Biomedical Application of Gold Nanoparticles in Different Cancers

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Abstract

Nanoparticles (NPs) have significantly advanced traditional cancer diagnosis, offering enhanced efficiency and expeditious processes. Their exceptional characteristics, including larger surface area, increased volume proportion, and superior targeting capabilities, contribute to their prominence. NPs exhibit low toxicity on healthy cells, thereby improving bioavailability and half-life. This is attributed to their effective penetration of epithelial fenestrations and tissues. Consequently, NPs have garnered considerable attention across diverse disciplines, emerging as highly promising materials in biomedical applications, particularly in the realm of disease diagnosis and treatment. In contemporary biomedical practices, numerous drugs are either presented in nanoparticle form or coated with them, facilitating precise targeting of tumors or afflicted organs while minimizing harm to normal tissues or cells. Various types of nanoparticles, encompassing metallic, magnetic, polymeric, metal oxide, quantum dots, graphene, fullerene, liposomes, carbon nanotubes, and dendrimers, exhibit significant potential in the domain of cancer treatment and diagnosis. Notably, nanoparticles have demonstrated intrinsic anticancer activity in several studies, exerting antioxidant effects and impeding tumor growth. They also make regulated drug release possible, which maximizes effectiveness and reduces negative effects. Nanomaterials such as microbubbles are used as molecular imaging agents for ultrasound imaging in the context of cancer diagnosis. This thorough analysis explores the various kinds of nanoparticles that are frequently used in cancer diagnosis and therapy, clarifying their various uses and contributions to the field.

Keywords: Nanoparticles, Nanodrops, Cancer Diagnosis, Cancer Imaging, Biological Active Molecules

1. Introduction

Cancer stands as one of the most fatal diseases, following heart attacks and strokes. Annually, it takes a significant toll on human lives, with a notable factor being the genetic mutations within the DNA's gene sequence that trigger cancer.[1] A key characteristic of this condition is the excessive division of cells, often accompanied by an abundance of blood vessels within the malignant cells. Research conducted in the year 2000 revealed a global population of 22 million individuals living with cancer, with an additional 6 million new cases and a staggering 10 million deaths attributed to the disease. Various types of cancer afflict humans worldwide. Western nations grapple with the prevalence of breast and colon cancer, while Japan faces a higher incidence of stomach cancer.[2] The factors contributing to these conditions often include diet, environmental influences, and, notably, alterations in gene sequences. These genetic changes can be passed from one generation to the next. However, it's crucial to emphasize that cancer is a potentially preventable disease. The identification of cancer cells is made possible through the analysis of nucleotide sequences and gene expression.[3]

The study of carcinogenesis in animals serves as a valuable tool for understanding cancer in humans. Various substances, whether chemical or physical, have the potential to harm DNA and lead to point mutations. For instance, cancer can be induced by tobacco, asbestos, arsenic, exposure to gamma and x-rays, sunlight, and specific pollutants emitted from vehicles. When the body encounters these

carcinogens, it generates free radicals that begin to steal electrons from other components within the body. Consequently, these free radicals cause damage to cells and impede their proper functioning. Additionally, cancer can also be triggered by the infection of numerous viruses.[4] The initial step involves examining the phenotype that emerges following the interaction between viral genes and the host's genetic makeup. The genetic alterations in neoplastic cells impact genes responsible for growth and control. These alterations can take various forms, including a) Subtle sequence changes b) Changes in chromosome number c) Chromosomal translocations d) Gene amplification. There are six common types of cancer in men, each with a different incidence rate. 5.8% of cases are non-Hodgkin's lymphoma; 4.5% are stomach cancer; 6.0% are esophageal cancer; 13.3% are liver cancer; 10.7% are prostate cancer; and 15.9% are Kaposi's sarcoma. On the other hand, women are more likely to experience the following cancer kinds. Breast cancer (17.4%), liver cancer (5.5%), stomach cancer (3.8%), Kaposi's sarcoma (6.2%), cervical cancer (25.4%), and non-Hodgkin's lymphoma (3.8%).[5]
Nanotechnology exhibits remarkable characteristics and capabilities, particularly in the field of biomedicine. This technology has advanced quickly in a comparatively short amount of time. It is extremely useful in oncology, where one of its main uses is to lessen the adverse effects of cancer therapy on other organs. The synthesis and manufacture of diverse nanoparticles for the treatment of a broad range of medical problems is greatly aided by nanotechnology. This use of nanotechnology is a major and quickly developing field of scientific inquiry.[6] A major factor in regulating the basic properties of cellular organization is nanotechnology. The establishment of multiple nanotechnology centers across the globe in recent times is indicative of the increasing importance of this discipline in diverse scientific and technical pursuits. A substantial six million dollars has been allocated for nanotechnology research in the United States. Furthermore, there are plans for the imminent opening of numerous nanotechnology centers. In future, nanotechnology will mature into clinically useful field. Nanoparticles are called “nano” because of their very small diameter and very small molecular mass. They have different chemical and physical characteristics as their large size molecule shows. Owing to their compact size, they have numerous uses in the delivery of medications as well as in the detection and treatment of certain illnesses. They have excellent correlations with various wavelength radiations.[7]
Metallic nanoparticles are synthesized using microorganisms of both the prokaryotic and eukaryotic species. When enzymes are present, the intracellular creation of nanoparticles utilizing fungus includes the movement of ions into the cells of microorganisms. They are smaller because they are prepared inside the cells (table 01). Because fungi have a combination of extracellular components that are not needed for cell formation, their external synthesis of nanoparticles is more appropriate than their internal synthesis. Fungi have components that are beneficial for reducing and capping nanoparticles, which is why we opted to utilize them.[8]

Table 1. synthesis of nanoparticles from different fungi species.

Fungi	Nanoparticles	Location	Size	References
Phoma sp.	Ag	Extracellular	71.06–74.46	[9]
Fusarium oxysporum	Au	Extracellular	20–40	[9]
Verticillium sp.	Ag	Extracellular	25 ± 12	[9]
Aspergillus fumigates	Ag	Extracellular	5–25	[9]
Trichoderma asperellum	Ag	Extracellular	13–18	[9]
Phaenerochaete chrysosporium	Ag	Extracellular	50–200	[9]

This interaction illustrates the connection between nanoparticles and various cellular components, including the cell membrane, organelles, cytoplasmic proteins, and cell surface receptors. This interaction is known as bio-nano interact. The colloidal forces, dynamic bio-physiochemical inter-pays and thermodynamics exchanges between nanoparticle surface and cell surface, help in this interaction.

For the designing of nanoparticles, the understanding of these interactions is very important. A nanoparticle's ability to pass through a cell membrane indicates how hazardous it may be. Iron oxide particles are the first nanoparticles to be approved for use in medicine by the US Food and Drug Administration (FDA).[10] They generate strong signals because of their incredibly tiny paramagnetic particles. Silver nanoparticles, or Ag NPs, have a strong antiviral and antibacterial effect on bacteria and other eukaryotic microorganisms shown in the **figure 1**. Plants such as Carica papaya, Capsicum annuum, and Azadirachta indica are used to make them.[11]

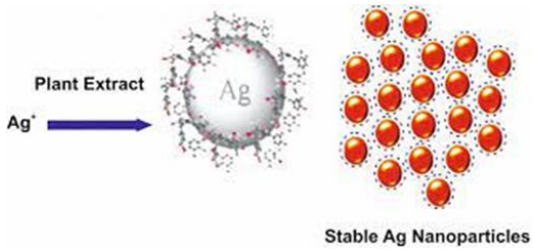

Figure 1. Biosynthesis of Silver nanoparticles.

Alloy nanoparticles show different properties as the whole molecule of sample. They have better conductivity property.[11] Magnetic nanoparticles are known as biocompatible that's why they are used in every filed of science. Metallic nanoparticles, when deal with magnetic field produce different kind of sound which change with time that's why they easily deliver the toxic drug to the target side. The ability of nanoparticles to modify their surfaces affects how they interact with cells. Gold nanoparticles (AuNPs) are used for detecting protein interactions and serve as tracers in DNA fingerprinting. They also recognized the antibiotics known as aminoglycosides.[12] GNPs are used in the development of vaccines by combination with carbohydrates and proteins. The cap of glycol conjugated GNPs are made of carbohydrates. These nanoparticles range in size from 1 to 5 nm. Because gold nanoparticles (GNPs) have special qualities, such as surface plasmon resonance (SPR), they are used in the detection and therapy of cancer. Graphene nanoparticles (GNPs) have the potential to produce heat energy upon exposure to specific wavelengths of near-infrared (NIR) laser light. This property makes them valuable for photothermal cancer treatment.[13]

GNPs have 5nm surface plasmon resonance, which is located at 520nm in ethanol, these particles are sensitive to their composition, size and shape. The distance between particles and their surroundings also has an impact on these particles. The diameter of GNPs (gold nanoparticles) typically falls within the range of 5 to 100 nm. Gold nanospheres, on the other hand, can vary in size from 2 to 100 nm. Gold nanospheres are produced through the reduction process involving sodium citrate and auric acid. The surfactant acetyl tri-methyl ammonium bromide (CTAB) is used to create the rod-like GNPs. Silver ions determine the breadth and length of the rods. The diameter of gold nanorods is determined by the pore size of the template membrane, while the length of the nanorods is influenced by the amount of gold present within the membrane's pores. GNPs not caused cytotoxicity in human cells proved by in vitro study. For cancer colloidal GNPs are best due to their strong enhanced optical property. Gold nano-shells have the coating of silica. They have the diameter of 2-4nm. Their diameter is determined by the diameter of core which is made up of silicon.

Gold nanoparticles (GNPs) can exhibit cytotoxicity because of their inherent physicochemical properties. To evaluate the embryo toxicity of GNPs, the embryonic stem cell test (EST) is employed. This test categorizes substances as strongly embryo toxic, weakly embryo toxic, or non-embryo toxic. In the case of 5 nm gold nanoparticles, it was observed that at a concentration of 750 ppb, they induced oxidative stress and toxicity in the blue mussel Mytilus edulis after a 24-hour exposure period. Sodium citrate effects the life duration of cell. An average urban environment has 107 air particles/cm^3 with a diameter smaller than 300 nm. These particles mostly damage the respiratory track. Lungs easily exposure to PM. Combustion derives nanoparticles are etiologic factor for many diseases and badly effects the airways (Clancy et al., 2002; Donaldson et al., 2005). Combustion-derived nanoparticles possess the capability to activate signal pathways for nuclear factor-kappa B and mitogen-activated protein kinase. This activation can lead to the transcription of various pro-inflammatory genes,

including IL-8, IL-6, and TNF-α.[14] A portion of the respiratory track's nanoparticles begin to enter the bloodstream or central nervous system (CNS). at get at the organs, they employ several strategies. The respiratory track's epithelia permit nanoparticles to enter the bloodstream, enter the interstitial space, and disperse during the first step. After exposure, the Tc-labeled carbon particles reach the bloodstream in one minute. Following their blood entrance, they have detrimental effects.[15]

2. Characteristics of Gold nanoparticles

Certain features of gold nanoparticles are crucial for their use in the detection and management of gold nanoparticles.

2.1 Biocompatibility

Nanomaterials (NMs) that are both biocompatible and bioinert are essential for use in injections and body transplants. There is continuous discussion over NMs' potential toxicity because of how they interact with mammalian cells and tissues differently than their bulk counterparts. The ability of metals to produce metal cations, which can destroy cell membranes, is the primary way in which they can be damaging to the body. However, because of its high reduction potential and low ionization tendency in comparison to other metals, gold is generally thought to be stable in the body. Previous studies have shown that gold is generally safe, both in vivo (inside the body) and in vitro (in a controlled laboratory setting), provided that the size and concentration of gold nanoparticles (AuNPs) are within permissible bounds. Because of their nature, inorganic NMs may have trouble decomposing and entering the body. The breakdown and processing of AuNPs once they are absorbed by cells are still mostly unknown. Murphy et al. highlighted the possible toxicity of AuNPs by demonstrating that, although a 13 nm citrate-capped AuNP did not show cytotoxicity, it did cause aberrant actin filament production, which changed the behavior of the cells.[16]

Using the Michael addition method, acryloyloxyethyl phosphorylcholine (APC) was changed into CSO with an amino group. Then, using carboimide chemistry, the amine and carboxylic acid groups of the zwitterionic CSO were able to combine to form lipoic acid (LA). Surface engineering has shown hemocompatibility, good cell survival, and intact cell membrane integrity at dosages < 0.12 mM, as proven by LA-CSO-PC. This implies that surface engineering methods may aid in the creation of biocompatible AuNPs for use in biomedical applications. The biocompatibility of nanoparticles (NPs) is mostly determined by their size and shape. It was discovered that the binding strengths to the membrane varied. showed, for instance, that the size and form of the NPs had an impact on the passive endocytosis process.[17] It was demonstrated that sphere-shaped NPs were less likely to be transported than spherically-shaped NPs during the endocytosis process. Various membrane-binding strengths were found.

2.2 Physiochemical characteristics of gold nanoparticles

2.2.1 Enhanced Permeability and Retention (EPR) Effect of Gold nanoparticles

Compared to healthy tissues, cancer tissues accumulate liposomes, macromolecular medications, and nanoparticles for longer periods of time due to the Enhanced Permeability and Retention (EPR) effect. Typically, a size of about 200 nm is thought to be optimal for enhancing the EPR effect. Particles of a diameter between 200 nm and 1.2 μm are known to aggregate more in tumors, with the amount of accumulation varied according to the particular type of tumor. The EPR effect is linked to a number of tumor characteristics, such as larger gaps or spaces between tumor tissues, an ineffective lymphatic drainage system, and aberrant blood vessel structure with increased production of vascular permeability factors that facilitate the passage of substances from blood vessels into the tissue. These properties allow injected gold nanoparticles (AuNPs) to be kept inside the tumor and to stay in the body for long periods of time, which makes them useful for cancer cell passive targeting. Several studies have shown that even in situations where gold nanoparticles (AuNPs) do not possess a specialized tumor-targeting domain, the Enhanced Permeability and Retention (EPR) effect enhances the presence of AuNPs in cancer tissues. This finding indicates that, independent of active targeting mechanisms, the EPR effect may promote the passive accumulation of AuNPs in tumor tissues.[18]

2.2.2 Localized Surface Plasmon Resonance (LSPR) of gold nanoparticles

The oscillation of electrons on a conductive metal surface in contact with a non-conductive substrate is known as surface plasmon resonance, or SPR. Conduction-band light can scatter or absorb

light when it strikes conductive metals at a wavelength that corresponds to the plasmon oscillation cycle. Surface plasmon resonance is the name given to this unique optical phenomenon (SPR). Since gold (Au) is a metallic element and other metallic elements do not have this property, it is often utilized in optical imaging. One of the special characteristics of nanomaterials is localized surface plasmon resonance (LSPR). These consist of fluorescence imaging, computed tomography (CT), photoacoustic tomography (PAT), and X-ray imaging, both in vitro (inside a live thing) and in vivo (in a specially prepared laboratory setting). Because of their adjustable characteristics, AuNPs are useful instruments for improving the sensitivity and contrast of many imaging modalities.[19]

2.2.3. Photothermal Effect of Gold nanoparticles:

The success of photothermal cancer treatment depends on precise temperature control. A thorough understanding of the photothermal characteristics of gold nanoparticles (AuNPs) is essential to achieving this. When AuNPs are exposed to photon irradiation, the absorbed energy is transformed into heat energy, causing the photothermal effect. By using this localized heating, particular tissues can be destroyed with precision, providing a noninvasive therapy method. By causing interactions among the excited electrons, localized surface Plasmon Resonance (LSPR) specifically contributes to the enhancement of the photothermal impact of gold nanoparticles (AuNPs). The quantized, collective, and coherent oscillation of the conduction band electrons is stimulated by light when the resonance criteria are satisfied, greatly increasing the photothermal effect of the AuNPs. To increase the effectiveness of AuNPs in photothermal applications, this phenomenon is crucial. It is beneficial to utilize Localized Surface Plasmon Resonance (LSPR) in order to maximize the photothermal effect since it offers high intensity at a relatively low overall capacity, hence encouraging the localized heating of a particular area. Nanorods or nano shells effectively absorb near-infrared (NIR) light, which causes electron oscillation and permits deeper tissue penetration. Conversely, Au-based nanomaterials known as nanospheres are less effective in absorbing near-infrared light (NIR) and have an absorption peak at about 520 nm. This solution looks promising in terms of addressing biocompatibility and clearance concerns while attaining the intended photothermal effect and imaging capabilities.[20]

2.2.4. Surface Enhanced Raman Scattering (SERS) of Gold nanoparticles

Compared to the usual cross-section of fluorescent dyes, which is 10^16 cm^2 sr^{-1}, the typical Raman cross-section is much less (about 10^14 times), measuring 1030 cm^2 sr^{-1}. Raman spectroscopy is difficult for biological imaging because of this constraint, which also causes comparatively delayed data gathering. On the other hand, an induced electromagnetic field is produced by the localized surface plasmon resonance of metal nanoparticles, which is attained when the incident light frequency coincides with the collective motion of conduction band electrons. Research has demonstrated that the Raman cross-section can be significantly enhanced through the Surface-Enhanced Raman Spectroscopy (SERS) effect, reaching levels comparable to those of fluorescent dyes. This enhancement, along with the high resolution achievable in SERS Raman spectroscopy, makes it a promising technique for applications such as spectroscopic cancer diagnosis. SERS enables the sensitive detection and characterization of molecules, offering the potential for precise and non-invasive diagnosis in the field of medical imaging and cancer research [21].

3. Synthesis of gold nanoparticles

3.1 Strategies for the synthesis of gold nanoparticles

Various approaches are employed in the creation of distinct gold nanoparticles. These tactics play similar functions, with the preparation of more particles coming next. Green, physical, and chemical procedures are examples of general strategies.

3.1.1 Chemical methods of gold nanoparticles

Gold nanoparticles supported on an insoluble chitosan derivative are produced by reducing $HAuCl_4$ using thiolate chitosan (QTDT) as a coupling and reducing agent. The reduction of methylene blue is subsequently effectively catalyzed by the ensuing QT/AuNPs. In order to create and stabilize gold nanoparticles, which can then be used as a catalyst for a variety of chemical processes, including the reduction of methylene blue, this approach makes use of thiolate chitosan. When imitol hexaphosphate (IP_6), an inexpensive reagent, was utilized as a reduction agent for $HAuCl_4$, the citrate thermal reduction process could proceed quickly, resulting in the production of gold nanoparticles with

effective surface enhanced Raman spectroscopy (SERS).[21] It has been discovered that there is another method for producing thermosensitive gold nanoparticles. In this process, trisodium citrate and hydrogen tetrachloroaurate (III) tetrahydrate (chloroauric acid) were used to reduce gold nanoparticles. 11-mercaptoundecanoic acid (MUA) was then used by self-assembling monolayers (SAM) to modify the reduced gold nanoparticles.[22] Gold nanoparticles encased in dendrimer-linked polyethylene glycol were used to create gold nanoparticles, and formaldehyde was used as a reducing agent during the process. In single-phase systems, peptide-biphenyl hybrids (PBHs) were utilized as effective gold stabilizers and capping agents to produce gold nanoparticles with a size range of 1.8 to 3.7 nanometers. With this technique, gold nanoparticles with precise properties and dimensions can be produced under control. The kind and composition of capping agent utilized determines the size of manufactured gold nanoparticles. Dendrimers and gold nanoparticles have been synthesized using reduction techniques. Here are a few instances of these synthesis techniques:

- Reduction of $HAuCl_4$ aqueous solutions and diluted dendrimer solutions with sodium borohydride.
- Direct, one-step synthesis of water-soluble gold nanoparticles with a size of less than 10 nm using one-mercaptoundec-11-yl-hexa (ethylene glycol) (EG_6) and do decanethiol (C12), as reported by Mathias Ulbricht et al (2018).
- High-temperature synthesis of gold nanoparticles without using seeds, where gold ions are reduced in ethylene glycol with NaOH as the reducing agent, resulting in gold nanoparticles with an average diameter of 75 + 10 nm.
- Production of gold nanoparticles using a flow micro-reactor system by reducing the gold (III) chloride complex ion with glucose as the reducing agent and polyvinyl pyrrolidone (PVP) as the stabilizing agent.
- Extremely stable gold nanoparticles measuring 7.8 + 1.7 nm in size produced by sodium borohydride reduction of $HAuCl_4$.
- Protein-capped gold nanoparticles created using bovine serum albumin as the capping agent.

3.1.2 Physical methods of gold nanoparticles

Gamma (γ) irradiation has been identified as an exceptionally efficient approach for generating gold nanoparticles characterized by high purity and adjustable sizes. Through the γ-irradiation technique, it is possible to synthesize gold nanoparticles within the small to 40 nm size range, employing natural polysaccharide solutions such as alginate as stabilizers. In a one-step γ-irradiation process, bovine serum albumin, a protein, serves as a stabilizer to produce gold nanoparticles with diameters ranging from 2 to 7 nm. Additionally, gold nanoparticles can be created through photochemical methods, offering diverse strategies for the controlled synthesis of gold nanoparticles with specific sizes and properties, making them suitable for various applications. The synthesis of gold nanoparticles can also be achieved through heating or a photochemical technique, involving the reduction of $HAuCl_4$ using ligands like citrate, tartrate, and malate.[23] It appears that you've accurately summarized the content, highlighting the diverse methods for producing gold nanoparticles with distinct properties. These techniques involve the use of water-soluble chitosan as a reducing agent, the creation of porous gold nanoparticles with gold-silver alloys, and the application of aqueous extracts of Cissus quadrangularis (CQE) in a microwave irradiation process. These methods underscore the versatility in synthesizing gold nanoparticles with varying sizes, compositions, and characteristics, catering to a broad spectrum of applications. Should you have specific inquiries or require additional information on this subject or any other, please feel free to inquire.

3.1.3 Green method of gold nanoparticles

Green chemistry synthesis techniques are environmentally friendly and non-toxic approaches to synthesizing various materials. In a simple and environmentally friendly biosynthesis method, 25 ± 7 nm-sized gold nanoparticles have been successfully produced using the natural biomaterial eggshell membrane (ESM). This method involves immersing ESM in an aqueous solution of $HAuCl_4$ without the need for a separate reducing agent. Such green synthesis methods are advantageous as they reduce the environmental impact and avoid the use of harmful chemicals, making them more sustainable and safer for various applications.

3.2 Synthesis of different nanoparticles

On the basis of applications, GNPs are of different shape, size and structures. GNPs may be in spheres, rods, shells and cages. All these particles are synthesized from different methods. GNPs are easily prepared because they are highly versatile.[24]

3.2.1 Synthesis of Gold nanospheres

Gold nanospheres, also called gold colloids, range in diameter from 2 to 100 nm. These particles are produced under specific conditions by reducing aqueous $HAuCl_4$ solutions with specific reducing agents. The most common reducing agent utilized in the production of nanospheres is citric acid. When utilizing citrate as a reducing and stabilizing agent in the synthesis of gold nanoparticles, the ratio of citrate to gold is an important factor in determining the size of the particles. Larger nanospheres are typically produced with less citrate[24]. However, this technique has two main drawbacks:

1. **Low Yield**
   One drawback is that this method typically yields a relatively low quantity of nanoparticles, making it less efficient for large-scale production.
2. **Prohibition on Water as the Solvent**
   Another limitation is that it prohibits the use of water as the solvent, which can be a drawback in certain applications where water-based solvents are preferred.

Despite these limitations, this approach remains a widely used method for producing gold nanoparticles with specific sizes and properties for various applications.

The two-phase system mentioned has served as a model for the approach employed in synthesizing gold nanoparticles, a method initially detailed in 1993. This technique involves the use of two immiscible phases to facilitate both the reduction and stabilization processes, enabling the controlled synthesis of gold nanoparticles with specific characteristics. The 1993 description of the two-phase approach has been instrumental in producing stable gold nanospheres resilient to both air and heat. To further refine and optimize this method, a phase-transfer reagent, such as tetraoctylammonium bromide, can be introduced. These reagents contribute to enhancing the efficiency and stability of the synthesis, resulting in gold nanoparticles with desirable properties. It's worth noting that the thiol-to-gold molar ratios during the synthesis process can significantly influence the average size of gold nanospheres. Increasing the thiol-to-gold ratio and introducing the reductant into cooled solutions at a faster rate can yield smaller and more monodisperse gold nanospheres. These variables play a pivotal role in controlling the size and uniformity of the resulting nanoparticles.[25]

3.2.2 Synthesis of Gold Nano Rods

A common method for synthesizing gold nanorods is the template method, while other approaches have also been used. By electrochemically depositing gold into the pores of nanoporous polycarbonate or alumina template membranes, gold nanorods are created using the template method. This technology is flexible and may be used to precisely regulate the size and aspect ratios of the produced gold nanorods, meeting specific requirements for research or applications.[26] In the template method employed for the production of gold nanorods, the nanorod's diameter is predominantly dictated by the pore diameter of the template membrane, while the nanorod's length is regulated by the amount of gold deposited within the membrane pores. A drawback associated with this method is its relatively low yield, often resulting in the formation of a monolayer of nanorods. As an alternative to the template approach, it has been proposed that gold nanorods can be synthesized through electrochemical methods. Electrochemical techniques offer added flexibility in controlling nanorod dimensions and properties, potentially yielding higher yields in certain instances. The selection of the synthesis method hinges on the specific requirements of the research or application. In the synthesis of gold nanorods, the aspect ratio defined as the ratio of the nanorod's length to its width can vary based on experimental conditions. Seed-mediated synthesis stands out as one of the most widely adopted and favored methods for crafting gold nanorods. This approach provides meticulous control over the aspect ratio, enabling the production of nanorods with higher aspect ratios compared to alternative synthesis methods. The capacity to tailor the aspect ratio is advantageous, empowering researchers to finely adjust the optical and physical

properties of the nanorods to meet specific applications and research objectives.[27] In the synthesis of gold nanorods, a common approach involves the following steps:

¬ **Formation of Gold Seeds:** Gold salts undergo chemical reduction using a potent reducing agent, such as sodium borohydride ($NaBH_4$), to generate small gold seeds.

¬ **Growth Solution:** These gold seeds are then introduced into a growth solution containing gold salt. This solution comprises a small amount of a reducing agent, such as ascorbic acid, and a surfactant like hexadecyltrimethylammonium bromide (CTAB).

¬ **Aspect Ratio Regulation:** The aspect ratios of the resulting gold nanorods can be manipulated by adjusting the ratio of gold seeds to gold precursor. This ratio directly impacts the final shape and dimensions of the nanorods.

¬ **Incorporation of $AgNO_3$:** To achieve a quantitative yield in the production of gold nanorods, silver nitrate ($AgNO_3$) is frequently introduced into the growth solution. $AgNO_3$ plays a pivotal role in governing the growth and shape of the nanorods.

The widely employed seed-mediated synthesis method is favored for its ability to precisely control the aspect ratio, yielding well-defined gold nanorods with specific optical and physical properties suitable for diverse applications. Beyond the aforementioned techniques, alternative approaches such as bio-reduction, growth on mica surfaces, and photochemical synthesis have also been explored for the synthesis of gold nanorods.[27]

3.2.3 Synthesis of Gold Nano shells

Optical imaging, particularly when employing gold nanoparticles as contrast agents, faces certain limitations in human research applications. However, a distinct opportunity arises in optical imaging, given that most biomolecules exhibit minimal absorbance in the near-infrared spectrum (NIR; 700–900 nm). Modifying the dimensions and composition of layers allows for the creation of gold nanoshells with surface plasmon resonance (SPR) peaks spanning from the visible to the near-infrared spectrum. Adjusting the SPR peak for a specific composition of gold nanoshells is achievable by altering the ratio between the core size and shell thickness. Gold nanoshells with near-infrared (NIR) SPR peaks can be generated by applying gold shells of varying thicknesses to polymer beads or silica. In the case of a particular gold nanoshell composition, modifying the SPR peak involves adjusting the ratio between the shell thickness and core size. Silica cores are manufactured using the Stöber procedure, entailing the reduction of tetraethyl orthosilicate in ethanol. Coating silica nanoparticles with gold in an aqueous environment commonly employs the seeded growth technique, where more gold is added until seed particles merge to form a complete shell. Attachment of small gold nanospheres (2-4 nm in diameter) to the silica core, facilitated by an amine-terminated silane molecule, plays a crucial role in this growth process. The silica core's diameter is pivotal in determining the gold nanoshells diameter, while the quantity of gold deposited on the core's surface influences the shell thickness. Another approach to gold nanoshell production involves the in-situ creation of gold nanoparticles using thermosensitive core-shell particles as a template. The use of microgel as the core material significantly reduces particle aggregation. Electroless gold plating provides precise control over the thickness of the gold nanoshells. Additionally, there have been endeavors to construct gold nanoshells using a viral scaffold, potentially yielding cores with smaller diameters (around 80 nm) and a more uniform size distribution compared to those made of silica.[27]

3.2.4 Synthesis of Gold nanocages

Regulated surface-pore gold nanocages were crafted employing a galvanic replacement technique, utilizing truncated silver nanotubes and aqueous $HAuCl_4$. Silver atoms and nanocrystals, also known as seeds, are formed by reducing $AgNO_3$ with ethylene glycol, allowing for the controlled development of silver nanostructures with specific shapes. Following the modification of their crystalline structures in the presence of poly(vinylpyrrolidone), a polymer selectively binding to the

(100) surface, the requisite nanostructures are generated by introducing silver atoms to the seeds. Through the galvanic replacement method, these silver nanostructures can be transformed into gold nanostructures with hollow interiors, serving as sacrificial templates. Precise manipulation of the size and wall thickness of the resulting gold nanocages is achieved by adjusting the molar ratio of silver to $HAuCl_4$.[28]

3.2.5 SERS nanoparticles:

Compared to conventional techniques like fluorescence and chemiluminescence, Surface-Enhanced Raman Spectroscopy (SERS) is an optical technology that offers several advantages, including increased sensitivity, high multiplexing capabilities, robustness, and superior performance in complex biological samples such as blood as shown in the figure 2. In a recent study, 13 nm-diameter gold nanospheres were loaded with alkylthiol-capped, Cy3-labeled oligonucleotide strands, which were then utilized as probes for the specific identification of target DNA strands. The silica coating offers straightforward surface modification through silica chemistry, increased physical durability, and resistance to various environmental conditions. Thiol groups subsequently added to the silica shell can be linked with maleimide-activated PEG chains to improve biocompatibility.[28]

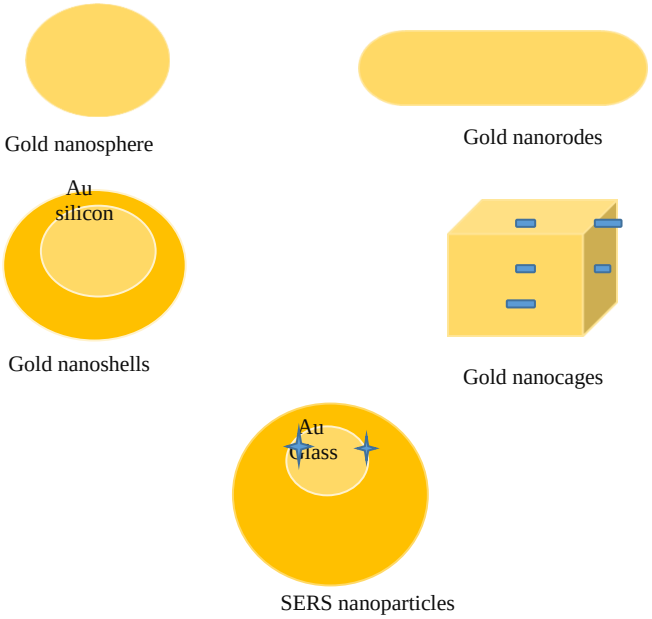

Figure 2. SERS nanoparticles with Au coating

4. Diagnosis of cancer by gold nanoparticles

Gold nanoparticles can be used in many different ways to diagnosis cancerous cells. The diagnostic methods used include nuclear imaging, photoacoustic imaging, positron emission tomography imaging, fluorescence imaging, X-ray scatter imaging, and magnetic resonance imaging. The following is how these methods work:

4.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging modality that is based on nuclear spin theory. MRI is a very useful tool for identifying degenerative disease's underlying causes. However, superparamagnetic inorganic nanoparticles' possible damage to people limits their therapeutic use in magnetic hyperthermia therapy and MRI shown in the figure 3.[28] To give one example, the use of superparamagnetic iron oxide nanoparticles (SPIONs) in magnetic resonance imaging (MRI) is now forbidden in clinical settings due to the toxicity associated with the reactive oxygen species (ROS) generated by SPIONs. These ROS have the potential to seriously damage proteins and DNA and to cause inflammation. Ultra-small gold nanoparticles (GNs) are widely used for in vivo medicinal applications since they do not exhibit the same kind of toxicity. In a work by Lee and colleagues, the hepatitis B virus (HBV) core protein was used as a template to make ultrasmall GNs with a particle size of 1.4 nm. When these GNs were applied for magnetic resonance imaging and magnetic hyperthermia

therapy, they significantly reduced the size of subcutaneous and deep-tissue tumors in living animals. Surprisingly, ultrasmall gold nanoparticles (GNs) can protect renal tissue against possible tissue damage caused by long-term inorganic nanoparticle retention. This implies that ultrasmall GNs could have a variety of uses in the clinical diagnosis of cancer.[28]

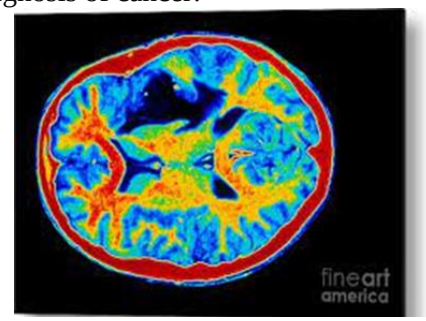

Figure 3. Brain cancer diagnose by MRI

4.2 Photoacoustic imaging

Photoacoustic imaging (PAI) is an innovative non-invasive biomedical imaging technique that doesn't involve ionizing radiation. In PAI, non-ionizing laser pulses are absorbed by biological tissues, either through natural substances found within the body (such as melanin or hemoglobin) or by using external contrast agents. The tissue's optical absorption, which reflects its physiological characteristics, is then transformed into ultrasound waves that carry this information. By utilizing specialized instruments for detection and conducting data analysis, it is possible to generate 2D or 3D images depicting the distribution of optical absorption within the tissue as showed in the figure 4.[29] Hence, it is crucial to concentrate on tailoring ultrasmall gold nanoparticles (GNs) for photoacoustic imaging (PAI). Researchers, exemplified by Sokolov and team, have employed GNs with particle sizes approximately 5 nm and 40 nm, along with a monoclonal anti-EGFR antibody, to identify cancer cells. This approach holds great promise for improving the precision and effectiveness of cancer imaging and diagnosis through PAI. The study outcomes revealed that, despite their notable near-infrared absorption, the 5 nm gold nanoparticles (GNs) demonstrated a comparable photoacoustic (PA) signal to that of the 40 nm GNs. Remarkably, the 5 nm GNs, due to their minute size, exhibited exceptional tissue penetration and in vivo clearance capabilities. These findings suggest that the utilization of ultrasmall GNs would enable highly sensitive in vivo photoacoustic imaging (PAI) of cancer cells.[29]

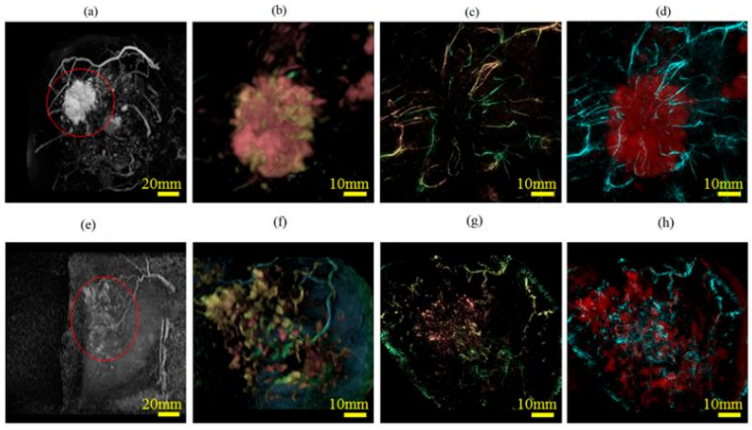

Figure 4. Breast cancer diagnosis by photoacoustic imaging

4.3 Positron emission tomography imaging

Positron emission tomography (PET) stands as a highly advanced clinical imaging technique that relies on the detection of positrons released during the decay of positron-emitting radionuclides. PET has emerged as an invaluable tool for the early diagnosis of various diseases, including tumors, and is extensively utilized in clinical practice. However, despite the promising potential of numerous nanoparticles for cancer identification and diagnosis in animal models, their tendency to accumulate in tissues presents a notable challenge, restricting their applicability in clinical settings. Ongoing efforts

are directed towards addressing this issue and enhancing the suitability of these nanoparticles for clinical use.[29] Ultrasmall gold nanoparticles (GNs), coated with glutathione (GSH) and measuring 3.5 nm in diameter, exhibit efficient clearance by the kidneys. These nanoparticles offer numerous advantages for diverse cancer-targeting imaging techniques and have been employed as contrast agents in single-photon emission computed tomography (SPECT) for deep tissue imaging and measurements. However, the limited temporal resolution of SPECT has constrained the full potential of these GNs in certain applications. Expanding on these findings, several researchers have proposed the use of ultrasmall gold nanoparticles (GNs) in conjunction with positron emission tomography (PET), an advanced form of nuclear medical imaging as shown in the figure 5.

In a study conducted by Cai and colleagues, the potential for assessing kidney disease in mice was explored by evaluating their kidney function through PET imaging, utilizing contrast agents comprising 64Cu-labeled ultrasmall GNs. This approach highlights the versatility of ultrasmall GNs (2.5 nm) across various imaging modalities, including PET, for studying and diagnosing medical conditions. The study affirms the rapid clearance of GSH-coated gold nanoparticles (GNs) by the kidneys and underscores the impressive capabilities of PET in non-invasive organ dynamics assessment. It is anticipated that the utilization of modified ultrasmall GNs as PET imaging contrast agents will continue to expand, encompassing the diagnosis and detection of cancer, thereby showcasing their potential as a valuable tool in cancer imaging and diagnosis.[29]

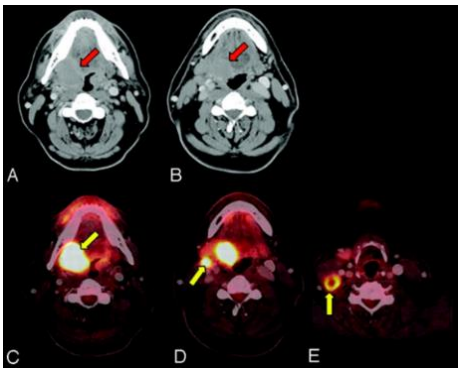

Figure 5. Diagnosis of Head and Neck squamous cell cancer by PET

4.4 Fluorescence imaging

Fluorescence is a common natural phenomenon, and fluorescence imaging relies on the linear correlation between the quantity of fluorescent material within a specific range and the intensity of the resulting fluorescent signal upon stimulation. Gold nanoparticles (GNs) exhibit well-documented optical properties and passively accumulate at tumor sites, making them an appealing option for early cancer diagnosis compared to small therapeutic compounds. However, it is essential to note that GNs tend to accumulate significantly in the liver, spleen, and other organs of the reticuloendothelial system (RES) during their use in cancer diagnosis. This accumulation can limit their therapeutic applicability and decrease their specificity for targeted imaging as shown in the figure 6.

Extending the circulation time of ultrasmall GNs significantly enhances their potential as effective agents for targeted cancer diagnosis and therapy. A comparative analysis was conducted between ultrasmall gold nanoparticles (GNs), measuring 2.5 nm and modified with glutathione (GSH), and a small dye molecule, IR Dye 800CW, for fluorescence imaging in mice with MCF-7 tumors. This study likely aimed to assess the effectiveness of these two distinct imaging agents for tumor visualization and evaluation. The results indicated that ultrasmall gold nanoparticles (GNs) modified with glutathione (GSH) proved to be a more reliable fluorescent reagent for tumor detection when compared to IR Dye 800CW. The ultrasmall GNs, with GSH modifications, enhanced the enhanced permeability and retention (EPR) effect and exhibited rapid elimination from healthy tissues. This research underscores the significant potential of renal-clearable ultrasmall fluorescent GNs for cancer diagnosis, emphasizing their suitability as promising tools for cancer imaging and detection.[29]

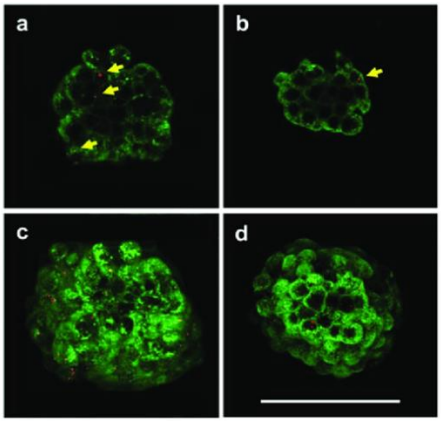

Figure 6. Fluorescence imaging cancer stem cells

4.5 X-ray scatter imaging

A growing number of people are using X-ray scatter imaging as a contemporary imaging method. X-ray scatter imaging, like other X-ray imaging techniques, depends on changes in tissue thickness and density that cause variations in X-ray penetration intensity. But unlike CT (computed tomography) imaging and conventional absorption X-ray imaging, X-ray scatter imaging doesn't require the patient to receive a large dose of contrast agent injected into them. For some applications, this makes it a more patient-friendly and minimally intrusive imaging technique as shown in the figure 7. Contrast chemicals are frequently employed in medical imaging of the human body to improve the visibility of particular structures or disorders. Since iodine-based nanoparticles may absorb X-rays and improve picture quality, they are frequently used as contrast agents, especially in procedures like CT (computed tomography) scanning. Gold nanoparticles (GNs) have a higher atomic number than iodine-based nanoparticles, which means they can have a higher X-ray absorption coefficient. This property can make GNs effective as contrast agents in X-ray imaging, potentially providing improved contrast and visualization of specific anatomical features or pathologies. However, the choice between iodine-based and gold-based contrast agents depends on the specific imaging application, the required contrast enhancement, and potential safety considerations, as each type has its advantages and limitations. Considering their low toxicity and the advantageous properties mentioned, gold nanoparticles (GNs) represent a prime choice for utilization as an X-ray contrast agent.[30]

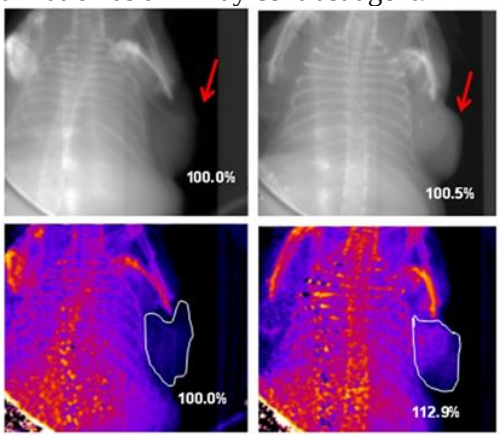

Figure 7. Diagnosis of cancer in mouse by X-ray scat

5. **Treatment of cancer by gold nanoparticles**

Gold nanoparticles are utilized in cancer treatment in addition to cancer diagnosis. Every kind of malignancy uses these particles. Cancer is becoming more commonplace worldwide in a short amount of time. Advanced technologies have been discovered to treat cancer. Many approaches exist, however the following three are the primary ones.

5.1 GNPs in Chemotherapy

Chemotherapy is a treatment approach that employs chemical drugs to combat cancer. Unfortunately, chemotherapy drugs often infiltrate healthy cells, leading to adverse side effects. Furthermore, cancer cells can develop resistance to these drugs through various mechanisms, such as alterations in drug targets, increased drug metabolism, and overexpression of drug efflux pumps. In this context, the development of effective drug delivery techniques is crucial. Gold nanoparticle (GN)-based nanocarriers are regarded as promising vehicles for transporting various types of payloads. This is because they exhibit low toxicity and possess a high capacity for loading therapeutic agents. Because of these characteristics, GN-based nanocarriers are a desirable alternative for enhancing medication delivery in the context of cancer treatment and other areas. A new method for delivering a platinum (IV) medication to prostate cancer cells has been devised. In this work, prostate cancer cells were used to assess the anticancer effects of this delivery method. The strategy made use of 5.2 nm-sized glutathione-modified gold nanoparticles (GNs) that carried the medication and the targeting peptide CRGDK (Cys-Arg-Gly-Asp-Lys). By enhancing the drug's targeted delivery to prostate cancer cells, this technique aims to increase the drug's potential efficacy in treating this particular kind of cancer as shown in the figure 8.[31]

Improved cellular uptake was achieved in this study because the targeting peptide precisely targeted the neuropilin-1 (Nrp-1) receptor found on the surface of the cancer cells. Because of this, the platinum (IV) medication was able to specifically target prostate cancer cells and use its cytotoxic qualities to kill them. Functionalized gold nanoparticles (GNs) also had a double effect: they increased the synthesis of nuclear factor kappa-B (NF-κB) proteins and stimulated NF-κB's ability to bind DNA, which helped the cancer cells undergo platinum-induced apoptosis. These results imply that, when paired with a targeting peptide and a platinum (IV) medication, these functionalized GNs have great potential for anticancer therapy.

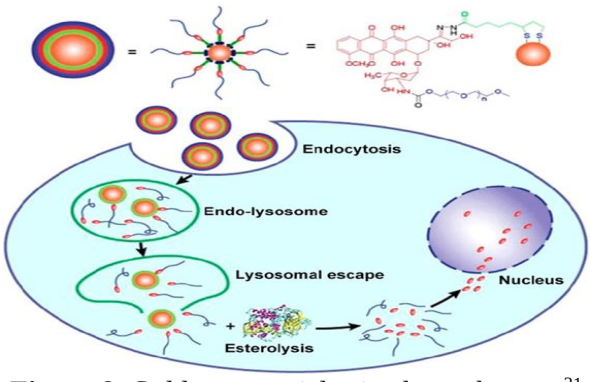

Figure 8. Gold nanoparticles in chemotherapy.[31]

One often used chemotherapy medication that has been shown to be successful in bringing many cancers into remission is doxorubicin, or DOX. In a different study, 12-nm-sized gold nanoparticles (GNs) were synthesized and mixed with DOX and an anti-PD-L1 drug. Using a mix of photothermal and chemotherapeutic approaches to improve the therapeutic approach, this combination was created for the specific treatment of colorectal cancer. The results of this study showed that the stable gold nanoparticles (GNs) exhibited a high affinity for CT-26 cells that overexpressed PD-L1. In addition to improving intracellular retention, the anti-PD-L1 antibody's binding to PD-L1 increased DOX's therapeutic effectiveness inside the cells.[32]

To address the hydrophobic nature of DOX, a solution was devised wherein multiple polyethylene glycol (mPEG) molecules, featuring a thiol group at one end and a drug molecule at the other, were covalently linked to form DOX-conjugated gold nanoparticles (GNs). This strategy markedly enhanced the selectivity and stability of the GNs, enabling better interaction with the surrounding biological environment and improving their efficacy in drug delivery for cancer treatment. However, challenges arise when PEG linker-connected drug molecules are exposed on the surface of conjugates, potentially leading to interactions with other proteins that may compromise therapeutic success. In response to these challenges, some scientists employed drug-conjugated gold nanoparticles (GNs) with a size of 4 nm. They presented a practical solution by altering the arrangement of the PEG and drug, aiming to

potentially enhance the efficacy of drug delivery and therapeutic outcomes. Instead of using PEG as a linker, a unique PEG derivative of DOX was generated, incorporating a modification involving lipoic acid (LA). This modification entailed altering the carbonyl and amino groups of DOX using mPEG and LA, respectively. By adopting this approach, the dispersion, stability, and solubility of the gold conjugate were significantly improved.[33]

Furthermore, once the nanoparticles were internalized by the cells, the drug was released in two phases. Initially, free DOX was produced in the cytoplasm through the enzymatic activity of esterase's, triggered by the liberation of DOX-mPEG from the GNs within acidic lysosomes. As a result, the gold conjugates exhibited superior anticancer activity compared to doxorubicin hydrochloride (DOX•HCl). In this context, the tumor cell cytoplasm served as a reservoir for sustained drug release, augmenting the therapeutic effect. The enhanced internalization of nanoparticles, facilitated by the selective binding of functionalized gold nanoparticles (GNs) to neuropilin-1 (Nrp-1) receptors, led to an increased delivery of the therapeutic peptide p12 to the targeted cells. This heightened internalization, combined with the presence of the therapeutic peptide p12, was found to elevate the expression of p53, making the functionalized GNs significantly more effective in combating cancer cells. These findings underscore the potential of tailored nanocarriers in achieving targeted and enhanced therapeutic outcomes in cancer treatment. In the study, animals administered MTC-100038 at a dose of 450 mg/kg did not display any adverse side effects or significant weight loss. Conversely, animals receiving DM1 at a dose of 150 mg/kg experienced adverse effects. This indicates that the GN platform improved systemic tolerability and facilitated effective drug distribution to hepatocellular tumors following intravenous injection, presenting a more promising and well-tolerated treatment approach.[34]

In a separate investigation, Arunakaran and collaborators explored the effects of 3 nm gold nanoparticles (GNs) conjugated with quercetin on breast cancer cell lines, specifically MCF-7 and MDA-MB-231. The objective of this research was to comprehend the impact of these conjugated GNs on breast cancer cells, potentially providing insights into novel therapeutic strategies for breast cancer treatment. The findings from this study revealed that quercetin-conjugated gold nanoparticles (GNs) surpassed free quercetin in terms of efficacy. This implies that such conjugated GNs could be utilized to deliver drugs to specific target sites, potentially enhancing their therapeutic effectiveness in combating breast cancer. The introduction of nanoparticles into breast cancer cells demonstrated a reduction in the activity of downstream components in the PI3K/Akt pathway as well as the phosphorylation of EGFR. These gold-based drug delivery techniques highlight the potential of ultrasmall GNs in cancer treatment and their capability to enhance the effectiveness of anticancer drugs.[34]

5.2 GNPs in Radiotherapy

Radiation therapy stands as a widely used approach for cancer treatment, employing high-energy radiation to target and eliminate tumor cells. Radio sensitizers are substances that can enhance cell sensitivity to radiation, thereby improving the effectiveness of radiotherapy. Gold nanoparticles (GNs) emerge as promising radio sensitizers in radiation therapy due to their ability to expedite DNA strand breakage when exposed to gamma or X-rays. This makes tumor cells more susceptible to radiation damage, enhancing the overall efficacy of radiation therapy in eradicating cancer cells shown in the figure 9.

To effectively harness gold nanoparticles (GNs) in radiation therapy, determining the optimal nanoparticle size for maximum therapeutic benefits is crucial. In a previous study, Smilowitz and colleagues administered 1.9 nm-diameter gold particles to mice with subcutaneous EMT-6 mammary carcinomas as a form of X-ray therapy. The research aimed to evaluate the impact of GN size on therapeutic outcomes, providing insights into the optimal GN size for enhanced radiation therapy. Results from the study suggested that ultrasmall gold nanoparticles (GNs) could achieve the high metal content in tumors necessary for effective radiation therapy. Building on this, Liang and colleagues conducted a comprehensive investigation into the effects of radiation on GNs of varying sizes. Their research encompassed in vitro and in vivo studies, evaluating the radio sensitization effects of 4.8, 12.1, 27.3, and 46.6 nm PEG-coated GNs. The objective was to gain insights into the size-dependent effects of GNs on radiation therapy and their potential as radio sensitizers. The study demonstrated that 12.1

and 27.3 nm gold nanoparticles (GNs) exhibited higher therapeutic effects, leading to a significant reduction in cancer, nearly causing it to disappear. These specific GN sizes were more widely dispersed within cells compared to the 4.8 and 46.6 nm particles, underscoring the influence of GN size on their distribution and therapeutic efficacy in radiation therapy.[35]

Indeed, the development of high-quality radio sensitizers that can effectively enhance tumor retention and significantly improve cancer radiotherapy represents a crucial goal in the field of oncology. Achieving this can lead to more precise and potent radiation therapy, ultimately improving the outcomes for cancer patients while minimizing the impact on surrounding healthy tissues. Liang and colleagues reported the use of glutathione-coated ultrasmall gold nanoclusters (2 nm) as radio sensitizers in a highly effective cancer treatment approach. This study demonstrates how such minuscule gold nanoclusters may improve the efficacy of radiation therapy in the treatment of cancer. Through the improved enhanced permeability and retention (EPR) effect, these nanoclusters' preferential aggregation in the tumor was caused by their ultrasmall hydrodynamic diameter and biocompatible surface. Radiation therapy was far more effective as a result of this tumor's selective accumulation. Furthermore, because of their small size, the kidneys were able to effectively eliminate the gold nanoclusters from the body following treatment, lowering the possibility of negative side effects from the accumulation of gold nanoclusters in the body. This method provides a viable and well-tolerated cancer therapy plan.[35]

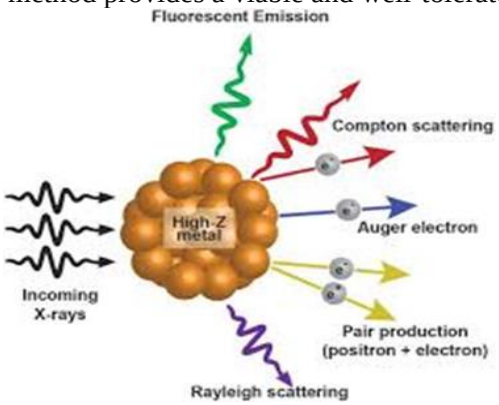

Figure 9. Gold nanoparticles in Radiotherapy

This paper proposes a novel and potential radiosensitizer for use in radiation therapy for cancer. This sensitizer has a number of noteworthy benefits, such as better tumor targeting, better radiation effects, and effective kidney removal. However, it's crucial to remember that untargeted radio sensitizers are still constrained by substantial off-target accumulation, especially when using the increased permeability and retention (EPR) effect to target tumors. Resolving this issue is essential to enhancing the accuracy and effectiveness of radiosensitizers in cancer treatment.[35-36] Basilion and collaborators have engineered Au25 nanoclusters with a size of 1.5 nm designed to specifically target a membrane antigen ligand unique to the prostate. These nanoclusters function as high-affinity radio sensitizers for targeted cancer tissues in mice, markedly enhancing the effects of X-ray irradiation. This groundbreaking approach highlights the potential of precisely targeted radio sensitizers in improving the outcomes of cancer radiation therapy. The use of gold nanoparticles (GNs) with a diameter of 1.5 nm is advantageous due to their rapid clearance from the body by the kidneys, preventing accumulation in other organs and reducing potential harm associated with gold exposure. This design provides valuable insights for further refining GNs to enhance the effectiveness of radiation therapy.

In radiation therapy, external X-ray or gamma-ray beams are utilized to induce direct or indirect damage to intracellular DNA. Precisely targeted radio sensitizers, such as these 1.5 nm GNs, hold the potential to significantly enhance the outcomes of radiation therapy in cancer treatment. The efficacy of radiation therapy is constrained by factors including the extent of DNA damage and the rapid repair of DNA, both during and after treatment. When administered at a dose of 5 mg/kg, ultrasmall GNs exhibited a slight inhibitory effect on tumor growth. Additionally, a noteworthy observation was that O2 (oxygen) could be rapidly released from the liquid perfluorooctyl bromide core following ultrasound therapy. This oxygen release may help alleviate tumor hypoxia, impede DNA repair, and eliminate cancer cells

by stabilizing DNA radical intermediates. Ultimately, the dual-DNA targeting strategy involving ultrasmall GNs and oxygen release yielded the most favorable outcomes in radiation therapy, presenting promising implications for cancer treatment.[36]

5.3 Photodynamic therapy

Photodynamic therapy (PDT) is a clinically approved cancer treatment that relies on the use of safe visible light, non-toxic dyes, and oxygen to generate high levels of reactive oxygen species (ROS) as shown in the figure 10. These ROS are capable of causing cellular damage and ultimately lead to the death of targeted cells. PDT is used in the treatment of certain types of cancer and other medical conditions, offering a less invasive and localized approach to therapy. Many photosensitizers used in photodynamic therapy (PDT) are hydrophobic, which means they have a tendency to repel water and are not readily soluble in physiological conditions. This hydrophobic nature can limit their systemic distribution in the body, making it challenging to deliver these agents effectively to the target tissues or cells. Researchers often explore strategies to improve the solubility and delivery of photosensitizers to enhance the efficacy of PDT. Gold nanoparticles (GNs) have demonstrated utility in delivering photosensitizers for photodynamic therapy (PDT) of cancer. GNs can serve as effective carriers for photosensitizers, enhancing their stability and promoting selective uptake into tumors. This targeted approach minimizes the nonspecific dispersion of photosensitizers throughout the body, which can be especially important when patients are exposed to sunlight, as photosensitizers can make the skin more sensitive to light. Additionally, when combined with metal nanoparticles like GNs, photosensitizers can enhance the production of singlet oxygen ($^1O_2$) compared to the free photosensitizer alone. This increased efficiency in generating reactive oxygen species can lead to improved outcomes in PDT for cancer treatment.[36]

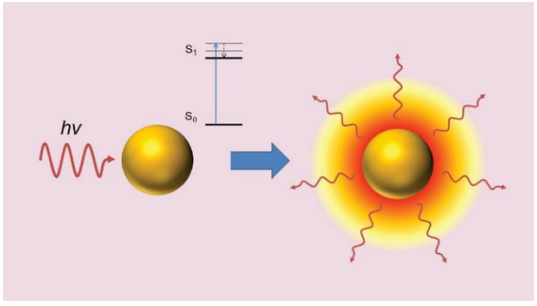

Figure 10. Gold nanoparticles in Photothermal therapy [37]

5.4 Gene therapy

Gene therapy, a medical approach harnessing genetic material to treat diseases, holds significant promise for various applications in cancer treatment[37]. Developing an effective gene delivery mechanism is essential for the success of gene therapy. Research has been carried out to investigate how the size-dependent permeability of gold nanoparticles (GNs) affects gene transport. Due to their ability to surmount cellular and systemic barriers to gene transfer, ultrasmall GNs have gained significant attention as gene delivery vectors as shown in the figure 11.[38] Gold nanoparticles (GNs) with a size of 2 nanometers, functionalized with triethylenetetramine-terminated dendrons, were employed as a carrier for delivering siRNA, as reported by Kim et al. in 2012. Liang et al. provided an extensive exploration of this. Initially, their study produced GNs with various diameters (2, 6, 10, and 16 nanometers) and investigated how these nanoparticles were distributed within MCF-7 cells.[38]

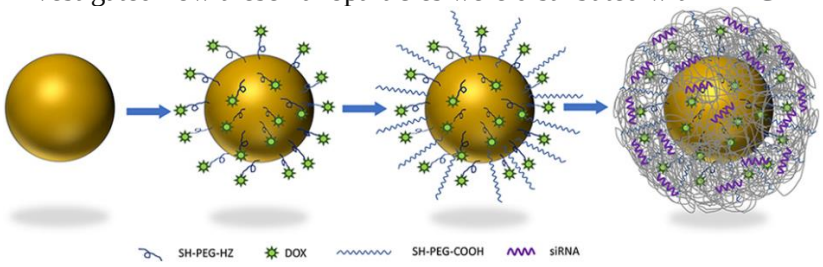

Figure 11. Gold nanoparticles in gene therapy

6. Applications of Gold Nanoparticles

Nano medicine has huge promise to improve human sickness diagnosis and treatment. It is acceptable for the environment to use bacteria in the manufacturing of nanoparticles. Nanotechnology has the potential to revolutionize several biotechnological instruments, making them more customized, portable, inexpensive, safe, and easy to use.

6.1 Gold nanoparticles in cancer therapy

Unchecked cell multiplication that can go to different parts of the body is a defining feature of a group of illnesses collectively referred to as cancer. After heart disease, cancer is the second most prevalent cause of death in the US, with an estimated 580,350 patients anticipated to die from it in 2013.[39] The global death toll is consistent: 7.6 million deaths globally in 2008 were due to cancer, or 13% of all fatalities. Chemotherapy, radiation therapy, and surgery are the main treatments for most cancer types; nevertheless, these methods can have a wide range of adverse effects and consequences. This calls for new, more effective, and non-toxic medications.[40] GNPs are becoming more and more popular as potential agents in cancer therapy. They can be used in a number of ways for both diagnosis and treatment, such as boosting the potency of current drugs or destroying cancerous cells with heat. Because gold nanostructures exhibit surface plasmon resonance (SPR) frequencies in the near-infrared (NIR) range (650–900 nm), where biological tissue and water seldom absorb any radiation, they are frequently used as efficient contrast agents in bio imaging to locate tumors in the body. When combined with cancer-specific medications, these gold nanostructures can allow for more accurate diagnosis and customized treatment.[40] Beyond its role in tumor diagnostics, GNPs have found increasing traction in the treatment of cancer.

6.1.1 By using GNPs recent studies in the field of cancer

Researchers have created gold nanoparticles (GNPs) for the purpose of gene delivery and have applied them for in vitro siRNA transfer to tumor cells. This approach enables the "knockdown" of specific mutant or overexpressed genes in malignant cells using small interfering RNA (siRNA), which in turn can reduce the size of the tumor. To date, a wide range of nanoparticles has been developed as effective carriers for siRNA, and each of them has been tested in vitro against well-characterized genes.[40] Recent endeavors in developing multifunctional gold nanoparticles (GNPs) for both in vitro and in vivo gene silencing have contributed significantly to an improved comprehension of the necessary conditions for nanoparticle functionalization. It was found that the release of active RNAi in mice is ensured by a single covalent interaction between siRNA and nanoparticles, and that this bond can be further enhanced by adding RGD peptide to the surface of the nanoparticle.[19]

Based on these findings, in an orthotropic cancer synergic mouse model, RGD peptide-functionalized GNPs loaded with siRNA were evaluated in vivo intratracheally against c-Myc, a regulator gene that is mutated in many malignancies. The results showed a significant downregulation of the gene, accompanied by tumor suppression and enhanced animal survival, indicating that these siRNA-conjugated GNPs could be a viable treatment option for cancer in the future.[20] A University of Minnesota study suggests that one of the vascular disrupting agents (VDAs), tumor necrosis factor alpha (TNF-α) conjugated with GNPs, may enhance multimodal cancer therapy. Clinical trials have not revealed much benefit from combining VDAs with radiation and chemotherapy because of the vast variety of side effects that these drugs have. The objective of this study was to repackage a Vascular Disrupting Agent (VDA) with nanoparticles to achieve tumor-specific distribution and therapeutic impact. The research employed a murine xenograft model of prostate cancer involving hind limb and dorsal skin fold tumors to investigate these effects. The results of the investigation showed that GNP-TNF began to destroy blood vessels after 90 minutes. The rats had chemotherapy and cryosurgery following their exposure to GNP-TNF, which hastened the tumor cells' continued demise. Surprisingly, every single rat survived many surgeries, proving the treatment's safety. This finding may open the door to studies on other powerful VDA nanoparticles, which may determine further phases in the clinical trial process. A recent study by a research team at Baylor College of Medicine demonstrated that GNPs conjugated with sizable quantities of nucleic acids that stimulate the immune system can be efficiently incorporated into macrophages and used to target tumors in mice. They conjugated a little amount of synthetic nucleic acid, which contained the molecule cytosine-phosphate-guanine (CpG), which

suppresses the immune system. The scientists decided to use GNPs as targeted delivery carriers for these nucleic acids in order to enhance immune response because macrophages and other immune-stimulating cells, such as dendritic cells, can absorb nanoparticles. The impact of CpG on activating macrophages was enhanced by the addition of a triethylene glycol (TEG) spacer.

6.2 GNPs in the regulating of blood clotting

Controlling blood clotting is a prerequisite for the successful outcome of many clinical processes, including surgery and wound healing. Researchers from the Massachusetts Institute of Technology (MIT) have created a brand-new method for switching blood coagulation on and off using GNPs. The novel approach uses gold nanorods of various diameters coupled with medications or other substances that are released when activated by infrared light of a certain wavelength. As a result, the scientists were able to use two different lengths of gold nanorods, each of which had a distinct purpose and could be activated using a certain wavelength. Two distinct gold nanorods were used in this investigation, one measuring 35 nm in length (small) and loaded with DNA thrombin inhibitor, and the other measuring 60 nm in length (big) and containing a complementary DNA strand intended to bind to the DNA thrombin inhibitor and turn off inhibition. By soaking the gold nanorods in human serum protein and DNA molecules, which made the nanorods sticky and enabled greater DNA attachment, researchers were able to increase the amount of DNA bound to the gold nanorod. Hospital blood donations were used to test the gold nanorods. Currently, work is being done to develop a method of onsite targeted administration such that the proteins adsorbed on gold nanorods won't interfere with biomolecular operation.[23]

6.3 GNPs in flexible of brain implants

Using spherical GNPs, University of Michigan researchers made a significant advancement in the field of nanotechnology by creating a stretchy, electrical nano-conductor. The layer-by-layer (LBL) method was used in the research to combine GNPs with polyurethane to create a nano particle polymer matrix. After 500 LBL deposition cycles, free-standing composite films of polyurethane-nanoparticles were produced. These were then laminated into stacks by hot pressing three to ten of the free-standing sheets together at 120 C and 20 Mpa for an hour. Even after being stretched to double its original length, the material still exhibited good conductivity according to testing. It was discovered that when the GNPs are stretched, they align into a chain shape with a blood vessel-like web appearance that nevertheless retains conductivity. There are several possible uses for this stretch ability and electrical conductivity combination, including brain implants for the treatment of Parkinson's, epilepsy, and other conditions.[23]

6.4 GNPs in heart diseases

In the entire world, heart-related illnesses are the leading cause of death. Because heart cells cannot divide and only a small fraction of cardiac cells have stem cells, recovering the heart's normal function after a heart attack or other heart damage is challenging. The tissue cannot heal itself as a result. Recently, scientists discovered a method to repair the heart's function by implanting cardiac patches with GNPs. The cardiac patches' main problem is to replicate the heart's coordinated electrical system, which regulates heartbeat and rhythm. Proteins found on the surface of heart cells are used for electrical signal transmission. The cells need a long time to produce the proteins that are lost throughout the tissue engineering procedure. Gold nanofibers, which may act as electrical connectors, were used in this study to optimize and improve the electrical signaling between cells. By seeding patient-derived cells onto a biomaterial 3D scaffold and then incorporating GNPs into it, new tissues are created. The study's findings demonstrated that such GNP-infused heart tissue is capable of electrical signaling successfully. The following phase entails conducting lab tests to see whether such GNP-cardiac patches have the ability to enhance function following a heart attack, and ultimately clinical trials.[38]

6.5 GNPs in the design of artificial skin

Israeli researchers have created a very sensitive film that, in response to physical force, changes its conductivity and can detect touch (pressure). Spherical GNPs (3-6 nm in diameter) are incorporated into the pattern onto a polyethyleneterepthalate (PET) substrate, a typical material found in soft drink bottles. This complex undergoes a conductivity change when bent, offering a sensitive gauge of physical force. The sensitivity was in the tens of milligram range, which is ten times more sensitive than the majority of artificial skin sensors now on the market. Another intriguing finding was that the film's

resolution remained intact even after numerous bending cycles. The film's low voltage requirement allows for reduced manufacturing costs. The next challenge for the researchers is to figure out how to connect the movie with the brain so that the brain can interpret the signals produced by the movie. These films are said to have been most widely used in prosthetics.[38]

6.6 GNPs in drugs delivery

In order to improve the potency and transport of a number of medicinal substances, GNPs have been widely employed because of their high surface-to-volume ratio, biocompatibility, and affordability. Covalent or noncovalent drug molecule attachment to GNPs is followed by a variety of techniques for controlled release of the drug molecule into the desired areas. Numerous methods, including biologically stimulated release, photothermal release, and ultrasonic drug release, are used to release the connected payloads. GNPs can release the payloads in response to biological cues such as pH, temperature, and specific biomolecule concentrations. Given that tumor tissue varies from normal tissue in the aforementioned parameters, this is essential for the treatment of cancer. Research on this concept includes the pH-responsive GNP-based doxorubicin release mechanism and the glutathione-mediated release of DNA fragments for transcription recovery.[41] A photothermal method of drug release from GNPs involves heating the GNP with a particular wavelength of light. this causes the GNPs to melt and release the payload or raises their temperature to a point where tumor tissue is irreparably damaged because tumors are more temperature sensitive than healthy tissues.

6.7 GNPs in the formation of vaccines

Gold nanoparticles (AuNPs) that have been linked with proteins and carbohydrates have been creatively employed in vaccine development. In this context, glycol-conjugated AuNPs serve as a scaffold for carrying a large number of carbohydrate derivatives. Specifically, glycol-conjugated AuNPs, typically ranging in size from 1 to 4 nanometers, have been used to incorporate carbohydrate-based antigens, such as the Thomsen-Friedenreich disaccharide, which is found in cancer cells. These constructs were studied for their immunological response, sialyl-Tn and Lewis-Y, and Tn, were found to display a notably stronger immunological response in comparison to the corresponding free carbohydrate.[41-42]

6.8 GNPs in in-vitro assay

It has been demonstrated that oligonucleotide-capped gold nanoparticles can be used to detect proteins or polynucleotides, including the tumor suppressor gene p53. To this end, a variety of detection and characterization methods have been used, such as gel electrophoresis, amplified voltametric detection, scanometric assay, chronocoulometry, Raman spectroscopy, and atomic force microscopy (AFM). DNA targets have occasionally been found in incredibly minute amounts, even in picomoles or femtomoles.[43] Surface-Enhanced Raman Spectroscopy (SERS) signals from bifunctional DNA-based adsorbate molecules have been analyzed as molecular rulers by measuring their intensity as a function of distance from the gold nanoshell surface. Additional applications of gold nanoparticles include capillary electrophoresis, time-of-flight secondary ion mass spectrometry, immunoassay protein assay, and cancer cell detection.[44] Research has shown that gold nanoshells are sensitive to the pH of the surrounding fluid within the pH range of 3 to 7, especially when functionalized with the SERS reporter compound 4-mercaptopyridine. Furthermore, the concentration of intravenously delivered gold nanoshells in mouse blood was quantitatively determined by Dynamic Light Scattering (DLS).[45] It is possible to determine the circulation lifetime of various solid nanoparticles using this technique. In a different study, streptavidin-biotin interactions in diluted human blood were monitored and detected in real-time using gold nanoshells as optical biosensors.[46] Unfortunately, this study's dynamic range (3-50 g/mL) and sensitivity (3 g/mL) were both determined to be noticeably poor. Inconsistent results are frequently found in scientific publications. To find out which assays have the most potential for clinical testing, it would be very helpful to evaluate multiple assays simultaneously using the same model system. All of the funded centers of the National Cancer Institute (NCI) alliance for nanotechnology in cancer are required to assess their recently created nano sensors using standard samples.[47]

7. Conclusion

Cancer stands as one of the most fatal diseases, following heart attacks and strokes. Annually, it takes a significant toll on human lives, with a notable factor being the genetic mutations within the DNA's

gene sequence that trigger cancer. Additionally, cancer can also be triggered by the infection of numerous viruses. The initial step involves examining the phenotype that emerges following the interaction between viral genes and the host's genetic makeup. The genetic alterations in neoplastic cells impact genes responsible for growth and control. A substantial six million dollars has been allocated for nanotechnology research in the United States. Furthermore, there are plans for the imminent opening of numerous nanotechnology centers. Nanotechnology plays a crucial role in controlling the fundamental characteristics of cellular organization. In recent years, numerous nanotechnology centers have been established worldwide, highlighting the growing significance of this field in various scientific and technological endeavors. The Enhanced Permeability and Retention (EPR) effect leads to the accumulation of liposomes, macromolecular drugs, and nanoparticles in cancer tissues for longer durations compared to healthy tissues.

Future prospects

The adverse impacts of nanomedicine distinguish themselves from conventional pharmaceuticals. Particulate matter toxicology diverges from that of chemical compounds, introducing a notable influence on potential organ exposure, given the dissolvability variability in biological matrices. Nanoparticles, owing to their diminutive size, exhibit the capacity to traverse numerous physiological barriers, with particular significance attributed to their ability to breach the blood-brain barrier, potentially impacting cerebral functions. Furthermore, their size facilitates facile passage through cellular membranes, intracellular organelles, and even the nucleus. Nanomedicine, as a strategic approach, serves to harmonize therapeutic efficacy and toxicity considerations. It amalgamates chemical, biological, and physical attributes to delineate their in vivo behavior. A pivotal aspect in the translational assessment of nanomedicine lies in the scrutiny of biodistribution profiles post-administration, a parameter crucially examined in both pre-clinical and clinical investigations. Each technological modality possesses distinct characteristics, limitations, and capabilities, influencing the real-time assessment of accumulation dynamics within cells, tissues, and organs.

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