Research Article

Somatostatin Analogs, How Biomarkers in the Diagnostic and Treatment for Cancer and Others Damages

Eva María Molina Trinidad*, Andrés Salas Casas
Circuito Ex-Hacienda La Concepción, Km 1.5. C.P. 42160. San Agustín Tlaxiaca, Hidalgo. México.
***Corresponding author's E-mail:** mariaeva_molina@yahoo.com.mx

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ABSTRACT

Biomolecules targets with radioactive nuclides and metallic nanoparticles currently are very use in practices nuclear medicine and general medicine for diagnostic and therapeutic diseases. The investigations new drugs to need go in the direction to obtain personality doses with minimum amount of drug to utilize for not induce adverse effects. Currently is very important know respect new techniques what strengthen the use adequate of minimum concentration at level pharmaceutics in organic fluids and that enable to towards the drugs in specific site for example in Diana cell or target cells. In this text, write the relevant information respect to use of radioactive nuclides and the synthetic peptides somatostatin derivates. Furthermore includes to functionalization of gold nanoparticles.

Keywords: Biomarkers, cancer, radionuclides, somatostatin, nanoparticles.

INTRODUCTION

A biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes [1, 2] or pharmacologic responses to a therapeutic intervention or a biomarker can be a traceable substance that is introduced into an organism as a means to examine organ function or other aspects of health.

Since discovery of radioactivity will meet one variety applications in several fields of science. In the area of Pharmacy is very relevant to knowledge of Radiopharmacy for to use of radioactive compounds or nuclides radioactive that using in Nuclear Medicine. In the practice medic, their use radioactive nuclides label with organic molecules for formed organic complex.

The experience based to use of nuclides radioactive for use in diagnostic and therapeutic of diseases relate with renal, heart and cancer diseases is very studied. For use compounds labeled with peptides and others organic molecules as ^{99}Tc-MAG$_3$, ^{99}Tc-glucarate, the ^{188}Re-lanreotide, Au-BzMAG$_3$ are extensively studied and currently the application of new drugs in the development of new compounds for use in the nanotechnology for example with peptides labeled with gold, cupper and silver metal nanoparticles and others polymeric substrates.

Currently the major experiences have priority in discovery news compound capable of minimize to symptoms and prevent diseases as renal diseases, cardiac diseases and cancer. The peptides synthetic analogue somatostatin is good candidates for labeling with nuclides radioactive and metallic nanoparticles as gold nanoparticles: GNPs.

RADIOACTIVE NUCLIDES

The radionuclide ^{99m}Tc is more utilize in Radiopharmacy Science for short cost, the physical characteristics, and the biodisponibility in the organism for use diagnostic.

The methods of labeling with ^{99m}Tc can be to divide in two groups, the method directs and the methods indirect. In this first the ^{99m}Tc occur reduction reactions when the nuclide it has reduced and formed one complex with SH group's endogens to obtain for partial reduction of protein. In the indirect methods the ^{99m}Tc to reduce previous a join and the hexogen agent, pre-conjugation or the conjugation occurs later labeling with radioactive nuclide.

The advantage more important in the indirect methods labeling it's applicability in the very biomolecules so antibodies mono and polyclonal, peptides, oligonucleotides and the stability of compounds labeling *in vivo* or *in situ*.

The radioactive nuclide more use is the ^{99m}Tc, his utilized in diagnostic and therapeutic system. The advantages are the emission gamma energy and biological half-life is ≅ 6.0 h; it is obtaining radioactive decay ^{99}Mo (half-life 2.75 days). One 80% of nuclides used in diagnostic your composition are ^{99m}Tc.

^{99m}Technetium is use as a radioactive tracer that medical equipment can detect in the body. It is well suited to the role because it emits readily detectable 140 keV gamma rays (these are about the same wavelength emitted by conventional X-ray diagnostic equipment), and its half-life for gamma emission is 6.0058 hours (meaning that 93.7% of it decays to ^{99}Tc in 24 hours). The "short" half-life of the isotope (in terms of human-activity and metabolism) allows for scanning procedures, which collect data rapidly, but keep total patient radiation exposure low.

As in all gamma decay reactions, a meta-stable nuclear isomer does not change into another element (transmute) upon its isomeric transition or "decay"; thus ^{99m}Tc decays to technetium-99 (^{99}Tc, the ground state of the same isotope) and remains technetium. The decay of technetium-99m is accomplished by rearrangement of nucleons in its nucleus, a process that allows energy emitted as a gamma ray.

Technetium-99m or ^{99m}Tc ("m" indicates that this is a meta-stable nuclear isomer) is use in radioactive nuclide medical tests: for example, as a radioactive tracer that medical equipment can detect in the human body [3]. It is well suited to the role because it emits readily detectable 140 keV gamma rays, and its half-life is only about six hours. It dissolves in aqua regia, nitric acid, and concentrated sulfuric acid, but it is not soluble in hydrochloric acid of any strength [4]. Klaus Schwochau's book *Technetium* lists 31 radiopharmaceuticals. Obtained with ^{99m}Tc for imaging and functional studies of the brain, myocardium, thyroid, lungs, liver, gallbladder, kidney, skeleton, blood, and tumors [5].

Technetium-99m is use in 20 million diagnostic nuclear medical procedures every year. Approximately 85 percent of diagnostic imaging procedures in nuclear medicine use this nuclide. Depending on the type of nuclear medicine procedure, the ^{99m}Tc is tagged (or bound to) a pharmaceutical that transports the Tc-99m to its required location. For example, when ^{99m}Tc is chemically bound to exametazime, the drug is able to cross the blood-brain barrier and flow through the vessels in the brain for cerebral blood flow imaging. This combination is also use for labeling white blood cells to visualize sites of infection. ^{99m}Tc Sestamibi is use for myocardial perfusion imaging, which shows how well the blood flows through the heart. Imaging to measure renal function is doing by attaching ^{99m}Tc to **M**ercapto **a**cetyl *tri***g**lycine (informal acronym: MAG_3); this procedure is known as a MAG_3 scan.

In general endogenous compounds (drugs) show distribution kinetics within the body. This distribution is not apparent from the plasma concentration measurements on the endogenous compounds under the usual steady-state conditions, but becomes so when a nuclide tracer dose of the compound, in a nuclide labeled form, is administered. In the analysis of the tracer data, two major assumptions are often made. First, the disposition of the nuclide is identical so that of the endogenous compound. Second, both input (formation) and elimination occur in the initial dilution volume.

The studies of transit of radionuclide in the body explained for mathematics models, that are includes mathematics functions.

1.1. Mean Residence Time

In this case when the two assumptions above hold, then a nuclide, on average, resides in the body the same length of time as a new endogenous molecule. This time is called the *mean residence time* (MRT); it is identical to the turnover time (t_t) of the endogenous compound. One method uses the area-under-the-first moment versus time curve, $\int_0^\infty t \cdot C_v^* \cdot dt$, denoted as AUMC, and AUC [5].

$$MRT = \frac{\int_0^\infty [(Ae]_\infty^* - Ae^*)dt}{Ae_\infty^*}$$

Where Ae_∞^* and Ae^* are the cumulative amounts of labeled tracer excreted to time infinity and to any specified time, respectively.

1.2. Distribution volume in steady state

Remembering that *MRT* (turnover time) is the ratio of pool size to turnover rate is:

$$MRT = \frac{A_{ss}}{R_t} = \frac{V_{ss} \cdot C_{ss}^*}{CL \cdot C_{ss}^*}$$

Thus, one arrives at the conceptually important relationship

$$MRT = V_{ss}/CL$$

The value of V_{ss} can be estimated using the plasma nuclide concentration, realizing that $CL = Dose^*/AUC^*$ and combining with $MRT = \frac{AUMC^*}{AUC^*}$, to give

$$V_{ss} = \frac{Dose^*}{AUC^*} \cdot \frac{AUMC^*}{AUC^*}$$

This terminology have link in studies of liberation drugs and others endogenous compounds. Studies to realize with ^{99m}Tc-MAG_3 molecule in pharmacokinetics for Renal Clearance and Dosimetry treatment it is determine radio pharmacokinetic parameters. The Technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) is a radiopharmaceutical for tubular function and can be prepared with 99m-technetium and the ligand Bz-MAG_3. Radio pharmacokinetic parameters have been found for the healthy adult Mexican population with ^{99m}Tc-MAG_3, prepared with the nationally produced or imported Bz-MAG_3 kit. The radio pharmacokinetic parameters and the clearance of ^{99m}Tc-MAG_3 in seven healthy Mexican volunteers were determined by the single- and multi-sample methods. Computer programs used for the calculations. The plasma samples (0–43 min) show values that were obtained in this study to ^{99m}Tc-MAG_3 follows a two-compartment kinetic model. Reporting an apparent volume (Vd_{cc} = 3.8 + 0.7 L) in the central compartment of, a volume of distribution at steady state of Vd_{ss} = 6.7 + 1.0 L, $T_{1/2\ \alpha}$ = 0.07 + 0.02 h^{-1}, $T_{1/2\ \beta}$ = 0.49 + 0.15 h^{-1}, a one mean residence time MRT = 0.60 + 0.17 h and clearance = 208 + 57 (ml/min)/1.73 m^2. In comparison, the clearance value with a single sample drawn 43 min post-injection and calculated with Tauxe's formula was 193 ± 59 (ml/min)/m^2. In this paper the authors indicate conclusions that the 15 ml difference between the two methods is neither statistically different (p = 0.11) nor important for routine clinical studies. The single-sample method is recommended because it is reliable and can be use at the same time that the dynamic renal scan is

acquired. Estimated absorbed radiation dose was calculated for several organs [6]. It is very important in studies of clearance of drugs of biomarkers in selective organs as kidney. Also, is very important use of analytic methods validate and high confidence and furthermore equipment optimize, allowing us to use reliable analytic methods. In the development of new analytic methods is necessary a quality control of a detector for the calculations of radio pharmacokinetic parameters of radionuclides. How is reported for ^{99m}Tc-glucarate in rats, the authors mentioned to that good manufacturing practices specify that a well-type scintillation NaI (Tl) crystal detector have to be validated in order to detect radioactivity from any radiopharmaceutical used to obtain radio pharmacokinetic parameters. One 5 cm well-type NaI (Tl) scintillation detector was couple to a multi-channel analyzer centered at the 140 keV ^{99m}Tc peak with a 20% window. In this paper the area represents counts per minute (cpm). All the net cpm was decay corrected. The activity source was ^{99m}Tc-glucarate developed as an imaging agent for acute myocardial infarction. The detector's efficiency for ^{99m}Tc was 15.03% and the sensitivity 1.12 kBq/ml in plasma. The response was linear between 0.31-14.3 kBq/ml of ^{99m}Tc-glucarate. The maximum assay variation coefficient was 2.79 and recovery of ^{99m}Tc-glucarate in plasma was 99.8 ± 0.2 %. LOD was 0.31 kBq and LOQ = 1.12 kBq in plasma samples. Your pharmacokinetic ^{99m}Tc-glucarate follows a two-compartment model of distribution with *Vd* of 21.74 ± 2.71 mL; a *Vdss* of 74.36 ± 12.67 mL; $t_{1/2\ a}$ 0.74 ± 0.19 h; $t_{1/2\ b}$ 18.98 ±4.36 h; AUC = 32.75 ± 3.73 mCi/min·ml; MRT = 24.35 ± 5.51 h and total clearance 3.05 ± 0.35 ml/h. The well-type detector fulfills the quality system requirements and the radiopharmacokinetic parameters for ^{99m}Tc-glucarate in rats are reliable [7].

In the practice of nuclear medicine, radioactive nuclides are still used, but it is important to conduct preclinical studies based applications before heading to clinical studies. Labeled with radioactive nuclides drugs may allow us to visualize in diagnosing functional abnormalities in patients. An interesting application of nuclides used for diagnostic coronary diseases as indicate in the application of ^{99m}Tc-glucarate radiopharmaceutical in detection myocardial infarction in induced rats with isoproterenol. The applications this radiopharmaceuticals and the utility in diagnostic clinic especially in diagnosis of acute myocardial infarction is very important. The high image quality suggests that high contrast images can be obtained in humans and the 96 h stability makes it an ideal agent to detect, in patients, early cardiac infarction (figure 1) [8]. Diagnostic radiopharmaceuticals can be used to examine blood flow to the brain, functioning of the liver, lungs, heart or kidneys, to assess bone growth, and to confirm other diagnostic procedures. Another important use is to predict the effects of surgery and assess changes since treatment. For targeted alpha therapy (TAT), actinium-225 is readily available, from which the daughter bismuth-213 can be obtained (via 3 alpha decays) to label targeting molecules. The bismuth is obtained by elution from an Ac-225/Bi-213 generator similar to the Mo-99/Tc-99 one. Bi-213 has a 46-minute half-life. The actinium-225 (half-life 10 days) is formed from radioactive decay of radium-225, the decay product of long-lived thorium-229, which is obtained from decay of uranium-233, which is formed from Th-232 by neutron capture in a nuclear reactor. Radionuclides how caesium, gold and ruthenium are also used in brachytherapy. See table 1 [9].

Somatostatine Analogs

In 1973 Brazeau et al., accidentally isolated the somatostatin, hormone that acts inhibiting growth hormone secretion and thyrotropin, insulin, glucagon, gastrin, CCK, VIP, GIP and others. Exist several form, in mammals exists two active forms: 14-amino-acid cyclic peptide (SS-14) and 28-amino-acid cyclic peptide (SS-28). Somatostatin has short half-life in plasma (3 minutes), its reason for that used others analogs peptides. Receptors SS find in hypothalamus, peripheral nervous system, in pancreas and in the gut. Several participate in the absorption process and in the control of proliferation cells [10-14].

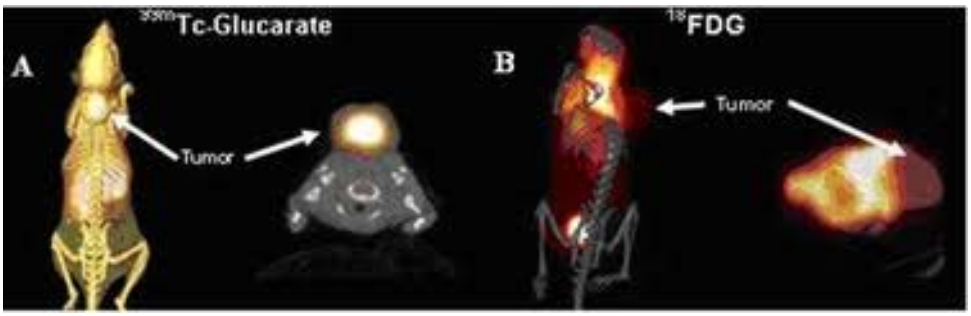

Figure 1: Identification of ^{99m}Tc-glucarate in **r**at induced with tumor. Currently will be any radionuclide in diagnostic and therapeutic damage, but the most commonly used is the nuclide ^{99m}Tc. To the technetium generator there are approximately eight generators of short-lived radionuclide in which the daughter, in some chemical form, has seen human use. D.J. Hnatowich in his article reviews progress in the development of imaging agents prepared with this eight short-lived radionuclide. The bulk of the report deals with ^{13m}In and ^{68}Ga radiopharmaceuticals (9).

Table 1: Radionuclides used in nuclear medicine [9]

Radionuclide used in nuclear medicine (202)		
Nuclide (reactor produce)	**Half-life**	**Use**
Bismuth-213	46 min	Used for targeted alpha therapy (TAT), especially cancers, as it has a high energy (8.4 MeV).
Chromium-51	28 d	Used to label red blood cells and quantify gastro-intestinal protein loss.
Cobalt-60	5.27 yr	Formerly used for external beam radiotherapy, now used more for sterilising.
Dysprosium-165	2 h	Used as an aggregated hydroxide for synovectomy treatment of arthritis.
Erbium-169	9.4 d	Use for relieving arthritis pain in synovial joints.
Holmium-166	26 h	Being developed for diagnosis and treatment of liver tumours.
Iodine-125	60 d	Used in cancer brachytherapy (prostate and brain), also diagnostically to evaluate the filtration rate of kidneys and to diagnose deep vein thrombosis in the leg. It is also widely used in radioimmuno-assays to show the presence of hormones in tiny quantities.
Iodine-131	8 d	Widely used in treating thyroid cancer and in imaging the thyroid; also in diagnosis of abnormal liver function, renal (kidney) blood flow and urinary tract obstruction. A strong gamma emitter, but used for beta therapy.
Iridium-192	74 d	Supplied in wire form for use as an internal radiotherapy source for cancer treatment (used then removed). Beta emitter.
Iron-59	46 d	Used in studies of iron metabolism in the spleen.
Lead-212	10.6 h	Used in TAT for cancers or alpha radioimmunotherapy, with decay products Bi-212 and Po-212 delivering the alpha particles. Used especially for melanoma, breast cancer and ovarian cancer.
Lutetium-177	6.7 d	Lu-177 is increasingly important as it emits just enough gamma for imaging while the beta radiation does the therapy on small (eg endocrine) tumours. Its half-life is long enough to allow sophisticated preparation for use. It is usually produced by neutron activation of natural or enriched lutetium-176 targets.
Molybdenum-99	66 h	Used as the 'parent' in a generator to produce technetium-99m.
Palladium-103	17 d	Used to make brachytherapy permanent implant seeds for early stage prostate cancer.
Phosphorus-32	14 d	Used in the treatment of polycythemia vera (excess red blood cells). Beta emitter.
Potassium-42	12 h	Used for the determination of exchangeable potassium in coronary blood flow.
Rhenium-186	3.8	Used for pain relief in bone cancer. Beta emitter with weak gamma for imaging.
Rhenium-188	17 h	Used to beta irradiate coronary arteries from an angioplasty balloon.
Samarium-153	47 h	Sm-153 is very effective in relieving the pain of secondary cancers lodged in the bone, sold as Quadramet. Also very effective for prostate and breast cancer. Beta emitter.
Selenium-75	120 d	Used in the form of seleno-methionine to study the production of digestive enzymes.
Sodium-24	15 h	For studies of electrolytes within the body.
Strontium-89	50 d	Very effective in reducing the pain of prostate and bone cancer. Beta emitter.
Technetium-99m	6 h	Used in to image the skeleton and heart muscle in particular, but also for brain, thyroid, lungs (perfusion and ventilation), liver, spleen, kidney (structure and filtration rate), gall bladder, bone marrow, salivary and lacrimal glands, heart blood pool, infection and numerous specialised medical studies. Produced from Mo-99 in a generator.
Xenon-133	5 d	Used for pulmonary (lung) ventilation studies.
Ytterbium-169	32 d	Used for cerebrospinal fluid studies in the brain.
Ytterbium-177	1.9 h	Progenitor of Lu-177.
Yttrium-90	64 h	Used for cancer brachytherapy and as silicate colloid for the relieving the pain of arthritis in larger synovial joints. Pure beta emitter and of growing significance in therapy, especially liver cancer.
Cobalt-57	272 d	Used as a marker to estimate organ size and for in-vitro diagnostic kits.
Copper-64	13 h	Used to study genetic diseases affecting copper metabolism, such as Wilson's and Menke's diseases, and for PET imaging of tumours, and therapy.
Copper-67	2.6 d	Beta emitter, used in therapy.
Fluorine-18	Tracer	Tracer.
Gallium-67	78 h	Used for tumour imaging and localisation of inflammatory lesions (infections).
Gallium-68	68 min	Positron emitter used in PET and PET-CT units. Derived from germanium-68 in a generator.
Germanium-68	271 d	Used as the 'parent' in a generator to produce Ga-68.
Indium-111	2.8 d	Used for specialist diagnostic studies, eg brain studies, infection and colon transit studies.
Iodine-123	13 h	Increasingly used for diagnosis of thyroid function, it is a gamma emitter without the beta radiation of I-131.
Iodine-124	Tracer	Tracer
Krypton-81m	13 sec	Kr-81m gas can yield functional images of pulmonary ventilation, e.g. in asthmatic patients, and for the early diagnosis of lung diseases and function.
Rubidium-82	1.26 min	Convenient PET agent in myocardial perfusion imaging.
Strontium-82	25 d	Used as the 'parent' in a generator to produce Rb-82.
Thallium-201	73 h	Used for diagnosis of coronary artery disease other heart conditions such as heart muscle death and for location of low-grade lymphomas.

The use of target biomolecules with high specify for the organs or particular receptor is the importance radical for to obtain of images for scintigraphic in the specify cities occur upper expression the specify receptors in the cells in study, for example the tumor cells. Cells of very types of tumors present abundant receptors of somatostatin [15].

In the use for diagnostic is because the endocrine system and the neurologic system present expression very high concentrations of receptors of thousands of times majors those normal cells, by this motive this molecule have be high potential and its very utilized for diagnostic [16, 17]. The method full utilized for labeling peptides very specify is by means of conjugation of metallic bifunctional agents.

Preparation of peptides requires protection of group amine in the some cases or other functional groups. Metallic agents also require protection. The peptides RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2) and the Tyr3-Octreotide (D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr) their cyclic octapeptides join Disulfide Bridge and both to contain remains of lysine, this very important from affinity for the receptors (figure 2).

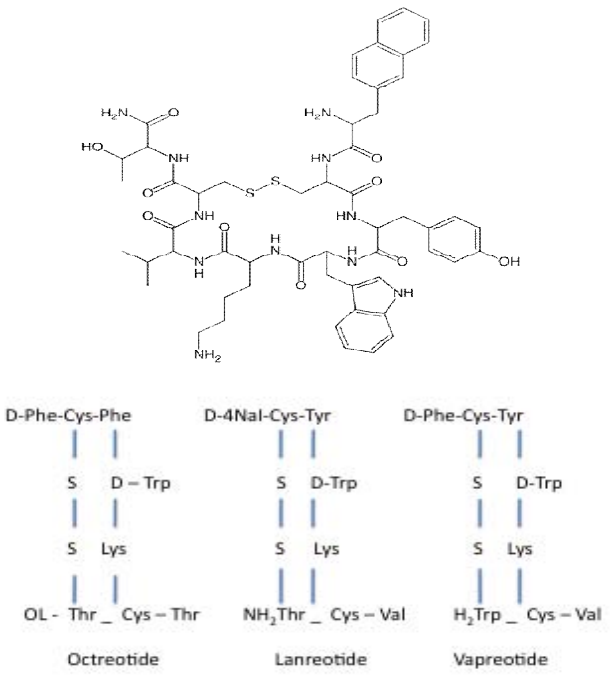

Figure 2: Chemist structure of Lanreotide and synthetic peptides: Octreotide, Lanreotide and Vapreotide.

In 1982 Bauer et al from Sandoz laboratory synthesized one potent SS analog, the octreotide, it is a cyclic peptide with longer plasma high life of about 1.5 hours when after subcutaneous injection its action is 6-8 hours. The Novartis laboratory (Switzerland) it was name *Sandostin* (18). The other analog Lanreotide, *Somatuline*, was approved for clinic use in Europe in 1994. It should be administer intramuscularly. Its duration action after one injection is from seven to 14 days. The formulations of octreotide incorporate in poly D; L (lactide-coglycolide) glucose microspheres can be administered intramuscularly for 4 weeks.

In the bibliography is description of different somatostatin analogs labeling. It has to use in very clinics applications. The somatostatin analogs 111In-DTPA-D-Phe-Octreotide (Ostreoscan) and 123I-Tyr-Octreotide used for obtain of different tumors so lymphomas and neuroendocrine tumors [19, 20].

The octreotide peptide is a synthetic somatostatin analogue that specifically targets somatostatin receptors. Somatostatin is acyclic peptide comprised of 14 amino acids that plays one important role in the secretion of hormones, such insulin, glucagon and the growth hormone. Pituitary adenomas and neuroendocrine tumors present in pancreas cancer and lung cancer over-express somatostatin receptors.

Since discovery, use peptides in therapeutic and diagnostic treatment will be mention of peptides analogues somatostatin, the RC-160 and Tyr_3Octreotide (TOC) peptides when labeling with ^{99m}Tc by an indirect method using S-Benzoyl- mercaptoacetyl triglycine (MAG_3) and hydrazinonicotinamide (HYNIC) as chelating agents. Synthesis of RC160 with S-Benzoyl MAG_3 and TOC with HYNIC, for labeling with ^{99m}Tc was also describe by E. Obenaus et al in 2003 [21].

The use of peptides in the treatment of cancer or carcinoma in the women who present with a carcinoma of the breast often are offered a number of surgical options for the treatment of their cancer. A trend favoring minimally invasive breast primary breast cancer has shifted from mastectomy to lumpectomy, and the evaluation of axillaries lymph node status has shifted from complete axillaries dissection (removal of levels II, III nodes, and I) to less complete dissections. Each of these trends has created new surgical dilemmas. The shift from mastectomy to lumpectomy has led to a significant risk of ipsilateral tumor recurrence. Local recurrence rates may be increase by undetected positive tumor resection margins or multifocal disease that remains undiscovered following lumpectomy [22, 23]. Up to 45% of initial excision, breast biopsy margins are positive and require subsequent re-excision. In addition, some patients may have clinically and mammographically occult multifocal disease that is not discovery during lumpectomy. In a meta-analysis of 11 studies with 2657 cases, only 32% of primary breast cancers were multifocal with residual tumor in other quadrants [24]. This finding has been confirme by Pittinger et al., who reported multifocal disease in 24% of patients with close margins and 44% in patients with positive margins. A variety of techniques have been develop to evaluate axillaries lymph nodes. These include the use of sentinel lymph node mapping, using Lymphazurin blue or Lymphazurin blue and technetium-99m (^{99m}Tc) sulfide colloid with intraoperative gamma detection, to identify sentinel nodes for excision (25, 26). A technique that accurately evaluates all axillaries lymph nodes and detects positive tumor resection margins would be a useful tool to guide intraoperative surgical decision-making in women with breast cancer [27].

Somatostatin receptors have been demonstrate to be present in a large proportion of breast carcinomas. Van Eijck et al. demonstrated that 75% of all women with primary breast cancers have positive ^{111}In- pentetreotide (a radio labeled, somatostatin receptor subtype 2-preferring, somatostatin analog) scintigraphic scans [28]. Parallel *in vitro* autoradiography demonstrated somatostatin receptor (SST) positivity in 28 of 30 (93%) of these patients. Positive scans are obtained more often in patients with ductal carcinomas than in those with lobular carcinomas (85% vs. 56%). Unfortunately, the relatively

long distance from the tumor (radioactive source) to the camera (the inverse-square law) decreases the sensitivity of external scintigraphic scanning. As expected, T2 carcinomas are more commonly visualized than are T1 carcinomas (86% vs. 61%). In nuclear medicine demonstrated that ^{125}I-lanreotide, when used with intraoperative gamma detection, can detect very small tumor burdens, including occult lymph node metastases in patients with gastrinoma [29]. The researchers hypothesized that intraoperative gamma detection of the radiolabeled somatostatin analog ^{125}I-lanreotide could detect positive breast cancer resection margins and accurately assess axillaries lymph node tumor status.

Analogs diverse to present affinity for the specify receptors SSR4 so Lanreotide, so have labeling with ^{90}Y and ^{111}In and the Vapreotide (RC-160) labeling with ^{111}In, ^{188}Re and ^{99m}Tc. The RC-160 can be cross hematoencephalic barrier and can been used in detection brain tumors [30-32].

The somatostatin analogs RC-160 and TOC to having the very more clinic potential very important and can serve so models for experiment with labeling methods different. For example to determine the biological and radiochemical behavior of two somatostatin analogues, the RC-160 and Tyr$_3$Octreotide (TOC) peptides when labeling with ^{99m}Tc by an indirect method using S-Benzoyl-mercaptoacetyl triglycine (MAG_3) and hydrazinonicotinamide (HYNIC) as chelating agents. Biodistributions studies in normal Wistar rats were performed and results were analyze with chromatographic studies and protein-binding properties test. Lower lipophilicity of the labeled conjugates resulted in a higher renal excretion. HYNIC-TOC complex showed promising results when labeling with ^{99m}Tc using tricine as co-ligand although higher stability should found for ternary co-ligands compared to tricine.

The ^{188}Re-lanreotide is very use in therapeutic damage, one example is the studies in pharmacokinetic and dosimetric parameters of ^{188}Re-lanreotide in athymic mice with induced human cancer tumors. Somatostatin analogs, have been used for peptide receptor-mediated radionuclide therapy (PRMRT) in metastatic neuroendocrine tumors. The eight amino acid peptide 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, cyclic (2-->7)-disulfide (9Cl) (lanreotide) was found to bind to the five-somatostatin tumor receptors and furthermore Lanreotide has been labeled via the bifunctional chelating agent, DOTA, to ^{111}In, and ^{90}Y. A direct labeling method was use to label lanreotide with ^{188}Re. The percentage-injected activity per gram of tissue (percentageIA/g) was extrapolated to the weights of a 70 kg male model organs and the number of nuclear transitions (N) were the input for the *OLINDA/EXM* program to obtain dosimetry estimates.

Induced uterine-cervix tumors (HeLa cells) show a mean 2.4 % IA/g uptake up to 24 h and the tumor/blood ratio was over 1.85 (1.5-24 h post-injection) confirming ^{188}Re-lanreotide remains bound to the tumor. The estimated tumor absorbed dose was 460 mGy/MBq. Human effective dose was 0.0182 mSv/MBq. Therefore, ^{188}Re-lanreotide is a good candidate for PRMRT and a clinical trial is being planner in order to acquire individual dosimetric data [33]. The table 2 show parameters radiopharmacokinetics obtain in the study.

Table 2: Pharmacokinetic parameters calculated with WinNonlin program for a non-compartmental model (mean n=3) [34].

Parameters	Balb-C	Athymic
Vd_z (ml)	76.59 ± 10.37	72.65 ± 3.54
V_{ss} (ml)	68.41 ± 19.89	69.62 ± 10.19
$T_{1/2}\ \lambda_z$ (h)	5.6 ± 2.49	43.05 ± 6.84
Cl (ml/min)	9.48 ± 3.61	1.17 ± 0.37
AUC (0→∞) (ml/min)/h)	10.55 ± 3.62	85.50 ± 13.23
MRT (h)	7.22 ± 4.08	59.49 ± 13.66

The dosimetry is important because permit customize the dose. The theory of dosimetry is base in MIRDOSE when it is consider absorbed dose, equivalent dose and effective dose in specific organs.

The radiolabelled somatostatin analogues have been use in diagnostic and therapeutic nuclear medicine to treat cancerous tumors. Lanreotide, a cyclic octapeptide, with antiproliferative action on human small cell lung carcinoma was ^{188}Re and characterized, and its biodistribution is report in mice. Molecular modeling indicates that the lipophilic radiopharmaceutical might be an oxo-rhenium (V) penta-coordinated complex. The implanted human cervical tumor of epidermoid origin was positive for cytokeratins and vimentin and cleared via the hepatobiliary system [34].

How therapeutic radiopharmaceutical ^{188}Re-lanreotide was compared in rats implanted with hepatocarcinoma tumors. The activity per gram of tissue (percentage IA/g) was calculated and the radio pharmacokinetic parameters determined. Data were fit using a two-compartment model. In this text the authors show significant differences between healthy and hepatoma rats. The scintigraphic images obtained therefore had high resolution and furthermore the ^{188}Re-lanreotide had a prolonged beta elimination half-life and increased volume of distribution in rats with hepatocellular carcinoma. This may be beneficial in the diagnosis and therapy of metastatic lesions in patients with cancer [35-39].

The importance in the therapy of receptors *SSTR* in others treatments considering the long acting somatostatin analogues like octreotide and lanreotide depends on the expression of specific somatostatin receptors on the target cells. The immunohistochemical method performed on surgically removed tumors searches the expression of receptors at the level of receptor protein and gives us insight into receptor's cellular localization.

Pizarek et al. mentioned the aim of study was to identify the presence of all the five subtypes of SSTR 1-5 (including 2A and 2B SSTR isoforms) in surgically treated human neuroendocrine tumors (NETs). They are establish which receptor subtype is the dominant form of somatostatin receptor in particular tumor and thus to be able to predict which somatostatin analog will be effective in NETs treatment. The domain of receptors are follow SSTR 1> SSTR 5> SSTR 3> SSTR 2A> SSTR 2B. The receptors were distributed mainly in the area of cells cytoplasm with a few specimens showing only membranous or mixed: membranous–cytoplasmic localization.

The observed pattern suggests that apart from octreotide and lanreotide, newly synthesized multiligand analogs such as SOM 230, KE 108 or SSTR 1 and SSTR 5 selective analogs could be effective in NETs treatment (40). Consider that specific receptors play an importan role in the action mechanism, so it is very important identify specific of somatostatin (SS) and SS receptors (ssts) as are broadly expressed in the human body where they exert many physiological actions, they can be expressed in many pathological tissues. Particularly, a high density of ssts has been described in human neuroendocrine tumors (NETs). SS and ssts receptors have a therapeutic and diagnostic value in several clinical conditions. For this reason stable SS-analogues have been develop. Among SS-analogues, octreotide long acting release (LAR), lanreotide-sustained-release (SR) and lanreotide autogel (ATG) are approved for clinical use and the pasireotide is in a late phase of clinical development. Presently, the SS-analogues are the standard treatment option for acromegalic patients and play a prominent role in the symptomatic control of patients with gastroenteropancreatic-neuroendocrine tumors (GEP-NETs).

SS-analogues are able to control hormonal hyperactive secretion and reduce tumoral growth in the majority of cases. However, some patients are resistant to SS-analogue treatment and other patients (often GEP-NETs), after a variable period of treatment, develop tachyphylaxis to these compounds. The mechanisms behind this treatment resistance or tachyphylaxis are presently in this research. The understanding of these mechanisms might help to develop new treatment modalities for patients not responding to the currently available SS-analogues. The high tumoral expression level of ssts, characteristic of many NETs, has been the rational to develop radiolabelled SS-analogues to visualize sst-expressing tumors and to treat unresectable tumors. For example, SS-analogues coupled with (111) Indium is use to perform sst-scintigraphy, which is a very useful first-line imaging technique in the diagnosis and follow-up of GEP-NETs. Moreover, SS-analogues conjugated to (111) Indium or to other radioisotopes, such as (177) Lu or (90) Y, have promising effects in the treatment of advanced NETs.

SSTS receptors are express in some non-neuroendocrine tumors as well and in some non-tumoral diseases, suggesting that SS-analogues might have a role in the diagnosis and treatment of these pathological conditions as well. The development of novel SS-analogues with new pharmacokinetic and pharmacodynamic characteristics may further improve the clinical applications of such compounds41. Furthermore recent data on the use of the somatostatin analogues (SSAS) as octreotide (OCT) and lanreotide for the treatment of patients with pituitary and neuroendocrine tumors (NETs) are relevant. As stated above these two analogues have a high affinity for somatostatin receptor (SSR) sub-types 2 and 5. The major indications of these compounds are GH- and TSH-secreting pituitary adenomas, secreting NETs and non-functioning NETs in progression. Other analogue is. Pasireotide with a receptor pattern different from previous analogues since it binds with high affinity to SSR types 1, 2, 3 and 5 [42]. Otherwise the studies aimed of pharmacokinetic of lanreotide are few, in the treatment of Acromegaly the analogs of Somatostatin (SSAS) are effective in controlling GH/IGF-1 hypersecretion and in reducing tumor size and according to Hu M. et al was compared the pharmacokinetic and clinical efficacy of lanreotide, the second SSA available in the market, in its different formulations.

Very effective in the treatment in acromegaly and the pharmacology and clinical efficacy of lanreotide and provides a detailed overview of its pharmacokinetic profiles in its slow release (SR) and autogel (ATG) formulations. Furthermore, the Lanreotide is an effective and well-tolerated drug for the treatment of acromegaly. Lanreotide ATG has a more favorable pharmacokinetic profile than lanreotide SR, which permits administration once every 28-56 days given deep subcutaneously and by self-injection rather than intramuscular injection every 7 – 14 days [43].

Broadly the Acromegaly in the major patients the disease is caused by a growth hormone (GH)-secreting pituitary adenoma with elevated GH levels that ultimately induce excessive hepatic secretion of insulin-like growth factor-1 (IGF-1). Somatostatin receptor ligands (SRLs) are considered the standard medical choice for the treatment of acromegaly, and normalization of GH and IGF-1 is attainable with effective therapy. The lanreotide (Autogel) is use in therapy of Acromegaly. The rationale and benefits of SRL dose optimization therapy with emphasis on describing the clinical recognition, treatment, and management of patients with acromegaly is very important. As dose escalation could provide additional biochemical control of acromegaly in patients who are inadequately controlled with conventional starting doses of octreotide LAR and lanreotide Autogel(®).

Furthermore, patients should routinely have their GH and IGF-1 levels closely monitored and their SRL dose increased or decreased thereafter according to individual

response [44]. Therefore, the dose must be individualized. The discovery of the new properties of SSRs and DRs has led to a renewed interest in agents targeting these receptors and has opened new perspectives for medical treatment of patients with pituitary and neuroendocrine tumors resistant to the "classical", currently available analogs. Moreover, SSRs and DRs Receptors permit cross at membrane level may trigger alternative intracellular pathways or enhance the signaling for the control of cell growth. Therefore, the receptor profile characterization is crucial for the accurate selection of patients potentially responsive to a given therapy [45].

The interest for to realize studies in relation of analogs somatostatine is because this hormone (SRIF) is a cyclic tetradecapeptide hormone initially isolated from ovine hypothalamic. It inhibits endocrine and exocrine secretion, as well as tumor cell growth, by binding to specific cell surface receptors. Its potent inhibitory activity, however, is limit by its quickly enzymatic degradation and the consequent short plasma half-life. Octreotide is for example a short SRIF analog with increased duration of action compared to SRIF. Octreotide is amine precursor uptake and decarboxylation, complications of pancreatic surgery and severe forms of diarrhea. Preclinical studies have focused on the anticancer effects of octreotide and the related SRIF analogs BIM 23014 and RC-160. *In vitro* at nanomolar concentrations, these analogs inhibit the growth of tumor cells that express high affinity SRIF receptors. Potently are inhibiting the growth of SRIF receptor-positive tumors in various rodent models, and, in particular, xeno transplanted human tumors in nude mice although related to other types as mammary, pancreatic, colorectal and lung.

Moreover, an indirect antiproliferative effect of SRIF analogs is achievable in SRIF negative-receptor tumors whose growth is drive by factors (gastrin, insulin-like growth factor-1, for example) that are down regulate by SRIF. Therefore, the use of radiolabeled somatostatin analogs represents a new diagnostic approach, as for example the radiopharmaceutical [111In-DTPA]-octreotide was developed for gamma camera imaging of SRIF receptor-positive malignancies, such as gastroenteropancreatic tumors. Visualization of SRIF receptor-positive tumors in humans is emerging as an important methodology, both in tumor staging and predicting therapeutic response to octreotide. Currently five SRIF receptor subtypes (SSTR1-5) have been cloned, all of which bind SRIF with high affinity [46]. Finally with respect Octeotride I can say that Octreotide, SSTR5, show moderate affinity for SSTR3 and fail to bind with high affinity to the other subtypes (SSTR1 and 4). The oncological profile of these three analogs is apparently similar [47].

For gastroenteropancreatic neuroendocrine tumors (GEPNETs) in the diagnosis it use [(111) In-DTPA (0)] octreotide in positron emission tomography (PET) imaging, and which have a higher affinity for the somatostatin receptor, especially receptor subtype-2, have been developed. It would be desirable, however, if one radiolabeled analog became the new standard for PET imaging, because the current application of a multitude of analogs implies a fragmented knowledge on the interpretation of the images that are obtain in clinical practice. The candidates for such a universal PET tracer for SRI are [(68) Ga-DOTA (0), Tyr (3)] octreotate or [(68) Ga-DOTA (0), Tyr (3)] octreotide. Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Symptomatic improvement may occur with all (111) In^{-}, (90) Y^{-}, or (177) Lu-labeled somatostatin analogs that have been used for peptide receptor radionuclide therapy (PRRT). The results that were obtained with [(90) Y-DOTA (0), Tyr (3)] octreotide and [(177) Lu-DOTA (0), Tyr (3)] octreotate are very encouraging in terms of tumor regression. Based on studies by Kwekkeboom DJ et al. the patients' self-assessed quality of life increases significantly after treatment with [(177) Lu-DOTA (0), Tyr (3)] octreotate. Lastly, compared to historical controls, there is a benefit in overall survival of several years from the time of diagnosis in patients treated with [(177) Lu-DOTA (0), Tyr (3)] octreotate. These data compare favorably with the limited number of alternative treatment approaches. If most widespread use of PRT can be guarantee it is use, such therapy may well become the therapy of first choice in patients with metastasized or inoperable GEPNETs [48].

Therefore, the peptide-based radiopharmaceuticals which are presently already commercially available or which are in advanced stages of their clinical testing so that their broader availability is anticipate soon. Physiologically, these peptides bind to and act through G protein-coupled receptors in the cell membrane. Historically, somatostatin analogs are the first class of receptor binding peptides having gained clinical application. 111In-DTPA-[D-Phe1]-octreotide is the first and only radiopeptide obtained regulatory approval in Europe and the United States to date. Extensive clinical studies involving several thousands of patients have shown that the major clinical application of somatostatin receptor scintigraphy is the detection and the staging of gastroenteropancreatic neuroendocrine tumors (carcinoids).

In these tumors, octreotide scintigraphy is superior to any other staging method. However, its sensitivity and accuracy in other, more frequent neoplasms is limited. Radio labeled vasoactive intestinal peptide (VIP) has been show to visualize the majority of gastrointestinal adenocarcinomas, as well as some neuroendocrine tumors, including insulinomas (the latter being often miss by somatostatin receptor scintigraphy). Due to the outstanding diagnostic accuracy of the pentagastrin test in detecting the presence, persistence, or recurrence of medullary thyroid cancer (MTC), we postulated the expression of the corresponding (i.e. cholecystokinin

[CCK-] –B) receptor type in human MTC. This receptor is also widely expressed on human small-cell lung cancer [49].

Other researchers reported molecular imaging and targeted radiotherapy are emerging fields in nuclear oncology. Five human somatostatin receptors (hsstr1-hsstr5) is known to be over-expressed to some degree on various tumors, the results to indicate that the receptor affinity profile showed high affinity of both peptides to hsstr2, hsstr3, and hsstr5 and some intermediate affinity to hsstr4, whereas [(111) In-DOTA]-TOC shows affinity only to sstr2. The internalization is fast in sstr2 expressing AR4-2J and in transfected sstr3 expressing human embryonic kidney 293 cells. Both radiopeptides internalize much more efficiently than [(111) In-DOTA]-TOC. Animal biodistribution studies showed very high and specific uptake of [(111) In]-1 and [(111) In]-2 in s.c. Implanted AR4-2J tumors (Lewis rats) and in somatostatin receptor expressing normal tissues. The uptake was at least 2-fold higher in these tissues and in the tumor compared with [(111) In-DOTA]-TOC [50]. Broadly, hSSTR2, the VIP acceptor hSSTR3, and hSSTR5 as the respective target receptors because these receptors are frequently expressed at high levels on primary tumor cells; 99mTc-P829 appears to be a promising novel peptide tracer for tumor imaging [51-56].

Metallic nanoparticles

Nanoparticles of gold (GNPs) are indicate in the treatment of rheumatic arthritis and agent of treatment cancer, on the one case the studied activity indicate in adult people of 40 years, not in adult to 60 years or more or in children. The stability of gold nanoparticles is good and yours use are their assembly of multiple types involving materials science, the behavior of the individual particles, size-related electronic, magnetic and optical properties (quantum size effect), and their applications to catalysis, biology and medic use [57]. However there optoelectronic properties of GNPs related to the surface Plasmon absorption, reflecting the collective oscillation of the conducting electrons of the gold core, a feature relevant to the quantum size effect.

The combination of photonics discipline with biology and medicine has already been demonstrate by the seminal work on GNPs-DNA assemblies and is very promising for future biomolecular manipulations and applications, such as labeling, detection, and transfer of drugs, including genetic materials [58]. Currently has been development spectrophotometric analytical method and the validation their same for determine gold colloids nanoparticles (GNPs) and to join the peptide lanreotide (LAN-GNPs) *in vitro*. The conjugate GNPs-LAN this investigation phase and this use toward for therapeutic cancer, therefore is important this studies and the analytic method appropriate to determinate in biological fluids [59-61].

In different studies in where we are involucrate any product organic so radiopharmaceutics, drugs and nanostructure systems considering the organic process such as biopharmaceutics and pharmacokinetic process.

In the clinical practice is very important to personalize doses and design therapeutics ranges such as doses adjustment.

Currently the studies in biotechnology are based in the study pharmacokinetics of new drugs: radiopharmaceuticals and nanodrugs based in development of biodegradables nanoparticles such as that use in the clinical practice for diagnostic and therapy, especially in cancer therapy.

In 2011, it is reporting information of use and methodological line in relation development and validation of a methods spectrophotometrics for Quantify GNPs and GNPs-Lanreotide *in vitro*, where indicate the importance of selection the quality one analytic method and easy use therefore economic. For characteristics of GNPs the method is easy and economic for quantify GNPs and conjugate of peptide lanreotide (LAN) and GNPs. The parameters of specificity, linearity, exactness and precision were evaluated [62-147].

In this same way other paper in relation with conjugation of GNPs and lanreotide peptide was a publication in this year when the Lanreotide so somatostatin analogue peptide used for peptide receptor mediated therapy in metastatic neuroendocrine tumors, was used as capping agent of gold nanoparticles (GNPs) obtained by citrate reduction method. The displacement of the citrate groups from the GNPs surface by lanreotide (LAN) molecules was evidence by infrared and Raman spectra. The nanoparticles system, Au@LAN, was also characterized from HRTEM (High-Resolution Transmission Electron Microscopy) and Z-contrast images, UV-Vis and EDS spectra.

The stability on aging in water solution of the composite is discussed from the UV-Vis spectra. The affinity constant of Au@LAN conjugate, calculated from Capillary Zone Electrophoresis data, found to be 0.52. All the experimental evidence supports that the gold nanoparticles is capped with the Lanreotide molecules through relatively strong covalent interactions. This result opens the possibility of combining the optical properties of gold nanoparticles and of Lanreotide molecule to form a bifunctional system for potential biomedical applications and includes the functionalization of new nanodrugs.

Currently not exist report for biodistribution and pharmacokinetic of Au@LAN conjugate to use in cancer therapy [63, 148-198].

In the tables (3 and 4), we are showing the abstract of all development [64, 199-202].

Table 3: Advantages and disadvantages research on uses of gold nanoparticles

Advantages	Disadvantages	Author
Nanoparticles of any sizes may possess unique and beneficial properties that are electronic, optical and thermal (gold nanoparticles: GNPs).	The particle size is not determined based on the physiological function in the body, since the mechanism of drug action is specific and must consider the passage of substances membrane level.	Agnieszka Sobczak-Kupiec et al. (2011). Molina-Trinidad Eva María (2011)
GNPs are used in immunohitochemistry to identify protein-protein interaction.	The immunodetection capabilities of this technique are limited.	D. Navarro Bosch et al. (2010)
Gold metallic nanoparticles are commonly used in the laboratory as a tracer (DNA, aminoglycosidic antibiotics: streptomycin, gentamycin and neomicina).	You must select the type of plotter as it should be specific for the functionalization of nanoparticles.	S. Azarmi et al. (2008). Nirmala Grace et al. (2007)
Gold is used for nanoparticle applications because it is unreactive and is not sensitive to air or light.	Care must be taken in the preparation of nanoparticles and to be controlled variables and environmental factors that influence the particle size.	Y. Ding et al. (2006)
GNPS as certain conditions are stable can be joined with other biomolecules or to functional groups such as thiols and amines or amino acids.	The agglomeration GNPS therefore the surface thereof must be covered with layers of protective molecules such as the compounds of brimstone.	S. Aryal et al. (2006)
Due to the large surface area presented by the gold nanoparticles and their stability are nontoxic and can spread easily and used in delivery Systems.	Its use is limited on the basis of route of administration and the particle s ize, ie its use is selective.	P. Ghosh et al. (2008)
To maintain stability of the nanoparticles are surfactants used nontoxic and biodegradable substances such as polyols such as polyethylene glycol (PEG).	To prevent agglomeration of the nanoparticles is necessary to use stabilizing agents to be modified with poly(ethylene oxide) (PEO) via noncovalent bonding to form gold nanoparticle/polymer composites (GNPPs).	Ming-Feng Huang et al. (2004) Kim Y. Et al. (1997) Han F. Et al. (1999) Zhou H. Et al. (2000)
To the characterization and quantification of gold nanoparticles using specific techniques such as capillary electrophoresis analysis.	Some nanoparticles identification techniques are expensive as the Raman and Infrared.	Bela Neiman et al. (2001)
The stability of gold nanoparticles is good, considering the appropriate pH conditions.	The synthesis of nanoparticles should be prepared carefully and with a lot of cleaning, because of these factors depends on the shape and size of nanoparticles.	K. Sokolov et al. (2003) D. Marie-Christine and A. Didier. (2004) E.M. Molina-Trinidad et al. (2011)
Nanoparticles show their promise for improving the efficacy of drugs with a narrow therapeutic window or low bioavailability, such as anticancer drugs and nucleic acid-based drugs.	In the development of new drugs should be considered the quality control tests as indicated by the FDA and these tests are expensive.	Li SD, Huang L. (2008)
Certain compounds pass through the cell membrane depends on the molecular size and shape, so that it limits the passage of large molecules to the cell membrane for this reason the use of nanoparticles would allow entry into the cell without limitation depending on the biomolecule bound to the nanoparticles.	The limited transport of nanoparticles in the body is via lysosomal.	Bawarski N. et al. (2008)
The rate at which a drug is dissolved is limited by the size and shape of the drug particles, therefore a smaller size and a uniform increase disolusion speed and therefore drug absorption.	Nanoparticles are not surface-modified are rapidly cleared by phagocytic. Particles larger than 200 nm are not used because they may activate the immune system and to be clarified in the blood by Kupffer cells.	Bawarski N. et al. (2008)
Another advantage of the nanoparticles onto the microparticles is that they are more suitable for intravenous administration, since its size is much smaller than the smaller diameter capillaries, preventing aggregate formation and ensures that particles do not form embolism or thrombosis.	Nanoparticles larger than 100 nm may not be as bioavailable and easily pass across biological membranes.	Moddaresi M, 2010.
Nano systems may increase the bioavailability of drugs in the body and serve as specific delivery Systems.	Nano drug bioavailability in the body depends on its solubility, the degree of absorption site and the size and shape of the nanoparticles.	Molina Trinidad E.M. (2011)

Table 4: Research will be use of gold nanoparticles.

Research	Outcome	Author
The nanoparticles may also form the basis of future cancer treatments. Lasers that react with gold nanoparticles could be used to destroy cancer cells.	Nanoparticles have the advantage of targeting cancer by simply being accumulated and entrapped in tumours (passive targeting). The phenomenon is called the enhanced permeation and retention effect, caused by leaky angiogenetic vessels and poor lymphatic drainage and has been used to explain why macromolecules and nanoparticles are found at higher ratios in tumours compared to normal tissues.	M. Wang et al. (2010) J.L. Li etb al. (2009)
Nanoparticles could be used as targeted drug-delivery Systems.	In the cell level, metal NP internalization or expulsion by cells controls the effectiveness of photothermal therapy and drug delivery. In the organ level, the larger-scale metal NP distribution determines the effective coverage of a lesion for diagnosis (imaging) and therapy (heating or drug delivery)	Xiaohua Huang, (2006)
Gold nanoparticles (AuNPs) provide non-toxic carriers for drug and gene delivery applications that provide a useful complement to more traditional delivery vehicles.	Of AuNPs is their interaction with thiols, providing an effective and selective means of controlled intracellular release.	P. Ghosh et al. (2008)
GNPs are used in assembly of multiple types involving materials science, the behavior of the individual particles, size-related electronic, magnetic and optical properties (quantum size effect), and their applications in catalysis, in biology and in the medicine.	GNPs are excellent intracellular targeting vectors, because they can easily be tailored to a size between 0.8 and 200 nm. Their surface can be modified to impart various functionalities and good biocompatibility.	S. Azarmi et al. (2008). Nirmala Grace et al. (2007)
Inorganic nanoparticles, including GNPs, are potential carriers for efficient cellular delivery of various drugs and bioactive molecules.	LAN contains eight amino acids retaining an internal disulfide crosslink (Cys–Cys). The main motivation to use this peptide as a new capping ligand for GNPs arises from its biological function as a synthetic somatostatin analogue which specifically targets somatostatin receptors. It has been used for peptide–receptor-mediated therapy in metastatic neuroendocrine tumors.	E.M. Molina-Trinidad et al. (2011)
Parmacokinetics and Biodistribution of nanoparticles.	Chemical and physical properties of the nanoparticles, including size, surface charge, and surface chemistry, are important factors that determine their PK and biodistribution.	Shyh-Dar Li and Leaf Huang, (2008)

REFERENCES

1. Ritter R. The Oxford Style Manual. Oxford University Press, 2002, 1.
2. Rowland M and Tozer TN. Clinical Pharmacokinetics. Concepts and Applications. Third edition 1995, 438, 439.
3. Arteaga de Murphy C, Molina-Trinidad E, Meléndez-Alafort L, Ferro-Flores G, Reyes-Herrera L, Sepúlveda-Méndez J, Sandoval-Guzmán B, Hoyo-Vadillo C. Radiopharmacokinetics, Renal Clearance and Dosimetry of ^{99m}Tc-MAG$_3$. Archives of Medical Research. (30), 1999, 49-54.
4. Molina-Trinidad EM, Arteaga de Murphy C and Jung-Cook H. Quality control of a detector for the calculations of radiopharmacokinetic parameters of ^{99m}Tc-glucarate in rats. Journal of Radioanalytical and Nuclear Chemistry. (3), 2010, 477-489.
5. Arteaga de Murphy C, Ferro-Flores G, Villanueva-Sanchez O., Murphy-Stack E., Pedraza-López M, Meléndez-Alafort L and Molinaina-Trinidad E. ^{99m}Tc-glucarate for detection of isoproterenol-induced myocardial infarction in rats. International Journal of Pharmaceutics. (233), 2002, 29-34.
6. Hnatowich DJ. A review of radiopharmaceutical development with short-lived generator-produced radionuclides other than ^{99m}Tc. The International Journal of Applied Radiation and Isotopes. (28), 1977, 169-181.
7. Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science. (179), 1973, 77-9.
8. Reichlin S. Somatostatin. New Engl J Med. (309), 1883, 1495-1501.
9. Word Nuclear Association, registered in England and Wales, 2014. United Kingdom.
10. Petel YC, Wheatley T, Ning C. Multiple forms of immunoreactive somatostatin comparison of distribution in neural and nonneural tissues and portal plasma of the rat. Endocrinology. (109), 1981, 1943-9.
11. Gerich JE. Somatostatin. In: Reichlin S, ed. Somatostatin. Basic and Clinical Status. Ney York, Plenum Press. 1987, 221-8.
12. Schally A.V. Oncological applications of somatostatin analogs. Cancer Res. (48), 1988, 6977-6985.
13. Virgolini I, Angelberger P, Li S, Yang Q, Kurtaran A, Raderer M, Neuhold N, Kaserer K, Leimer M, Peck M, Scheithauer W, Niederle B, Eichler H, Valent P. In vitro and in vivo studies of three radiolabelled somatostatin analogues: 123I-Octreotide, 123I-Tyr-3-Oct and 111In-DTPA-Phe-1-Oct. Europ J Null Med, 23, 1996, 1388-1399.
14. Bakker W, Kenning E, Bremen W, Kooij J, Reubi J, Koper J, de Jong M, Lameris J, Visser T, Lamberts SW. In vivo use of radioiodinated somatostatin analogue: dynamics, metabolism, and binding to somatostatin receptor-positive tumors in man; J. Nucl. Med, (32), 1991, 1184-1188.
15. Visser T, Bruns Krenning E, Bakker W, Kooij P, Breeman W, Oei H, de Jong M, Reubi JC, Kwekkeboom D, Reijs A, Van Hagen P, Koper J, Lamberts S. Somatostatin receptor scintigraphy with Indium-111-DTPA-Phe-1-Octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-Octreotide. J. Nucl. Med. (33), 1992, 652-658.
16. Danesi R, Del Tacca M. Effects of octreotide on angiogenesis. In: Scarpignato C, ed. Octreotide: frombasic science to clinical medicine. Basel, Karger, 1996, 234-45.

17. Krenning E, Kwekkeboom DJ, Pauwels S., Kvols L., Reubi JC: Somatostatin receptor scintigraphy. Nuclear Medicine Annual. (1995).
18. Duet M, Mundler O, Ajzenberg J, Berolatti B, Chedlin P, Duranteau L, Warnet A. Somatostatin receptor imaging in non-functioning pituitary adenomas: value of an uptake index; Eur. J. Nucl.Med. (21), 1994, 647-650.
19. Obenaus E, Crudo J, Edreira M, De Castiglia S.G. Análogos de Somatostatina Marcados con 99mTc. Alasbimn Journal (5), 2003, 19.
20. Gwin JL, Eisenberg BL, Hoffman JP, et al. Incidence of gross and microscopic carcinoma in specimens from patients with breast cancer after re-excision lumpectomy. Ann Surg. (218), 1993, 729–34.
21. Pitinger T, Maronian NC, Poulter CA, Peacock JL. Importance of margin status in outcome of breast-conserving surgery for carcinoma. Surgery. (116), 1995, 604–9.
22. Carter D. Margins of lumpectomy for breast cancer. Human Path. (17), 1986, 330–2.
23. Morton DL, Wen DR, Wong JH, Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 127, ,1993, 392–9.
24. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 220,1994, 391–401.
25. Montani M, Levine E, Watson J, Intraoperative gamma detection 125I-lanreotide in women with primary breast carcinoma. Abstract. Regul Pept. (64), 1996, 131.
26. Van Eijck CHJ, Krenning EP, Bootsma A, Somatostatin receptor scintigraphy in primary breast cancer. Lancet. 343, 1994, 640–3.
27. Woltering EA, Barrie R, O'Dorisio TM, O'Dorisio MS, Nance R., Cook D.M. Detection of occult gastrinomas with iodine 125-labeled lanreotide and intraoperative gamma detection. Surgery. (116), 1994, 1139–47.
28. Virgolini I, Szilvasi I, Smith-Jones P, Angelberger P, Kurtaran A. Mauritius: animal and human biodistribution and tumor localization. Eur. J Nucl. Med. (24), 1997, pág 874.
29. Breeman WAP, Hofland L, Pluijm M Van-der, Van Koetsveld P, de Jong M, et.al. A new radiolabelled somatostatin analogue [111In-DTPA-D-Phe1]RC-160: preparation, biological activity, receptor scintigraphy in rats and comparison with [111In-DTPA-D-Phe1]Octreotide. Eur. J. Nucl. Med. (21), 1994, 328-335..
30. Guhlke S, Schaffland A, Zamora P, Sartor J, Diekmann D, Bender H, Knapp F, Biersack H. 188 Re and 99mTcMAG3 as prosthetic groups for labeling amines and peptides approaches with pre and post conjugate labeling. Nucl Med. Biol. (25), 1998, 621-632.
31. Sokolov K, Follen M., Aaron J., Pavlova I., Malpica A., Lotan R., and Richards-Kortum R. Real- Time Vital Optical Imaging of Precancer Using Anti-Epidermal Growth Factor Receptor Antibodies Conjugated to Gold Nanoparticles. Cancer Research (63), 2003, 1999-2004.
32. Molina-Trinidad EM, de Murphy CA, Ferro-Flores G, Murphy-Stack E, Jung-Cook H. Radiopharmacokinetic and dosimetric parameters of 188Re-lanreotide in athymic mice with induced human cancer tumors. Int J Pharm. (310), 2006, 125-30.
33. Arteaga de Murphy C, Pedraza-López M, Ferro-Flores G, Murphy-Stack E, Chávez-Mercado L, Ascencio JA, García-Salinas L, Hernández-Gutiérrez S. Uptake of (188) Re-beta-naphthyl-peptide in cervical carcinoma tumours in athymic mice. Nucl Med Biol. (28), 2001, 319-26.
34. Molina Trinidad EM, Arteaga de Murphy C, Jung-Cook Helgi, Murphy-Stack E, Pedraza-López M, Morales-Márquez JL, Vertiz Serrano G. Therapeutic ^{188}Re-lanreotide: Determination of Radiopharmacokinetics Parameters in rats. Journal Pharmacy and Pharmacology. (62), 2010, 1-6
35. Taylor JE, Bogden AE, Moreau JP and Coy DH. In vitro and in vivo inhibition of human small cell lung carcinoma (NCIH69) growth by a somatostatin analogue. Biochemical and Biophysical Research Communications. (153), 1988, 81-86.
36. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111IN-dtpa-D-Phe1] and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur. J. Nucl. Med. (20), 1993, 716-731.
37. Reubi J, Schar J, Wasser B, Wenger S, et al. Affinity profiles for human somatostatin receptor subtypes SST1- SST5 of somatostatin radiotracers selected for scintigraphyc and therapeutic use. Eur. J. Nucl. Med. (27), 2000, 273-282..
38. Pizarek H, Pawlikowski M, Kunert-Radek J, Kubiak R, Winczyk K. SSTR1 and SSTR5 subtypes are the dominant forms of somatostatin receptor in neuroendocrine tumors. Folia Histochem Cytobiol. (48), 2010, 142-7.
39. De Martino M, Hofland L, Lamberts SW. Somatostatin and somatostatin receptors: from basic concepts to clinical applications. Prog Brain Res. (182), 2010. 255-80.
40. Colao A, Faggiano A, Pivonello R. Somatostatin analogues: treatment of pituitary and neuroendocrine tumors. Prog Brain Res. (182) 2010, 281-94.
41. Hu M, Tomlinson B. Pharmacokinetic evaluation of lanreotide. Expert Opin Drug Metab Toxicol. (6), 2010, 1301-12.
42. Fleseriu M. Clinical efficacy and safety results for dose escalation of somatostatin receptor ligand in patients with acromegaly: a literature review. Pituitary. (14), 2011, 184-93.
43. Ferone D. Somatostatin and dopamine receptors. Tumori.(96), 2010, 802-5..
44. Weckbecker G., Raulf F., Stolz B., Bruns C. Somatostatin analogs for diagnosis and treatment of cancer. Pharmacol Ther. (60) 1993, 245-64..
45. Behr TM, Béhé M, Becker W. Diagnostic applications of radiolabeled peptides in nuclear endocrinology. J Nucl Med. 43, 1999, 268-80.
46. Kwekkeboom D, Kam B, Van Essen M, Teunissen J, Van Eijck C, Valkema R, De Jong M, De Herder W, Krenning P. Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer. 17, 2010, 53-73.
47. Behr T.M, Gotthardt M., Barth A., Béhé M. Imaging tumors with peptide-based radioligands. Q J Nucl Med. 45(2), 2001, 189-200.
48. Ginj M, Chen J, Walter MA, Eltschinger V, Reubi JC, Maecke HR. Preclinical evaluation of new and highly potent analogues of octreotide for predictive imaging and targeted radiotherapy. Clin Cancer Res. (11), 2005, 1136-45.
49. Virgolini I, Leimer M, Handmaker H, Lastoria S, Bischof C, Muto P, Pangerl T, Gludovacz D, Peck-Radosavljevic M, Lister-James J, Hamilton G, Kaserer K, Valent P, Dean R. Somatostatin receptor subtype specificity and in vivo binding of a novel tumor tracer, 99mTc-P829. Cancer res. (58), 1998, 1850-9.
50. Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, Mäcke HR. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. (27), 2000, 273-82.
51. De Jong M, Valkema R, Jamar F, Kvols K, Kwekkeboom D, Breeman W, Bakker W, Smith C, Pauwels S, Krenning E. Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings. Semin Nucl Med. (32), 2000, 133-40.
52. De Jong M, Breeman W, Bernard H, Kooij P, Slooter G, Van Eijck C, Kwekkeboom DJ, Valkema R, Mäcke HR, Krenning EP. Therapy of neuroendocrine tumors with radiolabeled somatostatin-analogues. J. Nucl Med. (43), 1999, 356-66.
53. Bangard M, Béhé M., Guhlke S., Otte R., Bender H., Maecke H.R., Biersack H.J. Detection of somatostatin receptor-positive tumours using the new 99mTc-tricine-HYNIC-D-Phe1-Tyr3-octreotide: first

results in patients and comparison with 111In-DTPA-D-Phe1-octreotide. Eur J Nucl Med. (27), 2000, 628-37.

54. Virgolini I, Traub T, Leimer M, Novotny C, Pangerl T, Ofluoglu S, Halvadjieva E, Smith-Jones P, Flores J, Li SR, Angelberger P, Havlik E, Andreae F, Raderer M, Kurtaran A, Niederle B, Dudczak R. New radiopharmaceuticals for receptor scintigraphy and radionuclide therapy. Q J Nucl Med. (44), 2000, 50-8.
55. Daniels Marie-Christine and Didier A. Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-Size-Related Properties, and Applications toward Biology, Catalysis, and Nanotechnology. Chem. Rev. 104, 2004, 293-346.
56. Prabaharan M, Jamison JG, Srikanth P, Douglas AS, Shaoqin G. Gold nanoparticles with a monolayer of doxorubicin-conjugated amphiphilic block copolymer for tumor targeted drug delivery; Biomaterials (30) (2009), 6065–75.
57. Gu YJ, Cheng J, Lin C, Lam YW, Cheng SH, Wong WT. Nuclear penetration of surface functionalized gold nanoparticles, Toxicology and Applied Pharmacology. 237, 2009, 196–204.
58. Hassan Azzazy ME, Mai MH Mansour, In vitro diagnostic prospects of nanoparticles, Clinica Chimica Acta. (403) 2009, pág 1–8.
59. James Baker R., Brent B. Jr. Ward and Thommey P. Thomas, Nanotechnology in Clinical and Translational Research, Clinical and Translational Science. 2009, 123-135,
60. Molina-Trinidad EM, Ochoa-Arredondo L, Mendoza-Oaxaca E, Huerta-Valencia V, Escobar-Chávez JJ, Hoyo-Vadillo C. Development and Validation of a Method Spectrophotometric for Quantify GNPs and GNPs-Lanreotide In vitro. J. Pharm Science and Technology. 3 (6), 2011, 608-612.
61. Molina-Trinidad EM, Estévez-Hernández O, Rendón L, Garibay-Febles V, Reguera E. Electronic and vibrational spectra of novel Lanreotide peptide capped gold nanoparticles. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2011, 283-9.
62. Agnieszka Sobczak-Kupiec A, Dagmara M, Malgorzata Z, Zbigniew W. Characterization of gold nanoparticles for various medical application. Digest J of Nanomaterials and Biostructures. (6), 2011, 803 – 808.
63. Mazzola L. Commercializing nanotechnology. Nat. Biotechnol. (21), 2003, 1137.
64. Sanvicens MP, Marco N, Multifunctional nanoparticles--properties and prospects for their use in human medicine. Trends Biotechnol. (26), 2008, 425-33.
65. Fadeel B, Garcia-Bennett AE. Better safe than sorry: Understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. Adv. Drug Delivery Rev. 62 (3), 2010, 362-74.
66. Azarmi WHS, Roa RL. Targeted delivery of nanoparticles for the treatment of lung diseases. Adv. Drug Delivery Rev. (60), 2008, 863-875.
67. Nirmala G, Pandian K, Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—A brief study. Colloids Surf., A (297), 2007, 63-70.
68. Ding XY, Zhang X, Liu RG. Colloid Surf, A, pág, 2006, 82.
69. Aryal S, Remant Bahadur KC, Bhattarai N, Kim ChK, Kim HY. J Colloid Interface Sci. 299, 2006, 191.
70. Wang MM. Thanou. Pharmacol. Res. 62(2), 2010, 90.
71. Li JL, Wang L, Liu XY, Zhang ZP, Guo HCh, Liu WM, Tang SH, Cancer Lett. (274), 2009, 319.
72. Ghosh GP,I Han MD, Kim ChK, Rotello VM. Gold nanoparticles in delivery applications Adv. Drug Delivery Rev. 60 (11), 2008, 1307-1315.
73. Huan MF, Kuo YC, Huang CC and Chang HT. Electrophoresis Anal Chem**, (**76), 2004, 192-196.
74. Kim Y, Yeung ES. Separation of DNA sequencing fragments up to 1000 bases by using Poly(ethylene oxide)-filled capillary electrophoresis. J. Chromatogr., A, (781) 1997, 315-325.
75. Han F, Huynh BH, Ma Y, Lin B. *Anal. Chem.*, (*71)*, 1999, 2385-2389.
76. Zhou H, Miller AW, Sosic Z, Buchholz B, Barron AE, Kotler L, Karger BL. *Anal. Chem.* (*72),* 2000, 1045-1052.
77. Neiman EBG and Lev O. Use of Gold Nanoparticles To Enhance Capillary Electrophoresis. Anal Chem, (73), 2001, 5220-5227.
78. Sokolov KM, Follen J, Aaron IP, Malpica A, Lotan R, and Richards-Kortum R. Real- Time Vital Optical Imaging of Precancer Using Anti-Epidermal Growth Factor Receptor Antibodies Conjugated to Gold Nanoparticles. Cancer Research (63) 2003, 1999-2004.
79. Marie-Christine D and Didier A. Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-Size-Related Properties, and Applications toward Biology, Catalysis, and Nanotechnology. Chem Rev, 104, 2004, 293-346.
80. Navarro Bosch DP, Lara BN, Díaz C. Docencia en Oncología. BioCancer Research Journal. 1(6), 2012, 1697-6452.
81. Huang L, S.D. Li, Pharmacokinetics and biodistribution of nanoparticles. Mol Pharm. 5(4), 2008, 496-504.
82. Bawarski E, Chidlowsky JN, Bharali DJ, Mousa SA. Emerging nanopharmaceuticals. Nanomed Nanotech Biol Med, 4, 2008, 273-282.
83. Moddaresi MB, Brown YZ, Tamburic S, Jones SA. The role of vehicle nanoparticle interactions in topical drug delivery. Intern J Pharmac, 400 (1-2), 2010, 176-182.
84. Molina-Trinidad EM Farmacocinética Básica. Universidad Nacional Autónoma de México. Facultad de Estudios Superiores Cuautitlán. 1ra. Edición. 2011, 145-170.
85. Molina-Trinidad EM, Estévez-Hernández LO, Rendón V, Garibay-Febles E, Reguera E. Electronic and vibrational spectra of novel Lanreotide peptide capped gold nanoparticles. Spectrochimica Acta Part A (82) 2011, 283–289.
86. Huang IHX, El-Sayed WQ, and El-Sayed MA. Cancer Cell Imaging and Photothermal Therapy in the Near-Infrared Region by Using Gold Nanorods. J Am Chem Soc, 128 (6), 2006, 2115–2120,
87. Emsley J, Nature's Building Blocks: An A-Z Guide to the Elements. New York: Oxford University Press, 2001, 422–425.
88. Rimshaw SJ, Cifford A, Hampel Ed. The Encyclopedia of the Chemical Elements. New York: Reinhold Book Corporation, 1968, 689–693.
89. Al-Qadi S y Remuñan- López C, Nanopartìculas metálicas: oro, Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 2009, 223-241.
90. Takeuchi N. Nanociencia y Nanotecnología: algunas aplicaciones de la nanociencia y nanotecnología en la medicina. Universidad Nacional Autónoma de México. Anestesia en México 21 (3), 2009, 231-233.
91. Hullmann A. Measuring and assessing the development of nanotechnology; Scientometrics 70(3), 2007, 739-758,
92. González R, Suwalsky M. Oro y sus propiedades Terapéuticas, Ciencia Ahora, (24), 2012, 16 – 21.
93. Vinod P, Siddik, Berlin GVM, Guruvayoorappan Ch, "Nanoparticles in drug delivery and Cancer Therapy: The Giant rats Tail". Journal of cancer Therapy, Vol. (2), 2008, 325 – 334.
94. Brewer M, Tierui Z, Wenjun D, Michael Rutherford, y Z. Ryan Tian,"Futuros abordajes de la nanomedicina en la ciencia clínica", Medical Clinical North American,Vol. (91), 2007, 963 – 1015.
95. Thing CHG, Chang and HEW. "Cancer Nanotargeted Radiopharmaceutical for Tumor Imaging and Therapy", Anticancer Research, Vol. (29), No. 10, 2009, 4107 - 4108.

96. Yang WJI, Peters RO, and Williams Eds. Inhaled Nanoparticles-A Current Review, International Journal of Pharmaceutical, 22 (356), 2008, 239 – 247.

97. Dr. Noboru Takeuchi," Algunas Aplicaciones de la Nanociencia y la Nanotecnología en la Medicina", Revista Anestesia en México, 21 (3), 2009, 1-7.

98. Ventosa N. Materiales Moleculares nanoestructurados en el desarrollo de nuevos fármacos, Dossier Científico, 168, 2011, 18 – 22.

99. Bhattacharya R & Mukherjee P, "Biological properties of –naked-metalnanoparticles", Advanced Drug Delivery Reviews, 60, 2008, 1289 – 1306.

100. Hernando Grande A. Nanotecnología y nanopartículas magnéticas: La física actual en lucha contra la enfermedad. Rev.R.Acad.Cienc.Exact.Fís.Nat. (Esp) 101(2), 2007, 321-327.

101. Loo Ch, Lin A, Hirsch L, et al. Technology in Cancer Research and Treatment. Adenine Press, Inc. (3) 33, 2004, 1-6.

102. Thomas TP, Ye JY, Chang YC, Kotlyar A, Cao Z, Majoros IJ, Norris TB, Baker JR. Investigation of tumor cell targeting of a dendrimer nanoparticle using a double-clad optical fiber probe. J Biomed Opt, (13), 2008, 1-5.

103. Asasutjarit R, Lorenzen SI, Sirivichayakul S, Ruxrungtham K, Ruktanonchai U, Ritthidej GC. Effect of solid lipid nanoparticles formulation compositions on their size, zeta potential and potential for in vitro pHIS-HIV_Hugag transfection. Pharmaceutical Research, 24(6), 2007, 1098-1107.

104. Zehe AFK. Internet Electron. J Nanoc Moletrón, 4 (3), 873-888.

105. Meyer M, Kuusi O: Nanotechnology: Generalizations in an Interdisciplinary Field of Science and Technology. International Journal for Philosophy of Chemistry (Publicación internacional sobre la filosofía de la química); 10, 2002, 153-168.

106. Schmidt G, Decker M, Ernst H, Fuchs H, Grunwald W, Grunwald A et al. Small dimensions and material properties. (Dimensiones pequeñas y propiedades de los materiales). Europaische Akademie Graue Reihe. A definiton of nanotechnology (Una definición de nanotecnología), 134, 2003, 1.

107. Juárez Ramírez I, Torres Martínez LM, Cruz López A, Garza Tovar LL, Meza de la Rosa ME. Ciencia UANL, (11) 4, 2008.

108. Elder de la Rosa C. Nanofotónica: luz + nanopartículas. (2) 24, 2007, 3-8.

109. Sáez et al. Liberación controlada fármacos. Revista Iberoamericana de Polímeros, Volumen 5(2), 2004, 1-7.

110. Wolfgang M, Benito A, Martínez T. Nanotubos de Carbono: Objetos nanométricos fundamentales para el desarrollo de materiales de altas prestaciones. Departamento de Nanotecnología, Instituto de Carboquímica (CSIC). España, 2009, 1.

111. Wissing SA, Müller RH. Solid lipid nanoparticles as carrier for sunscreens: in vitro release and in vivo skin penetration. *Journal of Controlled Release*, (81), 2002, 225–233.

112. Müller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs: a review of drug nanocrystal technology and lipid nanoparticles. *Journal of biotechnology*, 13, 2004, 151-170.

113. Hu FQ, Hong Y, Yuan H. Preparation and characterization of solid lipid nanoparticles containing peptide. *International Journal of Pharmaceutics*, 273, 2004, 29-35.

114. Wissing SA, Mäder K, Müller RH. Solid lipidnanopartices (SLN) as a novel carrier system offering prolonged release of the perfume Allure (Chanel). *In Proc. Int. Symp. Control Rel Bioact Mater,* 27, 2000, 311–312.

115. Hu LD, Tang X, Cui FD. Preparation of solid lipid nanoparticles loaded with all-trans retinoic acid and their evaluation in vitro and in vivo. *Yao Xue Xue Bao*, 40, 2005, 71–75.

116. Jee JP, Lim SJ, Park JS, Kim CK. Stabilization of all-trans retinol by loading lipophilic antioxidantsin solid lipid nanoparticles. *Eur.Pharm.Biopharm,* 63, 2006, 134–139.

117. Mehnert W, Mäder K. Solid lipid nanoparticles. Production, characterization and applications. *Advanced Drug Delivery Reviews*, 47 (23), 2001, 165-196.

118. Mei Z, Wu Q, Hu S, Li X. Triptolide Loaded Solid Lipid Nanoparticle Hydrogel for Topical Application. *Drug Development and Industrial Pharmacy*, 31, 2005, 161–168.

119. Pople PV, Singh KK. Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. *AAPS PharmSciTech* 7(4) 2006.

120. Parhi P, Mohanty, C, Sahoo, SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. Drug Discov. 17, 2012, 1044-1052.

121. Sánchez A., Nanotecnología para aumentar el efecto de los fármacos, MoleQla Nanotecnológica, 3 (73), 2011,

122. Mundo Nano. Experiencias en micro y nanoescalas para niños y jóvenes. Revista interdisciplinaria en Nanociencia y Nanotecnología. 4 (2), 2011, 121-129.

123. Ramachandra C., Kulkarni G., Thomasa J., Edwards P., *Nanoparticles del metal y sus asambleas*, Quím. Soc. Inversor de corriente. 29, 2000, 27-35.

124. Vila J. Nanotecnología Farmacéutica: Una Galénica Emergente, 9 de marzo de 2006. 1-20.

125. Lai F, Wissing SA, Müller RH, Fadda AM. Artemisia arborescens L Essential Oil–Loaded Solid Lipid Nanoparticles for Potential Agricultural Application: Preparation and Characterization. *AAPS ParmSciTech*. 7 (1) 2006, 1-4.

126. Jores K, Mehnert W, Bunjes H, Drechsler M, Mäder K. From solid lipid nanoparticles (SLN) to nanospoons. Visions and reality of colloidal lipid dispersions. Controlled release Society, 30th Annual Meeting proceedings, 2003.

127. Béduneau A, Saulnier P, Benoit JP. Active targeting of brain tumors using nanocarriers. *Biomaterials*, 28, 2007, 4947–4967.

128. Yang SC, Zhu JB. Preparation and characterization of camptothecin solid lipid nanoparticles. *Drug Development and Industrial Pharmacy*, 28(3), 2002, 265-274.

129. Reddy LH, Vivek K, Bakshi N, Murthy R.S.R. Tamoxifen citrate loaded solid lipid nanoparticles (SLN): preparation, characterization, in vitro drug release and pharmacokinetic evaluation. *Pharmaceutical Development Technology*, 11, 2006, 167-177.

130. Yoncheva K, Vandervoort J, Ludwig A. Influence of process parameters of highpressure emulsification method on the properties of pilocarpine-loaded nanoparticles. *Journal of Microencapsulation*, 20(4), 2003, 449-458.

131. Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *International Journal of Pharmaceutics*, 278, 2004, 71-77.

132. Venkateswarlu V, Manjunath K. Preparation, characterization and in vitro release kinetics of clozapina solid lipid nanoparticles. *Journal of Controlled Release*, 95, 2004, 627-638.

133. Hsu CH, Cui Z, Mumper RJ, Jay M. Preparation and Characterization of Novel Coenzyme Q10 Nanoparticles Engineered from Microemulsion Precursors. *AAPS PharmSciTech*, 4(3), 2003, 32.

134. Cengiz E, Wissing SA, Müller RH, Yazan Y. Sunblocking efficiency of various TiO2-loaded solid lipid nanoparticle formulations. *International Journal of Cosmetic Science*, 28, 2006, 371–378.

135. Hitzman CJ, Elmquist WF, Wiedmann T S. Development of a Respirable, Sustained Release Microcarrier for 5-Fluorouracil II: In Vitro and In Vivo Optimization of Lipid Coated Nanoparticles, *Journal of Pharmaceutical Sciences,* 95 (5), 2006, 1127-1143.

136. Casadei MA, Cerreto F, Cesa S, Giannuzzo M, Feeney M, Marianecci C, Paolicelli P. Solid lipid nanoparticles incorporated in dextran hydrogeles: a new drug delivery system for oral

formulations. *International Journal of Pharmaceutics*, 325, 2006, 140-146.

137. Liu J, Gong T, Wang Ch, Zhong Z, Zhang Z. Solid lipid nanoparticles loaded with insulin by sodium cholate-phosphatidylcholine-based mixed micelles: Preparation and characterization. *International Journal of Pharmaceutics*, 340, 2007 (b), 153–162.
138. Liu J, Hu W, Chen H, Ni Q, Xu H, Yang X. Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. *International Journal of Pharmaceutics*, 328, 2007 (a), 191-195.
139. Souto EB, Müller RH. SLN and NLC for topical delivery of ketoconazole. *Journal of Microencapsulation*, 22(5), 2005, 501-510.
140. Hou DZ, Xie Ch S, Huang KJ, Zhu Ch H. The production and characteristics of solid lipid nanoparticles (SLNs). *Biomaterials,* 24, 2003, 1781–1785.
141. Iscan Y, Wissing SA, Hekimoglu S, Muller RH. Solid lipid nanoparticles (SLN) for topical drug delivery: incorporation of the lipophilic drugs N,Ndiethyl-m-toluamide and vitamin *K. Pharmazie,* 60, 2005, 905–909.
142. Souto EB, Anselmi C, Centini M, Müller RH. Preparation and characterization of ndodecyl-ferulate-loaded solid lipid nanoparticles (SLN). *International Journal of Pharmaceutics*, 295, 2005, 261-268.
143. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine 1, 2005, 193-212.
144. Junping W, Takayama K, Nagai T, Maitani Y. Pharmacokinetics and antitumor effects of vincristine carried by microemulsions composed of PEG-lipid, oleic acid, vitamin E and cholesterol. Int J Pharm, 251, 2003, 13-21.
145. Baker JR. The synthesis and testing of anticancer therapeutic nanodevices. Biomed Microdevices, 3, 2001, 59-67.
146. Cloninger MJ. Biological applications of dendrimers. Curr Opin Chem Biol. 6, 2002, 742-748.
147. Clavijo D, Grégory A, Mejía O, Ruiz A, García A, Torrado D, Mejía M. La frontera entre la Biología molecular y la Nanotecnología: impacto en la Medicina, Iatreia, 20 (3), 2007, 297-298.
148. Kumar A, Kumar VP, Ajayan PM, John G. Silver nanoparticle embedded antimicrobial paints based on vegetable oil. Nature Materials, 7, 2008, 236-241.
149. Thomas TP, Ye JY, Chang YC, Kotlyar A, Cao Z, Majoros IJ, Norris TB, Baker JR. Investigation of tumor cell targeting of a dendrimer nanoparticle using a double-clad optical fiber probe. J Biomed Opt, 13, 2008, 14-24.
150. Usos de la Plata, Disponible en: http://blog-static.hola.com/farmaciameritxell/2012/11/la-plata-tambien-es-util-en-medicina-y-en-cosmetica.html. Acceso el 2 de Enero del 2014.
151. Loo Ch, Lin A, Hirsch L, et al. Technology in Cancer Research and Treatment. Adenine Press, Inc., 3, 2004, 33.
152. Aplicaciones de la Nanotecnología. Disponible en: http://www.euroresidentes.com/Blogs/avances_tecnologicos/2004/08/ejemplos-de-aplicaciones-de-la.htm. Acceso el 2 de Enero del 2014.
153. Orozco A, Nanotecnología, Innovación Tecnológica y Transformación Social en i-Europ, 2003.
154. Hacia los Nanomedicamentos Inteligentes. Disponible en: http://www.elmundo.es-elmundo-2011-08-05-nanotecnologia-1312543351.html. Acceso el 3 de Enero del 2014.
155. Bozzola JJ and Russell LD. Electron Microscopy: Principles and Techniques for Biologists. Ed. Jones and Bartlett. Bos542.
156. Bhattacharyya JMA and Wazed Ali S, Characterization Techniques for nanotechnology Applications in Textiles. Indian Journal of Fibre and Textile Research, 33, 2008, 304-317.
157. Goodhew PJ, Humphreys FJ, Electron Microscopy and Analysis, Edit. Taylor & Francís, London, 1988, s/p.
158. Gardea-Torresdey JL, Peralta-Videa JR, Rosa G, Parsons JG. Phytoremediation of heavy metals and study of the metal coordination by X-ray absorption spectroscopy. Coordination Chemistry Reviews, 249, 2005, 1797–1810.
159. López ML, Parsons JG, Peralta Videa JR, Gardea-Torresdey JL. An XAS study of the binding and reduction of Au (III) by hop biomass. Microchemical Journal, 81, 2005, 50–56.
160. Jentys L, Simon JA, Lercher. On the Determination of the Location of Metal Clusters Supported on Molecular Sieves by X-ray Absorption Spectroscopy. Journal of Physics and Chemestry; 104, 2000, 9411.
161. Revista Digital Universitaria. Caracterización de Oro, ISSN: 1607-6079. 7, 2005, s/p.
162. Lewis LJ, Jensen P, Barrat J, "Melting, freezing and coalescence of gold nanonoclusters", Phys. Rev, 56, 1997, 2248.
163. Arcidiano S, Bieri N, Poulikakos D, Grigoropoulos CP. . International Journal of Multiphase Flow, 30 (7), 2004, 979-994.
164. Zhu H, Averback R, Sintering processes of two nanoparticles: A study of molecular-dynamics simulations, *Philosophical Magazine Letters*; 73 (27), 1996, s/p.
165. Zhao S, Wang S, Yang Z, Ye H, Coalescence of three silver nanoclusters: a molecular dynamics study. *J. Phys Condens Matter,* 13, 2001, 8061-8069.
166. Dong H, Molecular dynamics study on the coalescence of Cu nanoparticles and their deposition on the Cu substrate. *Journal of Electronic Materials*, 33 (11), 2004, 1326-1330.
167. Coblenz W, Dynys J, Initial stage solid state sintering models. A critical analysis and assessment. Materials Science Research; 13, 1980, 141-157.
168. Rojas J, Rojas Ch, Internet Electron, J. Nanoc. Moletrón. 4 (3), 2006, 805-814.
169. Marzán LL, Tailoring surface plasmons through the morphology and assembly of metal nanoparticles, Langmuir; 22(1), 2006, 32-41.
170. Prieto P, Introducción a Nanociencia, Universidad del Valle, Centro de Excelencia en Nuevos Materiales, CENM, 10, 2010.
171. Nanotecnología, "Ciencia de lo Pequeño". Disponible en: http://www.jmordoh.com.ar/clases/nanotec.pdf. Acceso 2 de Diciembre del 2013.
172. Nanopartícula de Oro. Disponible en: http://www.diariomedico.com/archivo?archiveDate=2010/06/11. Acceso 2 de Diciembre del 2013.
173. Nanopartículas de Oro. Disponible en: http://noticiasdeultima.blogspot.mx/search/label/Nanotecnologia. Acceso 3 de Diciembre del 2013.
174. Árbol de Madroño. Disponible en: www.chihuahuamexico.com/index.php?option=com_content. Acceso 3 de Diciembre del 2013.
175. Pileni MP, Ninham BW, Gulik-Krzywicki, Tanori J, Lisiecki I, Filankembo A. Direct Relationship Between Shape and Size of Template and Synthesis of Cupper Metal Particles. Adv. Mater, 11 (16), 1999, 1358-1362.
176. Turkevich J; Stevensen P.C.; Hillier J., Nucleation and growth process in synthesis of colloidal gold. Discuss Faraday Soc. 11, 1951, 55-75.
177. Daniel MC, Astruc D. Gold Nanoparticles: Assembly, supramolecular chemistry, quantum size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem. Rev., 104 (1), 2004, 293-346.
178. Pong BK; Nuevas penetraciones en el mecanismo del crecimiento de nanopartículas en la reducción del citrato de la sal del oro III, J. Phys. Quím. C, 111 (17), 2007, 6281-6287.

179. Shipway AN et al. Investigations into the electrostatically induced aggregation of Au nanoparticles. Langmuir, 16 (23), 2000, 8789-8795.

180. Bohinsky R. Aminoácidos y péptidos. En su: Bioquímica. 5 a edición. U.S.A. Addison-Wesley Iberoamericana, 1991, 63-111.

181. Fernández A, Explorando los cambios conformacionales de péptidos ricos en prolina mediante microscopía de fuerza atómica. Master experimental en química orgánica. Barcelona, España. Universidad de Barcelona, Departamento de Química Orgánica, 9, 2004, 20-39.

182. Hyslop GPH, Piecing together Alzheimer's Sci Am, 283 (6), 2000, 76-83.

183. Kisilevsky R, Fraser PE, Aβ amyloidogenesis: unique, or variation on a systemic theme? Crit. Rev. Biochem. Mol. Biol. 32 (5), 1997, 361-404.

184. Selkoe DJ, The molecular pathology of Alzheimer's disease. Neuron, 6 (4), 1991, 487-498.

185. Small GW, The pathogenesis of Alzheimer's disease. J. Clin. Psychiatry. 59 (9), 1998, 7-14.

186. Findeis MA, Peptide inhibitors of beta amyloid aggregation. Curr. Top. Med. Chem. 2, 2002, 417-423.

187. Caughey B, Lansbury P.T. Protofibrils, pores, fibrils, and neurodegeneration: separating the responsible protein aggregates from the innocent bystanders. J Annu Rev Neurosci, 26, 2003, 267-298.

188. Arimon M, Dìez-Pérez I, Kogan MJ, Durany N, Giralt E, Sanz F, Fernàndez-Busquets X. Fine structure study of Aβ 1-42 fibrils with atomic force microscopy. FASEB J, 19 (10), 2005, 1344-1346.

189. Bieler S, Soto CInfante R, Beta-Sheet breakers for Alzheimer's disease therapy. Curr. Drug Targets, 5 (6), 2004, 553-558.

190. Veciana J, Corma A. Nanomateriales y Nanoquímica, Nanomedicina, 155, 2005, 5811-5813.

191. Jores K, Mehnert W, Bunjes H, Drechsler M, Mäder K. From solid lipid nanoparticles (SLN) to nanospoons. Visions and reality of colloidal lipid dispersions. Controlled release Society, 30th Annual Meeting proceedings, 2003, 181-182.

192. Garzón M.L., Hernández A., Vázquez M.L., Villafuerte L., García B. Preparación de nanopartículas sólidas lipídicas (SLN), y de Acarreadores lipídicos nanoestructurados (NLC). Revista mexicana de Ciencias Farmacéuticas, 39(4), 2008, 50-71.

193. Callén Palacio JM, Bragós Bardia R. Sistemas de estimulación mecánica y caracterización de polímeros para Ingenieria Tisular. Escola Té cnica superior d`Enginyeria de Telecomunicació de Barcelona, 2009, 6-20.

194. Infante Blanco R. Los Polímeros en Medicina: polimeros biodegradables y biopolimeros, Química y Tecnología de Macromoléculas, Universidad de Valladolid, 2005-2006. [Consultado en febrero del 2014], Disponible en (http://www.ies.uva.es/~macromol/curso05-06/polimeros_biodegradables.htm)

195. Ramírez M, Ramírez BA, Posibles usos de las células madres, Electron J Nanoc Moletrón, 4 (3), 2006, 868.

196. Taboada T, Nuevos materiales nanoestructurados multifuncionales para aplicaciones biomédicas, Fundación Ramón Areces, Oct. 13, 2007, 1-26.

197. Bogunia-Kubik K, Sugisaka M, From molecular biology to nanotechnology and nanomedicine, Biosystems, 65, 2002, 123-138.

198. Zamboni WC, Gervais AC, Egorin MJ, Schellens JH, Zuhowski EG, Pluim D, et al, Systemic and tumor disposition of platinum after administration of cisplatin or STEALTH liposomal-cisplatin formulations (SPI-077 and SPI-077 B103) in a preclinical tumor model of melanoma, Cancer Chemother Pharmacol, 53, 2004, 329-336.

199. Donald PR, Sirgel FA, Venter A, Smit E, Parkin DP, Van de Wal BW, et al, The early bactericidal activity of a lowclearance liposomal amikacin in pulmonary tuberculosis, J Antimicrob Chemother, 48, 2001, 877-880.

200. Reubi JC, In vitro identification of vasoactive intestinal peptide receptors in human tumors: implications for tumor imaging, J Nucl Med, 36, 1995, 1846-1853.

201. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today, 8, 2003, 1112-1120.

202. Voura EB, Jaiswal JK, Mattoussi H, Simon SM, Tracking metastatic tumor cell extravasation with quantum dot nanocrystals and fluorescence emission scanning microscopy, Nat Med, 10, 2004, 993-998.

203. Ozkan M, Quantum dots and other nanoparticles: what can they offer to drug discovery?, Drug Discov Today, 9, 2005, 1065-1071.

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