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GOLD NANOPARTICLES FOR EARLY DETECTIONAND TREATMENT OF GASTRO OESOPHAGEAL JUNCTION (GEJ) CANCER

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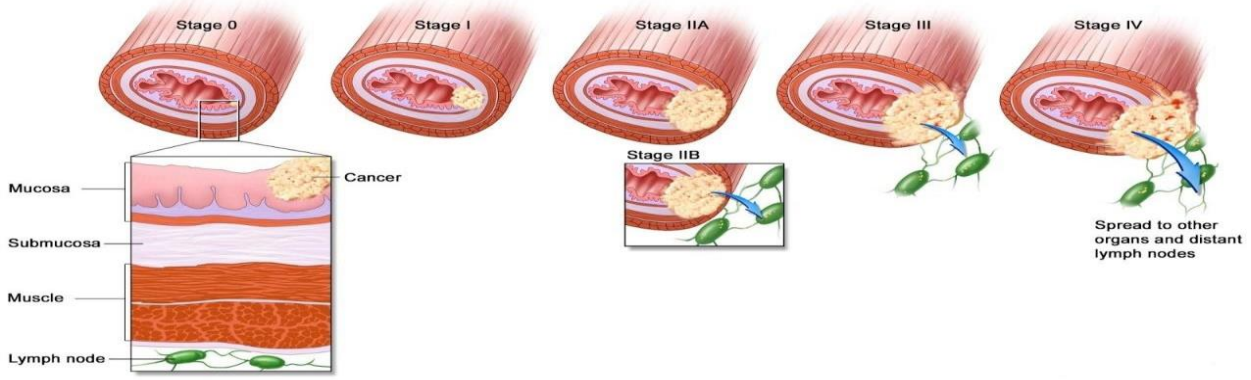
ABSTRACT

The Gastro Oesophageal Junction (GEJ) Cancer, a form of cancer at the junction where the oesophagus meets the stomach is mainly associated with Barrett's oesophagus and Gastro- Oesophageal Reflux Disease (GERD) affecting both the oesophageal and gastric tissues. The asymptomatic characteristic of this disease leads to the increased growth and development of the cancerous cells, also affecting the concentration of sodium ions. However, using gold nanoparticles can help in detecting the cancer at early period due to its high sensitivity, specificity and anticancer property. Usage of gold nanoparticles is now been investigated and proven to be advantageous due to its ability to detect extracellular cancer biomarkers and cancerous cells and in other in-vivo imaging techniques. This detailed current study focuses on the early detection of GEJ cancer using gold nanoparticles can reduce the need of surgeryby preventing the growth and mutation of cancerous cells.

I. INTRODUCTION

GEJ cancer lately has been an area of controversy and disagreement as it is either considered as gastric or esophageal cancer as the tumor forms between them. This cancer being mostly found in the Western part of the countries is likely estimated to have about 21,560 adults being diagnosed in the United States and is the seventh most common cancer among men inthose countries. The rate of GEJ tumors has increased between 4-10% every year in USA since 1976. GEJ is primarily of two types, adenocarcinoma, and squamous cell carcinoma, while adenocarcinoma being the most common type associated with the chronic acid reflux.The risk factors mainly being chronic GERD, smoking, obesity, Barrett's esophagus, and other genetic conditions. The early stages of GEJ cancer often present few or no symptoms,making early detection challenging. As the cancer progresses the main symptoms observed includes abnormal weight loss, chest discomfort, dysphagia, pale skin, trouble swallowing, vomiting bad odor burping and loss of appetite. The burning pain sensed in the chest and inthe upper regions of the food pipe is due to the abnormal and increased gastric acid reflux. Diagnosing GEJ cancer involves a comprehensive approach including medical history, imaging tests with the help of X-Rays, Positron emission tomography (PET), Computed tomography (CT) scans, endoscopy, and biopsy. Treatment methods depends largely on factors such as the stage of cancer, and the patient's overall health. Esophageal surgery is primary treatment modality and may involve the removal of the affected part of the junction. Chemotherapy, Radiation, Esophagus dilation and Targeted therapy with using specific drugs against specific changes in the cancerous cells like HER2 protein present on the surface to grow, are additional treatment options which can also be combined with the surgery. Using the Herceptin, it is targeted against the HER2 protein on the surface to prevent the growth. With poor prognosis, the sodium levels in the body fluctuates and declines rapidly thus leading to self-attack of the cells. Early detection thus plays an important role in improving prognosis and the treatment outcomes, alongside addressing the comprehensive supportive care involving the mental, emotional, and physical well-being.



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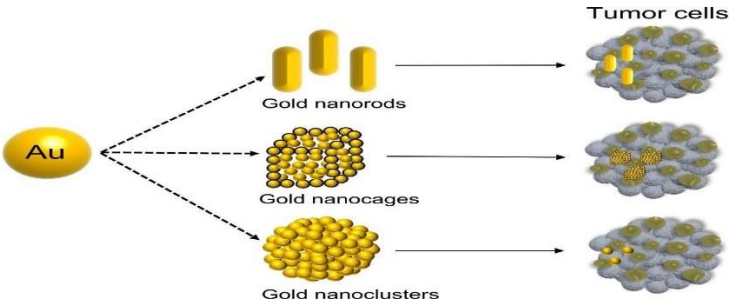
II. METHODOLOGY

WHAT IS GOLD NANOPARTICLE?

Gold nanoparticles (Au Np) are different from gold particles, the wine-red color compound with unique anticancer characteristic. Gold nanoparticles exhibit different sizes and have distinct forms like sub octahedral, spherical, octahedral, icosahedral multiple twined, decahedral, multiple twined, tetrahedral, irregular shape, nanotriangles, hexagonal platelets, nanorods, and nanoprisms. These are mostly known for the skin immunisation andoptimizing transdermal delivery systems.



Gold nanoparticles can be synthesized through various methods, including chemical reduction, seed-mediated growth, and template-assisted synthesis. Characterization techniques such as transmission electron microscopy (TEM), UV-Vis spectroscopy, and dynamic light scattering (DLS), Fourier-transform infrared spectroscopy (FTIR) provide insights into the morphology, size, distribution, and optical properties of the nanoparticles synthesized, ensuring their suitability for cancer detection applications.

WHY GOLD NANOPARTICLES?

Gold nanoparticles are more preferred than other metals as they are highly stable and do not oxidize easily, making them suitable for long term use and storage. These nanoparticles are considered biocompatible and exhibit low toxicity when properly engineered and limited usage to certain controlled parameters. They have been extensively studied for their interactions with biological systems and has high degree of safety. Gold nanoparticles have unique optical properties, including strong absorption and scattering in the visible and near-infrared regions of the electromagnetic spectrum. This property allows for easy and early detection and measurement, making them useful particularly for imaging and sensing applications. While this also has more consistent plasmonic effects compared to the nanoparticles synthesized fromother commonly stable metals. In addition to this, the surface of the gold nanoparticles can beeasily functionalized with various molecules, such as antibodies or by targeting ligands, allowing for specific binding to cancer cells or biomarkers. This also has a longer history of use in biomedical applications, because of its greater regulatory approval and acceptance for use in clinical applications.

USING GOLD NANOPARTICLES IN CANCER DETECTION

Synthesis of gold nanoparticles

Gold nanoparticles are typically synthesized by using the gold salt precursors such as gold chloride (HAuCl4). After dissolving of the precursor in the solvent and addition of the reducingagent such as the sodium citrate, sodium borohydride or ascorbic acid to initiate the reduction reaction. The reducing agent donates electrons, leading to the reduction of gold ions from oxidation state from +3 to +0. As this reaction progresses, gold atoms aggregate and nucleate to form small clusters. These continue to grow into larger nanoparticles, and the size and shapeof these nanoparticles can be controlled by adjusting reacting parameters.

Surface functionalization of gold nanoparticles

Stabilization agents: To prevent the agglomeration and stabilize the synthesized gold nanoparticles, stabilizing agents such as citrate, polyvinylpyrrolidone (PVP), or thiol-based ligands (thiolated polyethylene glycol) are commonly used. These agents adsorb onto the surface, providing electrostatic or steric repulsion to maintain their stability and prevent aggregation. Biomolecule Attachment: To enable cancer-specific targeting and detection, the surface of the stabilized gold nanoparticles is functionalized with specific biomolecules such as antibodies, peptides, or aptamers. This step involves attachment of thiolated biomolecules onto the gold nanoparticles surface through strong gold-thiol bonding or other appropriate surface chemistries. This process is crucial for imparting selectivity and specificity to the nanoparticlestowards cancer cells or biomarkers.

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Detection and analysis

After the gold nanoparticles have bound to the target cells or biomarkers, various techniques can be employed

Imaging techniques: Optical imaging techniques, such as fluorescence microscopy, con focal microscopy, or photoacoustic imaging, can be used to visualize and quantify the presence and distribution of gold nanoparticles in the targeted cancer cells or tissues.

Spectroscopic Analysis: In Surface-Enhanced Raman Scattering (SERS) based detection, the Raman signals generated by the gold nanoparticles can be measured using a Raman spectrometer. The unique spectral fingerprint obtained can be correlated with the presence and concentration of cancer-specific molecules or biomarkers.

Data analysis and Interpretation

The data obtained from the detection and analysis techniques are analyzed and interpreted to determine the presence or absence of cancer cells or biomarkers. This information provides insights into the diagnosis, staging and monitoring of cancer.

GASTRO OESOPHAGEAL JUNCTION (GEJ) CANCER

GEJ cancer, a malignancy arising at the junction of esophagus and stomach, poses significant challenges in diagnosis and treatment of the cancer. However, the early detection of this cancer is not practically possible to misinterpret due to its no-noticeable symptoms. Due to this, researchers are now being involved in studies which involve various techniques to detect and prevent the growth of cancer. Nanoparticles are now being largely studied by the scientists and has wide applications in cancer detection due to its anticancer property, multiplexed measurement capacity, specificity, and sensitivity. GEJ adenocarcinoma cancer, the most common type is distinctly divided into three types based on the location of the tumor growth. The Type I is 1 to 5 centimeters above the GE junction while the Type II cancer is between 1 centimeter above and 2 centimeters below the GE junction. Finally, the Type III is 2 to 5 centimeters below the GE junction. There are about four stages in this cancer type and are categorized based on the TNM staging of the adenocarcinoma.

GEJ can affect the normal functioning of the digestive system. The tumor may impair the production of digestive enzymes and acids, leading to difficulties in breaking down food and absorbing nutrients. This can result in deficiencies of essential vitamins, minerals and electrolytes. The GE cancer also disrupts the electrolyte balance, where these are minerals present to help maintain proper fluid balance, nerve function, and muscle contraction due to several reasons. In advanced stages of GEJ, individuals may experience vomiting, leads to the loss of stomach acid and electrolytes such as chloride and potassium. This results in electrolyte imbalances, including hypokalemia and hypochloremia. Further, the tumor can impair the absorption of nutrients in the gastrointestinal tract. This leads to the deficiency of the electrolytes such as magnesium, calcium, and sodium. GEJ cancer disrupts the metabolic process of a body to a large extent, thus affecting the regulation and balance of electrolytes and ions. For example, cancer-related inflammation and metabolic abnormalities may impact the regulation of sodium and potassium levels. Increased electrolyte imbalances are proven to affect the cardiac functioning, muscle contractions, nerve impulses and other physiological processes. Managing electrolyte instability in GEJ cancer often involves a combination of fluid and electrolyte replacement therapy, nutritional support, and specific interventions based on individual needs. The balance can also vary depending on the stage, location, and individual characteristic of the tumor. Regular monitoring, close medical supervision, and personalized treatment approaches are necessary to address and manage these imbalances effectively.

Gold nanoparticles in drug delivery systems

Gold nanoparticles when combined with specific active molecules, are able to actively target the tumor site and influence the tumor cells. For example, the ramucirumab antibody has been linked to gold nanorods to target gastric related cancer and provide the anti-cancer property of the drug. Therefore, gold nanoparticles can be used to delivery chemotherapeutic drugs and improve the efficacy of the active molecule. These particles can reprogram the tumor microenvironment and inhibit the tumor growth and development. To acquire a precise and accurate delivery of the drug, targeted drug delivery systems are used for GEJ cancer.

Nanocomposites combining the target drug trastuzumab (Tmab) with gold nanoclusters (AuNCs) were developed as a novel approach to specifically target human epidermal growth factor receptor-2 (HER2) in both Tmab-sensitive and Tmab-resistant gastric cancer cells. In another study by the researchers, gold nanoparticles

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were used to deliver the anti-tumor drug epigallocatechin gallate (EGCG) to gastric cancer cells and tissues, resulting in time- dependent inhibition of proliferation. Importantly, this approach demonstrated no toxic effects on normal epithelial tissue. For head and neck squamous cell carcinoma (HNSCC), gold nanoparticles encapsulated with cisplatin and glucose were developed to effectively deliver cisplatin to tumor cells. Compared to the free drug, these GNPs demonstrated enhanced inhibition of tumor cell proliferation and increased sensitivity to radiotherapy.Additionally, they served as a contrast agent in CT imaging, making them a potential adjuvant therapy for HNSCC diagnosis and treatment. To target pancreatic ductal adenocarcinoma (PDAC), Gold nanoparticles were modified with plectin-1-targeted multifunctional peptides. The anti-cancer drug gemcitabine (GEM) was conjugated to the surface of these gold nanoparticles, resulting in selective delivery of GEM to cancer cells anda significant anti-proliferative effect in PDAC cell lines.

DETECTION OF GEJ CANCER USING GOLD NANOPARTICLES

Early detection of any cancer is a major challenge as only visible changes in the cells are detected by the imaging techniques, leading to a large multiplying of the proliferating cells during the same period of time. The difference between benign and malignant lesions is not visible in the screening tests. While the nanotechnology has not yet deployed clinically for cancer diagnosis, but is available in the form of medical tests such as gold nanoparticles present in the home pregnancy tests. This study summarizes the various methods by which nanotechnology-based detection using gold nanoparticles can be applied for GEJ cancer. We also provide our perspective on challenges in the use of nanotechnology in cancer diagnosis.

The protein biomarkers approved by FDA for cancer detection, including the CEA (colorectalcancer), AFP (liver cancer), and serum CA724, alpha-fetoprotein, and CA125 for gastric and gastroesophageal cancer, has specific interactions with antibodies or aptamers that can help in the cancer detection. In addition, researchers are currently working in Quantum dot-based detection for cancer, by using the signals sent by the interaction, reflected, and collected fromthe biosensors to analyze and study later. Quantum dots are preferred due to their high resistance to degradation, high molar extinction coefficient, wide absorption with narrow, and high efficiency stokes shift.

The genome methylation landscape (Methylscape) was recently reported as the common characteristic for most of the cancer types, thus can be assumed to a large extent of being a common cancer biomarker. Y. Zhang et al observed the difference between cancer genomes and normal genomes based on DNA-gold affinity and solvation, and developed a simple,quick, and sensitive electrochemical or colorimetric one-step assay to detect cancer. Early detection of metastatic cancer cells in the bloodstream, also known as circulating tumor cells (CTC), can potentially affect cancer prognosis and diagnosis. In recent years, researchers have focused on using nanotechnology for the sensitive detection of CTCs. It is also possible for cell pseudopodia to form on surfaces with nanostructures, thus enhancing the topological interactions, thus enriching the CTCs. The detection sensitivity is improved,as nanomaterials have high surface-to-volume ratio thus enabling adsorption of high-efficiency targeting ligands with the ability to recognize specific molecules on cancer cells. This helps in detecting the cancer in early stages via different analyses. The current clinical trail approaches involve multiple nanotechnology-based cancer diagnostic techniques. Researchers have also developed silica-hybrid nanoparticles (C-dots) for PET imaging of patients with metastatic melanoma or malignant brain tumor. These nanoparticles coupled with 124I-labeled cyclo-[Arg-Gly-Asp-Tyr] (cRGDY) peptides that areable to selectively bind to integrins can be used to probe tumor cells. As the research progresses, more nanotechnology-based cancer diagnostic techniques will grow largely into clinical use.

TREATMENT FOR GEJ CANCER USING GOLD NANOPARTICLES

The main treatment modalities for GEJ cancer include surgery, chemotherapy, radiation

therapy, targeted therapy, and immunotherapy. Often, a combination of any two of these is employed for optimize outcomes. As the treatment varies to a large extent on the type of tumor cells, their origin, location and size, last stages of GEJ cancer mainly involves esophagectomy, where the tumor part of the esophagus is removed. Chemotherapy is often used as an adjuvant therapy after surgery to remove the remaining cancer cells or as a neoadjuvant therapy to shrink the tumor before surgery. Combination regimens such as FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) or ECF/ECX(epirubicin, cisplatin, and fluorouracil/ capecitabine), are commonly employed. The use of nanoparticles in the treatment of GEJ cancer is an area of active research and holds potential for improving treatment outcomes. Gold nanoparticles can be engineered to

carry anticancer drugs and deliver them specifically to the tumor site, increasing drug concentration at the target and minimizing systemic toxicity. The unique property of gold nanoparticles that can be harnessed for photothermal therapy, can be targeted to the tumor siteand upon exposure to near-infrared light, converts the light into heat leading to localized hyperthermia and thermal ablation of cancer cells. These nanoparticles can also be used as contrast agents for imaging techniques and can be engineered to carry fluorescent dyes or radioactive labels, enabling real-time imaging and guided surgical interventions. These can also help protect healthy tissues during chemotherapy by selectively shielding them against the radiation, reducing collateral damage. Nanoparticle-based therapies have the potential to revolutionize the treatment landscape for GEJ cancer by improving drug delivery, enhancingtherapeutic efficacy, and reducing side effects.

III. CONCLUSION

GEJ cancer has emerging surgical advances in terms, proximal gastrectomy being preferred over the total gastrectomy while aiming towards limiting the extent of recession as the patients undergoing total gastrectomy has higher morbidity related to the anastomosis between the esophagus and the jejunum. While using nanoparticles in early detection ofasymptomatic cancers can help preventing the further mutation of the tumor cells and decreases the survival risk rate of the cancer patients. Lately, the research involving the nanoparticles in cancer applications has been evolving due to its core-characteristics. Clinical trials and preclinical studies are ongoing to explore these applications and optimize their use in clinical practice. Further, the potential applications of nanoparticles for GEJ cancer detection and treatment are promising, further research is needed to validate their safety,efficacy, and long-term effects.

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