human cancer cells (benign or malignant), are generally positive for SSTRs (Patel, 1997). They are characterized by the changing their surface receptors (McMahon et al., 2009). So, targeting of SSTRs, especially $SSTR_2$, would be a promising target for nanoparticulate delivery systems (Nilsson et al., 1998). According to the latest market survey, numerous nanocarrier drug delivery systems were approved by USFDA, EMEA, MHRA and other global controlling organizations. Where as many other nanocarrier drug delivery products are under the preclinical and clinical progress phases (Rahman et al., 2012a, 2012b, 2012c; Aneja et al., 2014; Rahman et al., 2014).

2.2. Somatostatin and its analogs

SST and its analogs are qualified by altering the SST gene expression by stimulating GPCRs through a Gi/o-coupled receptor. Steady-state SSTRs mRNA concentrations are stimulated by various ligands which in turn minimize adenylate cyclase, forms cAMP, and can regulate several subsets of K^+ channels, voltage-dependent Ca^{2+}, guanylate cyclase, phospholipase C, phospholipase A2 and PTP (Kubota et al., 1996; Huang et al., 2006). Stimulation of SSTRs reduces Ca^{2+} concentration and intracellular cAMP levels. The interaction between SSTRs with some Ca^{2+} and K^+ channels is presented in Fig. 2 (Patel, 1999).

SST has various functions in mammals such as it regulates the secretion of growth hormones (Moaeen-Ud-Din and Yang, 2009). Furthermore, it is widely distributed throughout the central nervous system and peripheral tissues and plays different roles in the central nervous system (Bell et al., 1995; Reisine et al., 1995). SST prevents the regulation of numerous endogenous cell functions, such as modulation of neurotransmission, cell motility, cell proliferation and cell secretion (Florio et al., 1994; Lahlou et al., 2004). The amino acids sequence and structure of SST are shown in Figs. 3 and 4. SST soluble in water at a concentration of 6 mg/mL. Phenylalanine (Phe) (6&7), tyrosine (Try 8), and lysine (Lys 9) are essential amino acids for the biological activity of SST (Lamberts et al., 1996). However conjugation or deletion of Phe

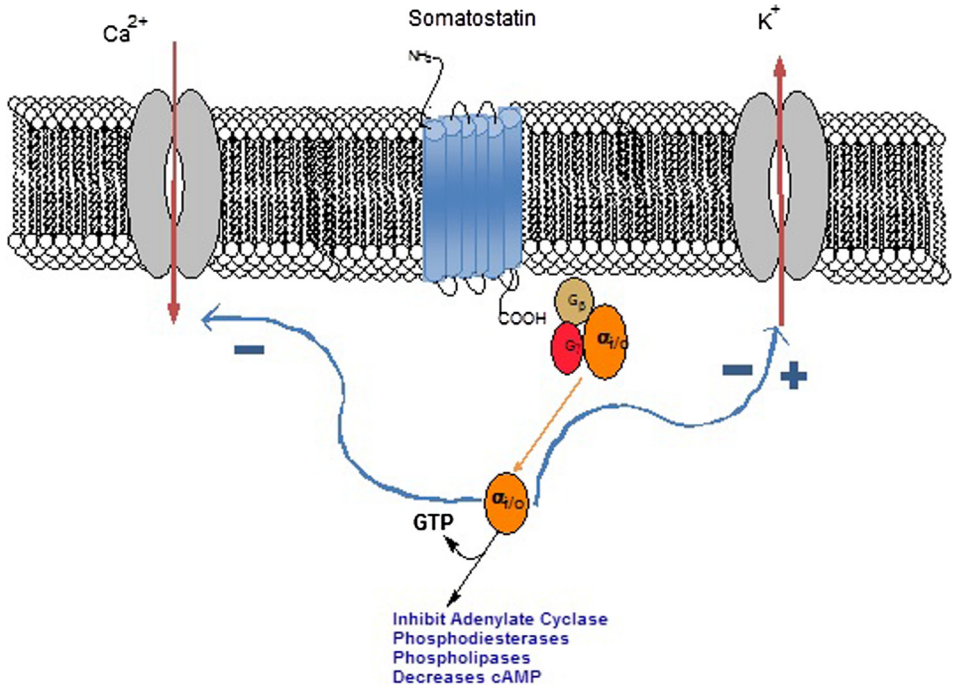

Fig. 2. Schematic drawing of the molecular interaction of SST and its analogs on G protein inhibitory. SST and its analogs are capable of altering the SST gene expression by stimulating GPCRs through a Gi/o-coupled receptor. Schematic drawing modified from (Neves et al., 2002; Dorsam and Gutkind, 2007).

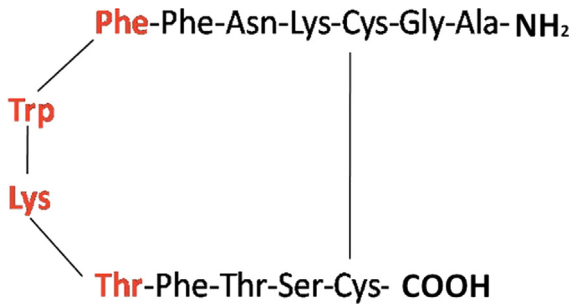

Fig. 3. Amino acids sequence of SST. Phenylalanine, tryptophan, lysine and threonine amino acids are essential for receptor binding.

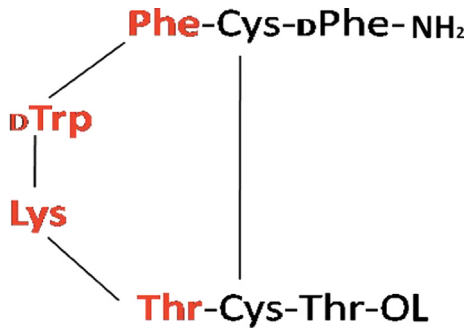

Fig. 5. Amino acids sequence of OCT. Phenylalanine, tryptophan, lysine and threonine amino acids are essential for receptor binding.

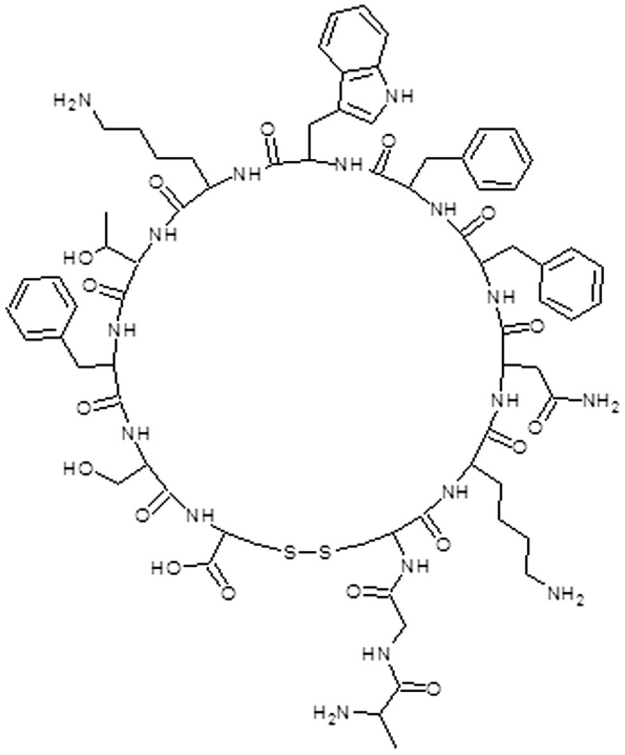

Fig. 4. Chemical structure of somatostatin.

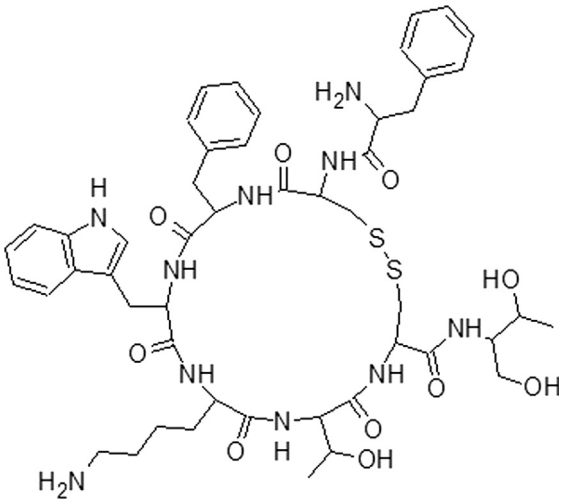

Fig. 6. Chemical structure of somatostatin analogous OCT.

or Lys 4 results in reducing the binding affinity of OCT (Rosenthal et al., 1983; Hirst and Coy, 1984).

2.3. Octreotide (OCT)

OCT is an SST analog and a shorter peptide, it has 8 amino acids. The sequence of amino acids is shown in Figs. 5 and 6. It is soluble in water and 1% acetic acid solution at a concentration of 6 mg/mL. It selectively interacts and targets $SSTR_2$, $SSTR_5$, especially more selective to $SSTR_2$ and less selective to $SSTR_3$. The plasma half-life of OCT is much higher than that of the endogenous SST. OCT had an apparent half-life of 1.7–1.9 h compared to 1–3 min with SST (Watt et al., 2008). Many studies reported that OCT was delivered to cancer cells expressed SSTRs (Dasgupta, 2004). SST analogs have been widely used to target tumor cells expressing SSTRs using radionuclides such as 90-Y or 177-Lu (Nayak et al., 2005). SST analogs were labeled with a radionuclide (i.e. 111-In, 90-Y, 177-Lu, 68-Ga) and injected intravenously, they showed a reduction of tumor growth (Reubi, 2003). Radio-materials labeled SST analogs, i.e. glucose-Tyr^3-octreotide and DOTA-Tyr^3-octreotide were used for the biological imaging and treatment of tumor cells expressed SSTRs (Petrik et al., 2007). Recently, OCT was conjugated to micellar nanoparticles for the targeting of specific tumor cells (Zhang et al., 2011; Zhang et al., 2012).

PEGylation of OCT showed improvement in its biological and physiochemical properties and demonstrate longer circulation time (Na and DeLuca, 2005; Na et al., 2005; Park and Na, 2008). Furthermore, PEGylation of OCT preserved the more stable secondary structure of OCT. OCT is usually PEGylated at its N-terminus, not the Lys side chain because the later is essential for its activity (Na et al., 2003; Na and DeLuca, 2005). The amino acids sequence Phe7-Trp8 -Lys9-Thr1 in SST and in OCT is essential for the biological activity. Replacing the L-Trp 8 by enantiomer (D-Trp 8) might, therefore, increase the biological activity as shown in Figs. 3 and 5. It was also reported that SST analog agonists are more stable *in vivo* when they contain (Phe7-(D)-Trp8-Lys9-Thrl) (Mather et al., 1992; Macke et al., 1993; Li et al., 2009; Huo et al., 2012). Many strategies such citrate reduction method of trichloroauric acid and silver nitrate have been developed to formulate nanoparticles conjugated OCT that can deliver OCT to the specific intracellular site and elicit a distinct biological effect (Abdellatif et al., 2015).

2.4. Challenges in nanomedicine formulation for receptor targeting

Many challenges have faced the nanoparticles formulated to active target specific receptors. SST dose not used for therapeutic purposes since it has a short plasma half-life than three minutes.

This could be due to rapid proteolytic degradation of amino-peptidases and endo-peptidases in plasma. This limits its applications to intravenous administration (Abdellatif et al., 2016). An additional problem is the rebound effects in terms of hormone secretion after cessation of therapy. The ability of SST to treat specific diseases is also limited by potential side effects which are widespread in different organs (Eriksson et al., 1990). Thus, the initial excitement and the great interest in SST soon vanished. A little later, initiatives to synthesize more stable and highly potent SST analogs with prolonged duration of action such as OCT and VAP has been investigated (Lamberts et al., 1996). For that reason, SST itself should be replaced with a highly stable peptide such as OCT. The plasma half-life of OCT is much higher than that of the endogenous SST. The elimination of OCT from plasma had an apparent half-life of 1.7–1.9 h compared to 1–3 min with the natural hormone (Watt et al., 2008). Specific interaction with OCT at the N-terminus which is based on the difference in reactivity of the amino group in the N-terminus (pKa 7.8) and an amino group in the Lys residue (pKa 10.1) at acidic pH (Wong, 1991). It was reported that PEGylation of OCT with ALD-mPEG at low pH produces selectively an N-terminal PEGylated molecule (Kinstler et al., 1996). Additionally, the main disadvantage of AuNPs is that these are not detectable by fluorescence in contrast to Qdots. Although AuNPs have lower toxicity than Qdots, Qdots appear to be far more superior in cell-based investigations (Frangioni, 2003). Qdots could be used as model particles for targeting drug delivery and imaging. Another challenge during formulation of these peptides is that SST has many functional groups which make it difficult to be selectively conjugated, such as the two Lys residues. As well as the terminal amino groups of alanine, asparagine, and tryptophan in SST which also makes SST positively charged at physiological pH as shown in Fig. 4 (Brown et al., 1990; Surujpaul et al., 2008).

3. Cellular uptake of nanoparticles

The intracellular delivery of nanoparticles is affected by numerous factors, such as size, charge, types of attached ligand, the degree of ionization and hydrophobicity (Pang et al., 2002). The intercellular delivery of nanoparticles to cells could be manifested through phagocytosis, macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated endocytosis and clathrin-caveolae-independent endocytosis (Conner and Schmid, 2003; Mayor and Pagano, 2007; Verma et al., 2008). In addition, there are various examples of receptor-mediated endocytosis which figured by a ligand binding to its receptor. AuNPs with different size (14, 50 and 74 nm) and shapes, spheres or rods, were internalized into Hela cells via a receptor-mediated endocytosis (clathrin-dependent) (Chithrani et al., 2006). Other studies showed the internalization of folate conjugated to Folic-PEG-coated-Qdots was confirmed via receptor-mediated internalization into cells expressed folate receptors overexpressed in human nasopharyngeal cells (KB cells) (Song et al., 2009). Furthermore, Qdots coated with octreotide and internalized via SSTRs (Abdellatif, 2015), AuNPs decorated with octreotide for targeting of SSTRs subtype 2 (Abdellatif et al., 2015) and AuNPs coated with SST via electrostatic attraction internalized via somatostatin receptors have been studied (Abdellatif et al., 2016).

The cellular uptake of nanoparticles is controlled by the regular size rules and receptionists within a mammalian cell. The depth of the plasma membrane bilayer is usually 4–10 nm. Also, the average sizes of endocytic vesicles in both phagocytosis and pinocytosis pathways for particle internalization are also presented (Mao et al., 2013). Phagocytes can take up large particles (or nanoparticle aggregates), opsonized nanoparticles, or particles with certain ligand alteration via phagocytosis. The accepted mechanism for nanoparticles internalization in a non-phagocytic mammalian cell

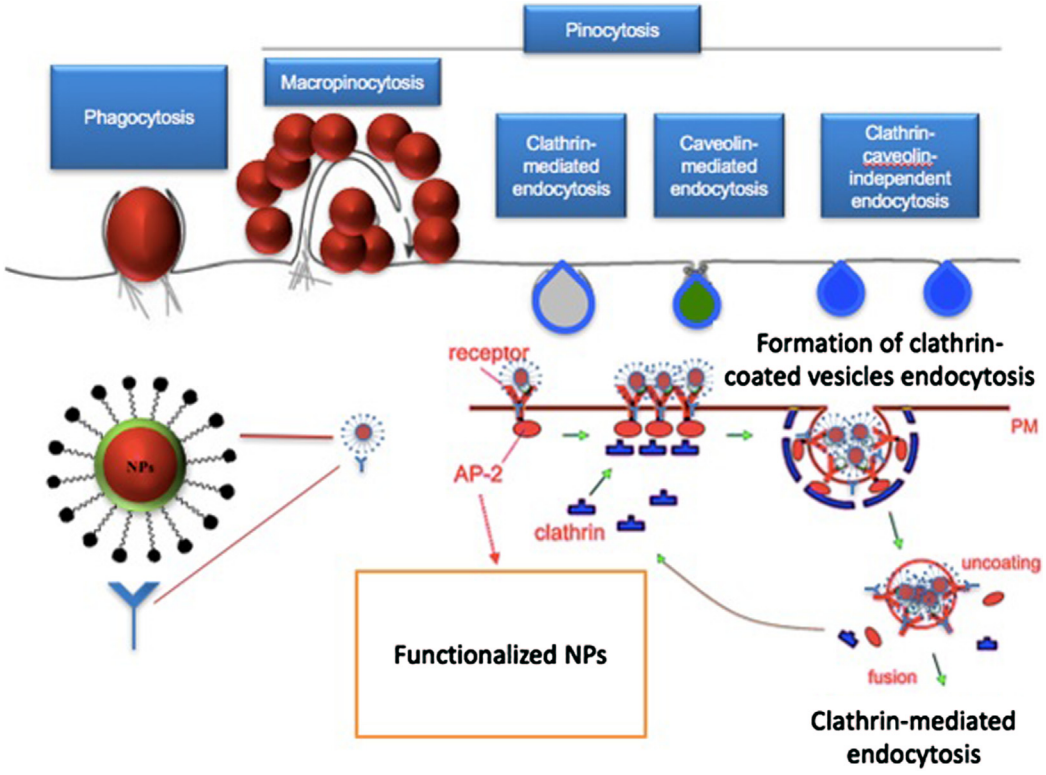

Fig. 7. Schematic drawing for the different types of cellular uptakes of nanoparticles.

is mostly through pinocytosis or direct diffusion. Moreover, many different surface modifications, particles can be taken up via specific (receptor-mediated) endocytosis or nonspecific endocytosis (Mao et al., 2013). Receptor-mediated endocytosis permits an import of extracellular large molecules as shown in Fig. 7 (Delehanty et al., 2009; Kelf et al., 2010). In this process, the plasma membrane is engulfed inwards by specialized membrane microdomains forming either clathrin or caveolin-coated pits (Kelf et al., 2010). However, the specific uptake of nanoparticles via surface receptors can be increased either by direct interactions between coated particles and receptors or via ligands attached to nanoparticles (Osaki et al., 2004; Hild et al., 2008; Kelf et al., 2010).

4. Diagnostic purposes of SST

Qdots are semiconductor nanoparticles, with diameters from 1 to 10 nm. The most common Qdots are made of cadmium selenide coated with zinc sulfide (CdSe/ZnS). Qdots have attracted tremendous interest due to their unique optical properties (Peng and Peng, 2001; Chan et al., 2002). Qdots have a higher molar extinction coefficient compared to organic dyes, making them brighter in photon-limited *in vivo* studies, which means that they can absorb light efficiently (Resch-Genger et al., 2008). Furthermore, Qdots are highly photostable compared to other fluorophores making them more easy to detect by fluorescence microscopy (Xu et al., 2012). Qdots are size-tunable and emit light of different wavelength depending on their size. Larger particles emit lights at the red end of the visible spectrum, while smaller particles emit at a shorter wavelength (Kim et al., 2005). Traditional biomedical dyes are replaced by Qdots due to their unique optical properties like high brightness and narrow emission bands, to be used as simple fluorescence materials in bio-imaging (Hutter and Maysinger, 2011; Vibin et al., 2011), immunoassays (Bustos et al., 2012; Zeng et al., 2012), microarrays, and other applications (Jain, 2003). Furthermore, Qdots are familiar in treatment and imaging of cancer compared to other nanoparticulate materials such as AuNPs, carbon nanotubes, silica nanoparticles, dendrimer, graphene and polymeric nanoparticles (Rahman et al., 2012a, 2012b, 2012c).

These FA-PEG-QD functioned as fluorescent nanoprobes that specifically recognized folate receptors (FRs) overexpressed in human nasopharyngeal cells (KB cells) but not in an FR-deficient lung carcinoma cell line (A549 cells). Using confocal fluorescence microscopy, we demonstrated uptake of FA-PEG-QDs by KB cells but no uptake of folate-free PEG-QDs. The specificity of this receptor-mediated internalization was confirmed by comparing the uptake by KB vs A549 cells. Furthermore, Qdots-loaded micelles accumulated in the tumor tissue in a passive way (Cao et al., 2012). In summary, Qdots are a precious tool for cellular and molecular imaging techniques to diagnose the nature and stage of cancer and other diseases (Dong and Ren, 2012; Pericleous et al., 2012).

5. Conclusions

SSTRs are one of the most important G protein-coupled receptors, which are more abundant in different cells and organs. SSTRs showed a higher expression during cancer development, which is beneficial in tumor diagnosis as well as in treatment. SST analogues are developed to best fit into the SSTRs and to counteract the disadvantages of the parent SST. Moreover, they could be conjugated to metallic nanoparticles and being actively delivered to those cells expressing SSTRs with an enhanced efficacy and stability. A lot of research and investigations should be performed in the field of receptor mediated active targeting, which will be an excellent step forward toward different disorders, especially for cancer treatment.

Conflict of interest

The authors confirm that this manuscript content has no conflicts of interest.

Acknowledgments

The authors are gratefully thankful for the team of central library of Al-Qassim University, Buraydah, Al-Qassim, Kingdom of Saudi Arabia for the informational support.

References

Abdellatif, A.A., 2015. Targeting of somatostatin receptors using quantum dots nanoparticles decorated with octreotide. J. Nanomed. Nanotechnol. S6, 1.
Abdellatif, A.A., El Rasoul, S.A., Osman, S., 2015. Gold nanoparticles decorated with octreotide for somatostatin receptors targeting. Int. J. Pharm. Sci. Res. 7 (1), 14–20.
Abdellatif, A.A., Zayed, G., El-Bakry, A., Zaky, A., Saleem, I.Y., Tawfeek, H.M., 2016a. Novel gold nanoparticles coated with somatostatin as a potential delivery system for targeting somatostatin receptors. Drug Dev. Ind. Pharm. 42 (11), 1782–1791.
Abdellatif, A.A., Zayed, G., El-Bakry, A., Zaky, A., Saleem, I.Y., Tawfeek, H.M., 2016b. Novel gold nanoparticles coated with somatostatin as a potential delivery system for targeting somatostatin receptors. Drug Dev. Ind. Pharm., 1–10
Ahmad, M.Z., Akhter, S., Anwar, M., Kumar, A., Rahman, M., Talasaz, A.H., Ahmad, F. J., 2013. Colorectal cancer targeted Irinotecan-Assam Bora rice starch based microspheres: a mechanistic, pharmacokinetic and biochemical investigation. Drug Dev. Ind. Pharm. 39 (12), 1936–1943.
Ahmad, M.Z., Akhter, S., Jain, G.K., Rahman, M., Pathan, S.A., Ahmad, F.J., Khar, R.K., 2010. Metallic nanoparticles: technology overview & drug delivery applications in oncology. Expert Opin. Drug Deliv. 7 (8), 927–942.
Akhter, S., Ahmad, Z., Singh, A., Ahmad, I., Rahman, M., Anwar, M., Jain, G.K., Ahmad, F.J., Khar, R.K., 2011. Cancer targeted metallic nanoparticle: targeting overview, recent advancement and toxicity concern. Curr. Pharm. Des. 17 (18), 1834–1850.
Alibakhshi, A., Abarghooi Kahaki, F., Ahangarzadeh, S., Yaghoobi, H., Yarian, F., Arezumand, R., Ranjbari, J., Mokhtarzadeh, A., de la Guardia, M., 2017. Targeted cancer therapy through antibody fragments-decorated nanomedicines. J. Control. Release 268, 323–334.
Aneja, P., Rahman, M., Beg, S., Aneja, S., Dhingra, V., Chugh, R., 2014. Cancer targeted magic bullets for effective treatment of cancer. Recent Pat. Antiinfect. Drug Discov. 9 (2), 121–135.
Antonelli, A., Fallahi, P., Tolari, S., Ferrari, S.M., Ferrannini, E., 2008. Thyroid-associated ophthalmopathy and TSH receptor autoantibodies in nonmetastatic thyroid cancer after total thyroidectomy. Am. J. Med. Sci. 336 (3), 288–290.
Appetecchia, M., Baldelli, R., 2010. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumours, current aspects and new perspectives. J. Exp. Clin. Cancer Res. 29, 19.
Auld, D.S., Diller, D., Ho, K.K., 2002. Targeting signal transduction with large combinatorial collections. Drug Discov Today. 7 (24), 1206–1213.
Ballou, B., Ernst, L.A., Waggoner, A.S., 2005. Fluorescence imaging of tumors in vivo. Curr. Med. Chem. 12 (7), 795–805.
Behr, T.M., Gratz, S., Markus, P.M., Dunn, R.M., Hufner, M., Becker, H., Becker, W., 1997. Enhanced bilateral somatostatin receptor expression in mediastinal lymph nodes ("chimney sign") in occult metastatic medullary thyroid cancer: a typical site of tumour manifestation? Eur. J. Nucl. Med. 24 (2), 184–191.
Bell, G.I., Yasuda, K., Kong, H., Law, S.F., Raynor, K., Reisine, T., 1995. Molecular biology of somatostatin receptors (discussion 80–68). Ciba Found Symp., vol. 190, pp. 65–79.
Bhattacharyya, S., Khan, J.A., Curran, G.L., Robertson, J.D., Bhattacharya, R., Mukherjee, P., 2011. Efficient delivery of gold nanoparticles by dual receptor targeting. Adv. Mater. 23 (43), 5034–5038.
Brown, P.J., Lee, A.B., Norman, M.G., Presky, D.H., Schonbrunn, A., 1990. Identification of somatostatin receptors by covalent labeling with a novel photoreactive somatostatin analog. J. Biol. Chem. 265 (29), 17995–18004.
Bustos, A.R.M., Trapiella-Alfonso, L., Encinar, J.R., Costa-Fernandez, J.M., Pereiro, R., Sanz-Medel, A., 2012. Elemental and molecular detection for Quantum Dots-based immunoassays: a critical appraisal. Biosens. Bioelectron. 33 (1), 165–171.
Cao, J., Zhu, H.Y., Deng, D.W., Xue, B., Tang, L.P., Mahounga, D., Qian, Z.Y., Gu, Y.Q., 2012. In vivo NIR imaging with PbS quantum dots entrapped in biodegradable micelles. J. Biomed. Mater. Res. Part A 100A (4), 958–968.
Chan, W.C.W., Maxwell, D.J., Gao, X.H., Bailey, R.E., Han, M.Y., Nie, S.M., 2002. Luminescent quantum dots for multiplexed biological detection and imaging. Curr. Opin. Biotechnol. 13 (1), 40–46.

Chen, H.P., Gai, H.W., Yeung, E.S., 2009. Inhibition of photobleaching and blue shift in quantum dots. Chem. Commun. 13, 1676–1678.
Chen, N., He, Y., Su, Y.Y., Li, X.M., Huang, Q., Wang, H.F., Zhang, X.Z., Tai, R.Z., Fan, C. H., 2012. The cytotoxicity of cadmium-based quantum dots. Biomaterials 33 (5), 1238–1244.
Chithrani, B.D., Ghazani, A.A., Chan, W.C.W., 2006. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. Nano Lett. 6 (4), 662–668.
Conner, S.D., Schmid, S.L., 2003. Regulated portals of entry into the cell. Nature 422 (6927), 37–44.
Dasgupta, P., 2004. Somatostatin analogues: multiple roles in cellular proliferation, neoplasia, and angiogenesis. Pharmacol. Ther. 102 (1), 61–85.
Delehanty, J.B., Mattoussi, H., Medintz, I.L., 2009. Delivering quantum dots into cells: strategies, progress and remaining issues. Anal. Bioanal. Chem. 393 (4), 1091–1105.
Deroo, B.J., Korach, K.S., 2006. Estrogen receptors and human disease. J. Clin. Invest. 116 (3), 561–570.
Dong, C.Q., Ren, J.C., 2012. Water-soluble mercaptoundecanoic acid (MUA)-coated CdTe quantum dots: one-step microwave synthesis, characterization and cancer cell imaging. Luminescence 27 (3), 199–203.
Dorsam, R.T., Gutkind, J.S., 2007. G-protein-coupled receptors and cancer. Nat. Rev. Cancer 7 (2), 79–94.
Elbakry, A., Zaky, A., Liebkl, R., Rachel, R., Goepferich, A., Breunig, M., 2009. Layer-by-layer assembled gold nanoparticles for siRNA delivery. Nano Lett. 9 (5), 2059–2064.
Eriksson, B., Skogseid, B., Lundqvist, G., Wide, L., Wilander, E., Oberg, K., 1990. Medical-treatment and long-term survival in a prospective-study of 84 patients with endocrine pancreatic tumors. Cancer 65 (9), 1883–1890.
Florio, T., Rim, C., Hershberger, R.E., Loda, M., Stork, P.J.S., 1994. The somatostatin receptor Sstr1 is coupled to phosphotyrosine phosphatase-activity in Cho-K1 cells. Mol. Endocrinol. 8 (10), 1289–1297.
Frangioni, J.V., 2003. In vivo near-infrared fluorescence imaging. Curr. Opin. Chem. Biol. 7 (5), 626–634.
Hazell, G.G., Hindmarch, C.C., Pope, G.R., Roper, J.A., Lightman, S.L., Murphy, D., O'Carroll, A.M., Lolait, S.J., 2012. G protein-coupled receptors in the hypothalamic paraventricular and supraoptic nuclei–serpentine gateways to neuroendocrine homeostasis. Front. Neuroendocrinol. 33 (1), 45–66.
Hild, W.A., Breunig, M., Goepferich, A., 2008. Quantum dots - nano-sized probes for the exploration of cellular and intracellular targeting. Eur. J. Pharm. Biopharm. 68 (2), 153–168.
Hirst, B.H., Coy, D.H., 1984. Structure-activity studies with somatostatin: role of lysine in positions 4 and 9 for gastric activity. Regul. Pept. 8 (4), 267–271.
Hoyer, D., Bell, G.I., Berelowitz, M., Epelbaum, J., Feniuk, W., Humphrey, P.P., O'Carroll, A.M., Patel, Y.C., Schonbrunn, A., Taylor, J.E., et al., 1995. Classification and nomenclature of somatostatin receptors. Trends Pharmacol. Sci. 16 (3), 86–88.
Huang, J., Mahavadi, S., Sriwai, W., Hu, W., Murthy, K.S., 2006. Gi-coupled receptors mediate phosphorylation of CPI-17 and MLC20 via preferential activation of the PI3K/ILK pathway. Biochem. J. 396 (1), 193–200.
Huo, M., Zou, A., Yao, C., Zhang, Y., Zhou, J., Wang, J., Zhu, Q., Li, J., Zhang, Q., 2012. Somatostatin receptor-mediated tumor-targeting drug delivery using octreotide-PEG-deoxycholic acid conjugate-modified N-deoxycholic acid-O, N-hydroxyethylation chitosan micelles. Biomaterials 33 (27), 6393–6407.
Hutter, E., Maysinger, D., 2011. Gold nanoparticles and quantum dots for bioimaging. Microsc. Res. Tech. 74 (7), 592–604.
Jain, K.K., 2003. Nanodiagnostics: application of nanotechnology in molecular diagnostics. Expert Rev. Mol. Diagnostics 3 (2), 153–161.
Jia, R.P., Jiang, Y.F., Xu, L.W., Wang, S.K., Wang, Z.Z., Li, W.C., He, B.S., 2008. Epidermal growth factor up-regulates the mRNA expression of endothelin-1 and its receptors in prostate cancer PC-3 cell lines. Zhonghua Nan Ke Xue 14 (1), 15–19.
Jiang, Y., Ma, W., Wan, Y., Kozasa, T., Hattori, S., Huang, X.Y., 1998. The G protein G alpha12 stimulates Bruton's tyrosine kinase and a rasGAP through a conserved PH/BM domain. Nature 395 (6704), 808–813.
Kang, B., Mackey, M.A., El-Sayed, M.A., 2010. Nuclear targeting of gold nanoparticles in cancer cells induces DNA damage, causing cytokinesis arrest and apoptosis. J. Am. Chem. Soc. 132 (5), 1517–1519.
Kelf, T.A., Sreenivasan, V.K.A., Sun, J., Kim, E.J., Goldys, E.M., Zvyagin, A.V., 2010. Non-specific cellular uptake of surface-functionalized quantum dots. Nanotechnology. 21, 28.
Kim, S.W., Zimmer, J.P., Ohnishi, S., Tracy, J.B., Frangioni, J.V., Bawendi, M.G., 2005. Engineering InAs(x)P(1−x)/InP/ZnSe III-V alloyed core/shell quantum dots for the near-infrared. J. Am. Chem. Soc. 127 (30), 10526–10532.
Kinstler, O.B., Brems, D.N., Lauren, S.L., Paige, A.G., Hamburger, J.B., Treuheit, M.J., 1996. Characterization and stability of N-terminally PEGylated rhG-CSF. Pharm. Res. 13 (7), 996–1002.
Kobilka, B.K., 2007. G protein coupled receptor structure and activation. BBA 1768 (4), 794–807.
Kubota, A., Yamada, Y., Kagimoto, S., Seino, S., Seino, Y., 1996. Effector coupling of somatostatin receptor subtypes on human endocrine tumors. Metabolism 45 (8 Suppl. 1), 42–45.
Kubota, A., Yamada, Y., Kagimoto, S., Shimatsu, A., Imamura, M., Tsuda, K., Imura, H., Seino, S., Seino, Y., 1994. Identification of somatostatin receptor subtypes and an implication for the efficacy of somatostatin analogue SMS 201–995 in treatment of human endocrine tumors. J. Clin. Invest. 93 (3), 1321–1325.
Lahlou, H., Guillermet, J., Hortala, M., Vernejoul, F., Pyronnet, S., Bousquet, C., Susini, C., 2004. Molecular signaling of somatostatin receptors. Ann. N. Y. Acad. Sci. 1014, 121–131.
Lamberts, S.W., van der Lely, A.J., de Herder, W.W., Hofland, L.J., 1996. Octreotide. N. Engl. J. Med. 334 (4), 246–254.
Li, X., Du, X., Huo, T., Liu, X., Zhang, S., Yuan, F., 2009. Specific targeting of breast tumor by octreotide-conjugated ultrasmall superparamagnetic iron oxide particles using a clinical 3.0-Tesla magnetic resonance scanner. Acta Radiol. 50 (6), 583–594.
Liakou, P., Tepetes, K., Germenis, A., Leventaki, V., Atsaves, V., Patsouris, E., Roidis, N., Hatzitheophilou, K., Rassidakis, G.Z., 2012. Expression patterns of endothelin-1 and its receptors in colorectal cancer. J. Surg. Oncol. 105 (7), 643–649.
Long, J.B., 1988. Spinal subarachnoid injection of somatostatin causes neurological deficits and neuronal injury in rats. Eur. J. Pharmacol. 149 (3), 287–296.
Luboldt, W., Zophel, K., Wunderlich, G., Abramyuk, A., Luboldt, H.J., Kotzerke, J., 2010. Visualization of somatostatin receptors in prostate cancer and its bone metastases with Ga-68-DOTATOC PET/CT. Mol. Imaging Biol. 12 (1), 78–84.
Macke, H.R., Smith-Jones, P., Maina, T., Stolz, B., Albert, R., Bruns, C., Reist, H., 1993. New octreotide derivatives for in vivo targeting of somatostatin receptor-positive tumors for single photon emission computed tomography (SPECT) and positron emission tomography (PET). Horm. Metab. Res. Suppl. 27, 12–17.
Mao, Z., Zhou, X., Gao, C., 2013. Influence of structure and properties of colloidal biomaterials on cellular uptake and cell functions. Biomater. Sci. 1, 9.
Mather, S.J., Ur, E., Bomanji, J., Ellison, D., Besser, G.M., Britton, K.E., 1992. Radiolabeled octreotide. What lessons for antibody-mediated targeting? Cell Biophys. 21 (1–3), 93–107.
Mayor, S., Pagano, R.E., 2007. Pathways of clathrin-independent endocytosis. Nat. Rev. Mol. Cell Biol. 8 (8), 603–612.
McMahon, K.A., Zajicek, H., Li, W.P., Peyton, M.J., Minna, J.D., Hernandez, V.J., Luby-Phelps, K., Anderson, R.G.W., 2009. SRBC/cavin-3 is a caveolin adapter protein that regulates caveolae function. EMBO J. 28 (8), 1001–1015.
Moaeen-Ud-Din, M., Yang, L.G., 2009. Evolutionary history of the somatostatin and somatostatin receptors. Journal of Genetics. 88 (1), 41–53.
Msaouel, P., Galanis, E., Koutsilieris, M., 2009. Somatostatin and somatostatin receptors: implications for neoplastic growth and cancer biology. Expert Opin. Invest. Drugs 18 (9), 1297–1316.
Na, D.H., DeLuca, P.P., 2005. PEGylation of octreotide: I. Separation of positional isomers and stability against acylation by poly(D, L-lactide-co-glycolide). Pharm. Res. 22 (5), 736–742.
Na, D.H., Lee, K.C., DeLuca, P.P., 2005. PEGylation of octreotide: II. Effect of N-terminal mono-PEGylation on biological activity and pharmacokinetics. Pharm. Res. 22 (5), 743–749.
Na, D.H., Murty, S.B., Lee, K.C., Thanoo, B.C., DeLuca, P.P., 2003. Preparation and stability of poly(ethylene glycol) (PEG)ylated octreotide for application to microsphere delivery. AAPS PharmSciTech. 4 (4), E72.
Nayak, T., Norenberg, J., Anderson, T., Atcher, R., 2005. A comparison of high- versus low-linear energy transfer somatostatin receptor targeted radionuclide therapy in vitro. Cancer Biother. Radiopharm. 20 (1), 52–57.
Neves, S.R., Ram, P.T., Iyengar, R., 2002. G protein pathways. Science 296 (5573), 1636–1639.
Nilsson, O., Kolby, L., Wangberg, B., Wigander, A., Billig, H., William-Olsson, L., Fjalling, M., Forssell-Aronsson, E., Ahlman, H., 1998. Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy and response to octreotide treatment in patients with carcinoid tumours. Br. J. Cancer 77 (4), 632–637.
Nimmagadda, S., 2012. Differential expression of chemokine receptors and their roles in cancer imaging. Front. Oncol. 2, 46.
Oddstig, J., Bernhardt, P., Nilsson, O., Ahlman, H., Forssell-Aronsson, E., 2011. Radiation induces up-regulation of somatostatin receptors 1, 2, and 5 in small cell lung cancer in vitro also at low absorbed doses. Cancer Biother. Radiopharm. 26 (6), 759–765.
Oliveira, L., Paiva, A.C.M., Vriend, G., 1993. A common motif in G-protein-coupled 7 transmembrane helix receptors. J. Comput. Aided Mol. Des. 7 (6), 649–658.
Osaki, F., Kanamori, T., Sando, S., Sera, T., Aoyama, Y., 2004. A quantum dot conjugated sugar ball and its cellular uptake on the size effects of endocytosis in the subviral region. J. Am. Chem. Soc. 126 (21), 6520–6521.
Pang, S.W., Park, H.Y., Jang, Y.S., Kim, W.S., Kim, J.H., 2002. Effects of charge density and particle size of poly(styrene/(dimethylamino)ethyl methacrylate) nanoparticle for gene delivery in 293 cells. Colloids Surf. B-Biointerf. 26 (3), 213–222.
Park, E.J., Na, D.H., 2008. Optimization of octreotide PEGylation by monitoring with fast reversed-phase high-performance liquid chromatography. Anal. Biochem. 380 (1), 140–142.
Patel, Y.C., 1997. Molecular pharmacology of somatostatin receptor subtypes. J. Endocrinol. Invest. 20 (6), 348–367.
Patel, Y.C., 1999. Somatostatin and its receptor family. Front. Neuroendocrinol. 20 (3), 157–198.
Peng, Z.A., Peng, X.G., 2001. Formation of high-quality CdTe, CdSe, and CdS nanocrystals using CdO as precursor. J. Am. Chem. Soc. 123 (1), 183–184.
Pericleous, P., Gazouli, M., Lyberopoulou, A., Rizos, S., Nikiteas, N., Efstathopoulos, E. P., 2012. Quantum dots hold promise for early cancer imaging and detection. Int. J. Cancer 131 (3), 519–528.
Petrik, M., Laznickova, A., Laznicek, M., Zalutsky, M.R., 2007. Radiolabelling of glucose-Tyr3-octreotate with 125I and analysis of its metabolism in rats:

comparison with radiolabelled DOTA-Tyr3-octreotate. Anticancer Res. 27 (6B), 3941–3946.
Pierce, K.L., Premont, R.T., Lefkowitz, R.J., 2002. Seven-transmembrane receptors. Nat. Rev. Mol. Cell Biol. 3 (9), 639–650.
Prades, R., Guerrero, S., Araya, E., Molina, C., Salas, E., Zurita, E., Selva, J., Egea, G., Lopez-Iglesias, C., Teixido, M., Kogan, M.J., Giralt, E., 2012. Delivery of gold nanoparticles to the brain by conjugation with a peptide that recognizes the transferrin receptor. Biomaterials 33 (29), 7194–7205.
Rahman, M., Ahmad, M.Z., Kazmi, I., Akhter, S., Afzal, M., Gupta, G., Jalees Ahmed, F., Anwar, F., 2012a. Advancement in multifunctional nanoparticles for the effective treatment of cancer. Expert Opin. Drug Deliv. 9 (4), 367–381.
Rahman, M., Ahmad, M.Z., Kazmi, I., Akhter, S., Kumar, Y., Ahmad, F.J., Anwar, F., 2012b. Novel approach for the treatment of cancer: theranostic nanomedicine. Pharmacologia 3 (9), 371–376.
Rahman, M., Beg, S., Ahmed, A., Swain, S., 2014. Emergence of functionalized nanomedicines in cancer chemotherapy: recent advancements, current challenges and toxicity considerations. Recent Pat. Nanomed. 3 (2), 128–139.
Rahman, M., Zaki Ahmad, M., Kazmi, I., Akhter, S., Afzal, M., Gupta, G., Ranjan Sinha, V., 2012c. Emergence of nanomedicine as cancer targeted magic bullets: recent development and need to address the toxicity apprehension. Curr. Drug Discov. Technol. 9 (4), 319–329.
Ramzy, L., Nasr, M., Metwally, A.A., Awad, G.A.S., 2017. Cancer nanotheranostics: a review of the role of conjugated ligands for overexpressed receptors. Eur. J. Pharm. Sci. 104, 273–292.
Reisine, T., Woulfe, D., Raynor, K., Kong, H., Heerding, J., Hines, J., Tallent, M., Law, S., 1995. Interaction of somatostatin receptors with G proteins and cellular effector systems. Ciba Found Symp., vol. 190, pp. 160–167 (discussion 167–170).
Resch-Genger, U., Grabolle, M., Cavaliere-Jaricot, S., Nitschke, R., Nann, T., 2008. Quantum dots versus organic dyes as fluorescent labels. Nat. Methods 5 (9), 763–775.
Reubi, J.C., 2003. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr. Rev. 24 (4), 389–427.
Reubi, J.C., Waser, B., Schaer, J.C., Laissue, J.A., 2001. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur. J. Nucl. Med. 28 (7), 836–846.
Reynaert, H., Rombouts, K., Vandermonde, A., Urbain, D., Kumar, U., Bioulac-Sage, P., Pinzani, M., Rosenbaum, J., Geerts, A., 2004. Expression of somatostatin receptors in normal and cirrhotic human liver and in hepatocellular carcinoma. Gut 53 (8), 1180–1189.
Rivera, J.A., Alturaihi, H., Kumar, U., 2005. Differential regulation of somatostatin receptors 1 and 2 mRNA and protein expression by tamoxifen and estradiol in breast cancer cells. J. Carcinog. 4 (1), 10.
Roosterman, D., Brune, N.E.I., Kreuzer, O.J., Feld, M., Pauser, S., Zarse, K., Steinhoff, M., Meyerhof, W., 2008. Intracellular degradation of somatostatin-14 following somatostatin-receptor 3-mediated endocytosis in rat insulinoma cells. FEBS J. 275 (19), 4728–4739.
Rosenthal, L.E., Yamashiro, D.J., Rivier, J., Vale, W., Brown, M., Dharmsathaphorn, K., 1983. Structure-activity relationships of somatostatin analogs in the rabbit ileum and the rat colon. J. Clin. Invest. 71 (4), 840–849.
Rufini, V., Calcagni, M.L., Baum, R.P., 2006. Imaging of neuroendocrine tumors. Semin. Nucl. Med. 36 (3), 228–247.
Sonia, S., Ruckmani, K., Sivakumar, M., 2017. Antimicrobial and antioxidant potentials of biosynthesized colloidal zinc oxide nanoparticles for a fortified cold cream formulation: a potent nanocosmeceutical application. Mater. Sci. Eng. C Mater. Biol. Appl. 79, 581–589.
Sharma, K., Srikant, C.B., 1998. Induction of wild-type p53, Bax, and acidic endonuclease during somatostatin-signaled apoptosis in MCF-7 human breast cancer cells. Int. J. Cancer 76 (2), 259–266.
Shi, C.S., Lee, S.B., Sinnarajah, S., Dessauer, C.W., Rhee, S.G., Kehrl, J.H., 2001. Regulator of G-protein signaling 3 (RGS3) inhibits Gbeta1gamma 2-induced inositol phosphate production, mitogen-activated protein kinase activation, and Akt activation. J. Biol. Chem. 276 (26), 24293–24300.
Singh, R.K., Sudhakar, A., Lokeshwar, B.L., 2010. Role of chemokines and chemokine receptors in prostate cancer development and progression. J. Cancer Sci. Ther. 2 (4), 89–94.
Song, E.Q., Zhang, Z.L., Luo, Q.Y., Lu, W., Shi, Y.B., Pang, D.W., 2009. Tumor cell targeting using folate-conjugated fluorescent quantum dots and receptor-mediated endocytosis. Clin. Chem. 55 (5), 955–963.
Sun, L.C., Coy, D.H., 2011. Somatostatin receptor-targeted anti-cancer therapy. Curr. Drug Deliv. 8 (1), 2–10.
Surujpaul, P.P., Gutierrez-Wing, C., Ocampo-Garcia, B., Ramirez Fde, M., Arteaga de Murphy, C., Pedraza-Lopez, M., Camacho-Lopez, M.A., Ferro-Flores, G., 2008. Gold nanoparticles conjugated to [Tyr3]octreotide peptide. Biophys. Chem. 138 (3), 83–90.
Szepeshazi, K., Schally, A.V., Halmos, G., 2007. LH-RH receptors in human colorectal cancers: unexpected molecular targets for experimental therapy. Int. J. Oncol. 30 (6), 1485–1492.
Taniyama, Y., Suzuki, T., Mikami, Y., Moriya, T., Satomi, S., Sasano, H., 2005. Systemic distribution of somatostatin receptor subtypes in human: an immunohistochemical study. Endocr. J. 52 (5), 605–611.
Tawfeek, H.M., 2013. Evaluation of PEG and mPEG-co-(PGA-co-PDL) microparticles loaded with sodium diclofenac. Saudi Pharm. J. 21 (4), 387–397.
Torosian, L., Manrique, G., Alvarez, B., Lago, G., Roca, R., Belzarena, C., 2010. Blood thyroglobulin and TSH receptor mRNA detection by RT-PCR in the follow-up of differentiated thyroid cancer patients. Rev. Esp. Med. Nucl. 29 (3), 109–113.
Treglia, G., Rindi, G., Rufini, V., 2012. Expression of somatostatin receptors may guide the use of somatostatin receptor imaging and therapy in differentiated thyroid cancer. Hormones (Athens) 11 (3), 230–232.
Verma, A., Uzun, O., Hu, Y.H., Hu, Y., Han, H.S., Watson, N., Chen, S.L., Irvine, D.J., Stellacci, F., 2008. Surface-structure-regulated cell-membrane penetration by monolayer-protected nanoparticles. Nat. Mater. 7 (7), 588–595.
Vibin, M., Vinayakan, R., John, A., Raji, V., Rejiya, C.S., Vinesh, N.S., Abraham, A., 2011. Cytotoxicity and fluorescence studies of silica-coated CdSe quantum dots for bioimaging applications. J. Nanopart. Res. 13 (6), 2587–2596.
Virgolini, I., Traub, T., Novotny, C., Leimer, M., Fuger, B., Li, S.R., Patri, P., Pangerl, T., Angelberger, P., Raderer, M., Burggasser, G., Andreae, F., Kurtaran, A., Dudczak, R., 2002. Experience with indium-111 and yttrium-90-labeled somatostatin analogs. Curr. Pharm. Des. 8 (20), 1781–1807.
Watt, H.L., Kharmate, G., Kumar, U., 2008. Biology of somatostatin in breast cancer. Mol. Cell. Endocrinol. 286 (1–2), 251–261.
Weiner, R.E., Thakur, M.L., 2005. Radiolabeled peptides in oncology: role in diagnosis and treatment. BioDrugs 19 (3), 145–163.
Wente, W., Efanov, A.M., Treinies, I., Zitzer, H., Gromada, J., Richter, D., Kreienkamp, H.J., 2005. The PDZ/coiled-coil domain containing protein PIST modulates insulin secretion in MIN6 insulinoma cells by interacting with somatostatin receptor subtype 5. FEBS Lett. 579 (28), 6305–6310.
Wettschureck, N., Offermanns, S., 2005. Mammalian G proteins and their cell type specific functions. Physiol. Rev. 85 (4), 1159–1204.
Wong, S.S., 1991. Chemistry of Protein Conjugation and Cross-linking. CRC Press, Boca Raton.
Xu, J., Ruchala, P., Ebenstein, Y., Li, J.J., Weiss, S., 2012. Stable, compact, bright biofunctional quantum dots with improved peptide coating. J. Phys. Chem. B. 116 (36), 11370–11378.
Ye, L., Yong, K.T., Liu, L.W., Roy, I., Hu, R., Zhu, J., Cai, H.X., Law, W.C., Liu, J.W., Wang, K., Liu, J., Liu, Y.Q., Hu, Y.Z., Zhang, X.H., Swihart, M.T., Prasad, P.N., 2012. A pilot study in non-human primates shows no adverse response to intravenous injection of quantum dots. Nat. Nanotechnol. 7 (7), 453–458.
Zacharias, S., Singh, V., Mergler, S., Grotzinger, C., Wiedenmann, B., Strowski, M.Z., 2005. Insulinoma (Ins-1) and glucagonoma (InR1-G9) cells express pharmacologically distinctive somatostatin receptor subtypes. Eur. J. Endocrinol. 152.
Zeng, Q.H., Zhang, Y.L., Liu, X.M., Tu, L.P., Kong, X.G., Zhang, H., 2012. Multiple homogeneous immunoassays based on a quantum dots-gold nanorods FRET nanoplatform. Chem. Commun. 48 (12), 1781–1783.
Zhang, T.T., Stilwell, J.L., Gerion, D., Ding, L.H., Elboudwarej, O., Cooke, P.A., Gray, J. W., Alivisatos, A.P., Chen, F.F., 2006. Cellular effect of high doses of silica-coated quantum dot profiled with high throughput gene expression analysis and high content cellomics measurements. Nano Lett. 6 (4), 800–808.
Zhang, Y., Zhang, H., Wang, X.Q., Wang, J.C., Zhang, X., Zhang, Q., 2012. The eradication of breast cancer and cancer stem cells using octreotide modified paclitaxel active targeting micelles and salinomycin passive targeting micelles. Biomaterials 33 (2), 679–691.
Zhang, Y.A., Wang, X.Q., Wang, J.C., Zhang, X.A., Zhang, Q.A., 2011. Octreotide-Modified Polymeric Micelles as Potential Carriers for Targeted Docetaxel Delivery to Somatostatin Receptor Overexpressing Tumor Cells. Pharm. Res. 28 (5), 1167–1178.