Published in final edited form as:

Anticancer Agents Med Chem. 2011 December ; 11(10): 965–973.

Cancer Nanotechnology: Emerging Role of Gold Nanoconjugates

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Abstract

Over the last few decades, the study of nanotechnology has grown exponentially. Nanotechnology bridges science, engineering and technology; it continues to expand in definition as well as practice. One sub-set of nanotechnology is bionanotechnology, this will be the focus of this review. Currently, bionanotechnology is being studied and exploited for utility within medicinal imaging, diagnosis and therapy in regard to cancer. Cancer is a world-wide health problem and the implication rate as well as the death rate increase year to year. However promising work is being done with gold nanoparticles for detection, diagnosis and targeted drug delivery therapy. Gold nanoparticles can be synthesized in various shapes and sizes, which directly correlates to the color; they can also be manipulated to carry various antibody, protein, plasmid, DNA or small molecule drug. Herein we summarize some of the very influential research being done in the field of Cancer Nanotechnology with an emphasis on gold nanoparticles.

Keywords

Cancer; Gold; Nanoparticles; Targeted Drug Delivery

1. INTRODUCTION

Cancer is a general term for an immensely complex disease. It can invade the human body, survive extermination attempts, mutate to protect itself and undergo unbridled growth while evolving [1]. It exploits the fundamentals of evolution unlike any other illness and remains a leading cause of death worldwide. According to the World Health Organization there were 7.6 million cancer deaths in 2008 and that number is projected to rise to over 11 million by 2030. Cancer is the uncontrolled or abnormal division of cells, these cells do not look or behave like normal cells and may be caused by environmental or genetic factors. The uncontrolled growth and division can begin and then spread all over the body, such as to the breast, prostate, lung and bronchus, thyroid, urinary bladder, colon and rectum, stomach, liver, pancreas, melanoma of the skin, esophagus, tongue, oral cavity, kidney, leukemia, lymphoma, brain and ovaries [2].

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A plethora of treatments lay testimony to the challenge that is cancer and range from chemotherapy, photodynamic therapy, laser therapy, monoclonal antibody therapy, gene therapy, anti-angiogenic therapy, immunotherapy, stem cell transplantation, radiation therapy and surgery [3-6]. A number of factors determine which treatment venue to take; they include the stage and location of the cancer as well as the overall health and age of the patient. The ideal situation would be to completely remove the tumor tissue through a non-invasive therapy that has minimal side effects. However due to the heterogeneous and potentially aggressive nature of malignant cells this is an incomprehensible outcome. Frequent challenges encountered by current anti-cancer and anti-angiogenic agents include nonspecific systemic distribution, drug resistance, intolerable toxicity and poor bioavailability [7-10].

Researchers and clinicians agree the plaguing issues lie in early detection, more sensitive imaging and achieving the desired localized concentration of the anti-cancer agents while minimizing damage to healthy cells. Advances in cancer nanotechnology have shown promise for detecting cancer at its early stages, delivering anti-cancer agents in passive and active formulations as well as increasing the efficacy of traditional anti-cancer therapeutics [11-16]. Cancer nanotechnology is an interdisciplinary field that combines biology, chemistry, medicine and engineering [17]. Recent success in this area, particularly with gold nanoparticles is proving exciting for changing the foundations for detection, diagnosis and therapy. More sensitive diagnostics have been shown with the implementation of poly-ethylene glycol coated gold nanoparticles for use as a contrast agent for computed tomography (CT) [18]. Gold particles have also been explored for their potential to cross the blood brain barrier, alter traditional endocytosis, and be successfully utilized as a targeted drug delivery system [16, 19-23]. In this review the focus will be on the use of gold in medicine with an emphasis on the developing implications in the cancer nanotechnology field.

2. MEDICINAL USE OF GOLD: A HISTORICAL PERSPECTIVE

Gold has been used for art, jewelry, coinage and medicine throughout the history of civilization. The extraction of gold dates back to the 5th millennium B.C. near Varna in Bulgaria. By 1200 B.C., it was being extracted by the ton in Egypt and was used in the construction of the statue of King Tut (Touthankamon) [24]. The use of gold in stained glass and ceramics is the first known example of colloidal gold. Depending on the size, shape and degree of aggregation, colloidal gold can appear red, purple, and blue amongst many other colors (Figure 1) [25]. The Lycurgus cup from Roman times, 4th century A.D., is an example of the unique optical properties of nanoparticles; it appears green in reflected light yet red in transmitted light. Various colors reflect the plasma oscillations upon irradiation with Ultra-Violet light at various wavelengths [25]. The bulk dielectric constant for gold lies in the visible region of the electromagnetic spectrum, which is why we see such brilliant colors [26].

In the middle ages, the exploration of the curative properties of gold had begun. Gold was utilized for the treatment of various diseases, such as venereal problems, heart disease, tumors, dysentery, epilepsy and the diagnosis of syphilis. In the 17th century, Nicholas

Culpepper advocated for the use of gold in treatment of fevers, depression and fainting. During the 19th century, a 'muriate of gold and soda,' a mixture of gold chloride and sodium chloride was used to treat syphilis [27]. In 1890, German scientist Robert Koch discovered that gold cyanide was bacteriostatic towards *tubercle bacillus*. Subsequently, in 1920 gold therapies were introduced to treat tuberculosis. It had been suggested that tubercle bacillus was a potential cause for rheumatoid arthritis and in turn gold was implicated in the treatments for this disease as well. Over time, gold therapy was proven fruitless for tuberculosis. However, the Empire Rheumatism Council sponsored a thirty year clinical study which proved the effectiveness of using gold compounds to treat rheumatoid arthritis [27]. After this confirmation, gold drugs were implemented in the treatment for a variety of other rheumatic diseases, including psoriatic arthritis, juvenile arthritis, palindromic rheumatism, and discoid lupus erythematosus, not to mention the use in treating numerous inflammatory skin disorders [27].

Rheumatoid arthritis is an autoimmune disease; progressive inflammation erodes the cartilage in the joints and leads to pain, deformity and immobility. Raised levels of cytokines, leukotrienes and prostaglandins are responsible for the progressive inflammation [27]. The gold compounds initially used to treat rheumatoid arthritis were oligomers, sodium aurothiomalate (MyocrisinTM) and aurothioglucose (SolganolTM); both gold (I) thiolates. Unfortunately, these compounds needed to be administered by deep intramuscular injection, this promoted rapid absorption but also caused a major side effect. Gold was rapidly cleared by the bloodstream and distributed into the kidneys, where it accumulates and causes nephrotoxicity, other side effects include occasional liver toxicity, mouth ulcers and skin reactions [28]. In 1985, auranofin (RidauroTM) was introduced as the first orally-available gold-based therapeutic (Figure 2) [27]. The paramount and unprecedented oral administration of RidauroTM provided several advantages, including a reduced tissue retention of gold which appreciably reduces renal toxicity. Unfortunately, the decrease in side effects is countered by a decrease in efficacy compared to the oligomeric gold (I) thiolates.

Since the mid 80's, few gold based drugs have entered clinical trials, but several studies have been done to evaluate the medicinal potential. The research efforts for disease detection and treatment utilizing gold has skyrocketed, particularly in the field of cancer.

3. CANCER STATISTICS: MODALITY OF CANCER TREATMENTS

According to the Centers for Disease Control and Prevention, the leading causes of cancer deaths in men and women are 1) prostate and breast, respectively 2) lung and bronchus 3) colon and rectum, followed by 4) urinary bladder and gynecologic cancers. The mortality rates for cancer overall is staggering [2, 29]. As years progress, early detection remains the foremost significant factor for successfully combating any type of cancer from lung, to pancreatic. The traditional modes of treatment (surgery, chemotherapy, and radiotherapy) have been the standard options for decades [9]. However, the key issue with these treatment strategies is toxicity to normal or healthy cells. In addition, due to late presentation of symptoms and diagnosis, many patients are not good surgical candidates, therefore rendering therapeutic intervention the last and only resort [7-9, 30].

4. DRUG DELIVERY IN CANCER: DIFFERENT METHODS, ADVANTAGES AND DISADVANTAGES

Conventional cancer treatment options, such as chemotherapies and radiation therapies are distributed non-specifically in the body. Non-specific therapies affect both malignant cells and healthy cells, in turn, this systemic distribution limits the dose achievable within the tumor environment leading to suboptimal therapeutic effect, excessive toxicity and the development of multiple drug resistance [7-9, 17, 31, 32]. Molecularly targeted therapy has emerged as a possible, and has grown into a probable, solution to overcome the lack of specificity and the development of resistance in cancer cells as well as the other critical pitfalls that come along with it [32-35]. Targeted therapy may be obtained through intelligent design and implementation of gold nanoparticles.

4.1 TARGETED DELIVERY

Targeted delivery via gold nanoparticles can be split into two major categories, passive and active targeting (Figure 3). Both can increase intracellular concentration of the anti cancer agent directly in the tumor environment leading to a potential decrease in toxicity to healthy cell [36-41]. Gold nanoparticles can be functionalized with a gamet of biological molecules, rendering them an ideal and somewhat endless option for therapeutic intervention. Depending on the ligand bound to the surface of the particle, gold nanoparticles can be designed to cross the blood brain barrier, target over-expressed receptors and enter into the cell through an alternative path. Passive targeting of nanoparticles relies heavily on the enhanced permeability and retention (EPR) effect, and tumor angiogenesis. Active targeting relies on ligand-directed binding to over-expressed receptors expressed by tumor cells. Anticancer agents can also be designed to release from the particle in a pH or temperature dependent manner [32]. The *in vivo* toxicity of metallic gold as well as gold particles has been well investigated since the 1950s and continues to prove to be non-toxic [14, 22, 42-48].

4.1.1 PASSIVE TARGETING—Passive targeting is based on concentration and size; the accumulation of a drug or drug delivery system in the desired site due to the physico-chemical and pharmacological factors [17]. This approach takes advantage of the anatomical and functional differences between the vasculature in normal versus cancerous cells. Tumor vasculature has different angiogenic properties. Angiogenesis is simply the growth of new blood vessels, however tumor blood vessels have much larger gaps than blood vessels in normal cells and leaky in nature; the gaps are as large as 600-800 nm between endothelial cells [38]. The differences in vasculature might be attributed to elevated levels of vascular mediators such as nitric oxide, prostaglandins, fibroblast growth factor and vascular endothelial growth factors (VEGF) [17, 38]. The characteristic nature of these blood vessels induces the EPR effect, which enables nanoparticles to travel through these gaps in the tumor vasculature and accumulate in tumor tissues [38, 39, 49]. This accumulation can greatly increase the local concentrations of drugs attached to gold nanoparticles. Passive targeting can be successful but it is an imperfect model, unfortunately the size of the particles is limited to more than 40 nm. Particles less than 20 and up to 30 nm can easily pass through the leaky capillary wall of the tumor and enter into the blood circulation,

rendering them having good permeability but poor retention [36-39, 49-51]. However, the fundamentals behind active targeting can combat this short coming.

4.1.2 ACTIVE TARGETING—Active targeting takes a more direct approach and utilizes a homing moiety, such as a monoclonal antibody to exploit molecular recognition and cross biological barriers. In addition to tumor environments having leaky vasculature they also over-express various receptors. The over-expression of these receptors makes direct targeting a possibility. Numerous targeting agents have been studied, such as growth factors, antibodies, lectins, cytokines and small molecule have all shown various specificity to the tumor cells [16, 52-57]. Active targeting exploits these direct interactions through conjugation to the particle surface and increases the local concentration of anti tumor agents specifically in the tumor environment while decreasing the unwanted toxicity to the normal tissue.

Nanoconjugates can be designed to have a targeting agent and a cytotoxic drug attached. This type of design also has its imperfections but has been shown effective for decreasing toxicity to healthy cells [16]. Active targeting can also be useful for multiple drug resistance, by modifying the surface coverage of the particle one can intelligently mediate the pathway for internalization [23, 58].

With the use of gold nanoparticles via passive or active targeting the local concentration can be increased, multi drug resistance may be combated (due to alternative cellular internalization routes), and toxicity could be minimized.

5. APPLICATIONS OF GOLD NANOCONJUGATES

Great advances have been made in the design and synthesis of pharmaceutical compounds for the treatment of human disease in the past century. Diseases such as breast cancer and chronic myelogenous leukemia, once thought to be completely untreatable, are now survived by a large percentage of patients [2, 29, 59]. However, it is common knowledge that the depletion of commercial drug pipelines forecasts a grim future for molecular medicine and human health [60]. The underlying cause for the upcoming shortfall of next generation drugs resides fundamentally in the approach that is taken to conduct drug discovery and detection of disease. Medical challenges to overcome in the 21st century include the emergence of drug resistant bacteria, evolving viral strains and poorly treated diseases such as brain and lung cancer, autoimmunity and neurodegenerative disorders (Alzheimer's, Parkinson's, etc.).

Medicinal research efforts with gold nanoparticles have been directed towards drug delivery systems, catalysis, anti-infective agents, chemotherapeutics, detection and diagnostics, as well as disruption of protein/protein interactions [57, 61-66]. Gold nano-systems are attractive due to the unique properties of gold nanoparticles. The optical properties are dependent on size and shape, as well as the lack of toxicity and ease of monolayer manipulation render gold nanoparticles as a technology worth pursuit [24, 25, 30, 67-69].

Gold nanoparticles have been fabricated for use as sensors for early detection of many diseases and disorders [64, 65, 70, 71]. Alzheimer's disease and breast cancer have been

targeted for essential early detection [65, 70]. Alzheimer's is a progressive disease in the brain that has been associated with high levels of tau protein. This devastating disease affects 26.6 million people worldwide and there is currently no cure. With early diagnosis, current drugs have a chance at prolonging the onset of symptoms such as intense irritability, memory loss, and aggression [72]. The Ray group at Jackson State University in Mississippi has designed a monoclonal antibody coated gold nanoparticle based assay that can detect tau protein levels to 2 orders of magnitude better than previous assays [70]. This group has also fabricated a gold nanoparticle detection assay to target breast cancer [73]. Breast cancer is the most common cancer in women and the leading cause of cancer deaths in women, but early detection has been vital for successful treatment and survival [2, 29, 73].

The Joshi group is utilizing gold nanoshells as theranostics for the diagnosis and photothermal therapy of breast cancer cells *in vitro* [65]. They have also used their system *in vivo* by simultaneously enriching the near-infrared fluorescence and magnetic resonance imaging capacity of a multivalent system. The Jon group has also employed the multifunctional capabilities of gold nanoconjugates for combined CT imaging and therapy for prostate cancer [18]. Through functionalization of the particle surface with a prostate specific membrane antigen RNA aptamer they were able to specifically image prostate cancer cells with CT at a more than 4-fold greater intensity over the nontargeted counterpart. With further manipulation of the particle surface with doxorubicin they demonstrate a more effective and targeted killing of the prostate cancer cells over nontargeted cells [18].

Similar findings have also been reported with pancreatic cancer cells. The *in vitro* and *in vivo* results of a gold nanoparticle delivery system with cetuximab as a targeting agent and gemcitabine as an anticancer drug have been reported from Patra et al. [16]. They make use of the over expression of epidermal growth factor receptor (EGFR) in pancreatic adenocarcinomas and target this receptor with cetuximab, while also employing an FDA approved anticancer drug, gemcitabine. These results show increased inhibition of tumor growth through a targeted system.

Furthermore, El-Sayed et al. has also examined targeted delivery of multifunctional nanoparticles [14]. They used a single-chain variable fragment peptide that recognizes EGFR, an amino terminal fragment peptide that recognizes urokinase plasminogen activator receptor and a cyclic RGD peptide that recognizes the $\alpha_v\beta_3$ integrin receptor all bound to gold nanorods to study gold accumulation in the tumor models. These experiments indicated only a minimal improvement in tumor uptake in comparison to control particles *in vivo*.

In contrast, Patra et al. has fabricated gold nanoparticles with a thiolated derivative of cisplatin [74]. The cisplatin gold nanoparticle conjugate was subsequently tested against ovarian cancer cells and healthy cells. The results showed the cisplatin gold nanoparticle conjugate had comparable efficacy to cisplatin alone. It also showed the toxicity to healthy cells was nearly none, as opposed to the toxic nature of cisplatin alone [74]. The reduction in healthy cell toxicity is an important and exciting finding; this is one of many reasons why gold nanoparticle therapeutics could prove superior to small molecule drugs (Table 1).

There are two distinct benefits associated with fabricating a ligand as a multivalent unit. The first is the potential for polyvalent binding (or even proximity binding), and the second is control of local ligand concentration. Polyvalent binding is ubiquitous in biology [75]. The valency of a particle (protein, virus, cell, gold nanoparticle, etc.) is the number of connections it can make with another constituent. A few examples of polyvalency in biology include: (1) influenza attachment to cells via trimeric hemagglutinin association with sialic acid receptors, (2) *E. coli* attachment to epithelial cells via P-fimbriae proteins, and (3) regulation of gene expression by transcription factors [76, 77].

It has been proposed that biological systems exploit polyvalent interactions because they allow an organism to take advantage of an existing set of monovalent (and perhaps weak) ligands rather than evolving completely new, higher affinity monovalent ligands for every function. Indeed, polyvalent interactions can be very favorable, as seen in the binding of a trivalent oligosaccharide ligand to its asialoglycoprotein cell surface receptor occurs with a binding constant of 10^8 M^{-1} , even though the binding constant of the corresponding monovalent interaction between each distinct monosaccharide and asialoglycoprotein is only 10^3 M^{-1} [78].

Polyvalent binding is not the only advantage of displaying multiple copies of a ligand on a nanoparticle support. Attaching ligands to a gold nanoparticle in a multivalent display is an effective way to generate a high local concentration of binding ligands. The effect of a high local ligand concentration on binding equilibrium can be understood simply by considering Le Chatelier's principle. Binding equilibria between the surface-bound ligand and the receptor may be shifted toward the formation of more ligand-receptor pairs in the presence of a high local ligand concentration [77].

Many other groups have utilized the unique properties of gold nanoparticles for detection assays, exploited their use as cell permeable multivalent systems, as well as further investigating promising therapeutics and targeting known receptors [50, 55, 57, 79, 80]. Fundamentally the use of gold particles is sound but with differing experimental findings for the efficacy of targeting agents on the particle surfaces, it is clear more investigation is essential.

6. SYNTHESSES

The synthesis of gold nanoparticles can be classified into three main groups 1) the chemical method; 2) the physical method or 3) the biological method [24]. Herein the focus will be on the chemical method. Synthesis of metal nanoparticles is typically achieved via solution-phase procedures in which a metal precursor complex is reacted with a chemical reducing agent. The first reduction of a gold salt was performed by Michael Faraday in 1857 with phosphorous in a two phase system [81]. The two most common synthetic routes to gold nanoparticles employ either trisodium citrate or NaBH_4 as reducing agents and HAuCl_4 as the metal precursor [82-85].

The citrate reduction method yields gold particles whose diameters are determined largely by the initial citrate: $[\text{AuCl}_4]^{1-}$ stoichiometry. Turkevich in 1951 and Frens in 1973 both utilized the citrate reduction method [25]. Syntheses employing the reduction of gold salts

with citrate generally yield particles with diameters ranging from 5 nm to 200 nm with <10 % size dispersity.

Research in nanotechnology skyrocketed after Brust reported new synthetic conditions for organic-soluble gold nanoparticles in 1994 [83]. The Brust synthesis of gold nanoparticles employs NaBH_4 in the reduction of $[\text{AuCl}_4]^{1-}$ and is typically performed in the presence of long-chain alkyl thiol ligands [86]. Thiols bind to the metal cluster early in the growth phase providing a steric barrier that prevents further growth. Particles isolated using NaBH_4 reduction can be tuned from 1 nm to ca. 10 nm in diameter with 10% polydispersity. Both the citrate and NaBH_4 reduction syntheses require purification steps to obtain a narrow range of nanoparticle sizes. This purification can be achieved by fractionalization, ripening, etching or size chromatography. In the past few years, Murray, Tsukuda, Hakkinen, Kornberg, Dass and Jin have all reported molecular formulas after purification for their gold nanoparticle conjugates [87-92].

6.1 SYNTHESIS OF NANOCONJUGATES

A key feature of gold nanoparticles is that their surfaces may be modified with nearly any thiol or amine-containing small molecule, antibody or polymer [93]. These modifications can be achieved through simple mixing and ligand exchange or through an organic reaction that covalently binds a new molecule to the existing monolayer (Figure 4). All of these modification steps involve one or multiple types of interactions, electrostatic, covalent and hydrophobic.

Using ligand place exchange reactions first described by Murray [68], combinations of two or more chemically distinct ligands can be attached to a single nanoparticle to impart multiple functions and versatility [94]. Gold nanoparticles have a well documented affinity to bind thiol and amine containing molecules in a covalent or pseudo covalent way. The surface of the particle is negatively charged which also aids in the simple mixing to obtain conjugation through electrostatic interactions with positively charged moieties [61, 94-97].

Modifying the particle surface employing covalent or electrostatic interaction in a layer on top of the monolayer assembly has also been utilized. First the surface of the particle must be functionalized with ligands that contain amine, thiol, cyano, carboxyl, or chloro functional groups. Once the particle has the appropriate functional group on the surface nearly any amide bond formation coupling agents may be utilize, such as NHS (N-hydroxy-sulfo-succinimide) and EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride to covalently link bio-recognition molecules [98].

The ability to create mixed monolayers on a nanoscale platform provides a powerful tool that can be used to improve water solubility, tune sterics, target receptors and control cellular internalization. In addition, it allows the fabrication of multivalent molecules that have a countless number of potential benefits and applications.

7. CLINICAL TRIALS

In late 2010, the first gold nanoparticle based nanomedicine successfully passed phase I clinical trials. The nanocojugate, CYT-6091, is comprised of recombinant human tumor necrosis factor alpha (rhTNF) bound to the surface of 27 nm gold particles. This study is monumental because it is the first in man clinical trial that is unique to nanomedicine. These data indicate that simple conjugation of rhTNF to a gold nanoparticle surface can render previously toxic doses, nontoxic [99].

8. FUTURE DIRECTIONS/QUESTIONS STILL TO BE ADDRESSED

Significant progress has been achieved in the last 10-15 years, despite this, there are still fundamental issues to be understood and overcome in order to use gold nanoconjugates in the clinical setting. There are many complex interactions within biological system and how exactly the nanoconjugates enter the cellular environment, are cleared by the reticuloendothelial system organs are questions that need more extensive investigation. Targeted delivery is one of the most challenging and important issues in cancer medicine. Gold nanoparticles have shown to have great promise in alleviating these issues, but the design parameters and detailed delivery mechanisms still need some further exploration.

9. CONCLUSION

Gold nanoparticles have been used for medicinal purposes for centuries. Recent advances include developments in drug delivery for the treatment of cancer, progress in disease detection, successes in targeted delivery (both active and passive), as well as the first in man clinical trial of a gold nanocojugate. The benefits of using a gold nanoparticle scaffold include the tunability of size and shape, the versatility of a mixed monolayer, diversity and simplicity of characterization and the ease of synthesis. Gold nanoparticles have the potential to combine the cell permeability of a small molecule drug with the size comparability of protein therapeutics. The monolayer of a gold nanoparticle can be modified with virtually any thiolated or amine containing compound, for example: known drugs, antibodies, proteins and PEG. A mixed monolayer can increase the local concentration of a drug, bypass traditional drug resistance mechanisms and increase the binding affinity to the target. These reasons combined with the ease of modification and the inertness of gold makes gold nanoparticles a very attractive drug delivery and detection scaffold to explore.

Acknowledgments

This work was partially supported by two grants awarded to P. Mukherjee from the National Institute of Health (CA 135011 and CA136494).

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Figure 1.

Photographs of aqueous solution of gold nanospheres (upper panels) and gold nanorods (lower panels) as a function of increasing dimensions. Corresponding transmission electron microscopy images of the nanoparticles are shown; all scale bars = 100 nm. The difference in color of the particle solutions is more dramatic for rods than for the spheres. This is due to the nature of plasmon bands (one for spheres and two for rods) that are more sensitive to size for rods compared with spheres. For spheres, the size varies from 4 to 40 nm (TEMs a-e), whereas for rods, the aspect ratio varies from 1.3 to 5 for short rods (TEMs f-j) and 20 (TEM k) for long rods. Murphy, C.J.; Gole, A.M.; Stone, J.W.; Sisco, P.N.; Alkilany, A.M.; Goldsmith, E.C.; Baxter, S.C. Gold Nanoparticles in Biology: Beyond Toxicity to Cellular Imaging. *Accounts Of Chemical Research*, **2008**, 41(12), 1721-1730.

Figure 2.
Gold Based Drug Compounds; Sodium Aurothiomalate (Myocrisin™), Aurothioglucose (Solganol™) and Auronofin (Ridauro™).

Figure 3.

Depicts targeting strategies for cancer therapy. The leaky vasculature of malignant tissue in comparison to normal tissue, leads to the enhanced permeability and retention effect of passive targeted drug delivery as shown with the gold nanoparticles coming through gaps. This figure also illustrates active targeting with the over expression of receptors on malignant tissue and the direct binding of the gold nanoparticles to the receptors with targeting ligands.

Figure 4.

General schematic of the preparation of gold nanoparticles followed by the formation of nanoconjugates A) Illustrates the Murray place exchange B) Illustrates a covalent bond formation. It is also important to not nearly any amine containing molecule could be substituted for the thiol ligands.

Table 1

Properties of Small Molecule Drugs versus Gold Nanoparticle Therapeutics.

Small Molecule Drugs	Nanoparticle Sized Drugs
Unlimited Chemical Diversity	Large Chemical Diversity
Short Circulation Lifetimes/Fast Degradation	Long Circulation Lifetimes/Slow Degradation
Frequently Difficult to Pass Through Cell Membranes	Can be Designed to Pass Through Cell Membranes
Limited Valency (A few contacts must be VERY strong)	High Valency (Many weak contacts can provide activity)
Mode of Action Limited to Blocking the Action of an Enzyme	Could Open Up New Modes of Action