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Review

Bioconjugated gold nanoparticles as an efficient colorimetric sensor for cancer diagnostics

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ABSTRACT

The chances of curing and reducing the adverse effect of cancer partly lie in early detection. Colorimetric sensor-based technique show promising results since the target is detected with high sensitivity but without the use of advanced/costly techniques through a simple visual color change. In most cases, gold nanoparticles (Au Nps) functionalized with biomolecules complementary to target analyte are used for colorimetric detection. The interaction of functionalized Au Nps with target analytes induce aggregation or dispersion where the color of the solution changes from red to blue or blue to red respectively, which can be visualized by the naked eyes. Such a facile technique has a high commercial viability and therefore, understanding its concept is essential. Here, some of the reported studies are discussed technically for better understanding about the *invitro* colorimetric detection of cancer.

1. Overview

In the present decade, intensive research has been carried out globally for early detection of cancer. Cancer is a disease of abnormal cell division or growth which may occur in almost every part of the human body [1–3]. Cancer/tumor is normally of 2 types; the first one is solid tumours (organ tumours) and the later is liquid tumours (blood cancer) where both types are characterised by abnormal growth [4,5]. Depending upon the nature of spread, tumour may sometimes also be classified as benign or malignant [6]. A benign tumour will remain confined to its original location; it does not invade surrounding tissue or spread to distant organs but still may need to be treated due to local signs and symptoms [7]. In contrast, malignant tumour invades nearby tissue and may spread throughout the body by a process termed metastasis [8]. Commonly found cancers are breast cancer, oesophagus cancer, liver cancer, lung cancer, oral cavity cancer, prostate cancer, etc. named after its site of occurrence. Cancer is the second leading cause of death worldwide next to diabetes mellitus and responsible for 9.6 million death in 2018 [9]. Global statistics for the occurrences of common cancers are lung cancer: 2.09 million, breast cancer: 2.09 million, colorectal: 1.80 million, prostate cancer: 1.28 million, skin cancer (non-melanoma): 1.04 million, and stomach cancer: 1.03 million [10]. Also, it is estimated by WHO that 70 % of cancer occurrence is targeted to low- and middle-income countries. Depending on various parameters such as size, rate of growth, origin of spread, etc. the cancer can be differentiated into different stages such as stage I, stage II, stage III and stage IV [11]. The early diagnosis is vital to survival from cancer since the 5-year survival rate often depends on the stage at which the cancer is diagnosed [12].

Even though, there are many existing techniques available for cancer detection, they have their own inherent drawbacks such as false-positive/false-negative result, radiation exposure, delayed interpretation, cost and availability. [33,34]. Some of the existing cancer detection methods are tabulated in Table 1 Developing facile and quick respons methods especially sensor devices for identifying cancer is in its initial stage. However, the current methods adopted are bulky, complex and they require various units such as transducer, processing unit, a detection unit, etc. leading to a delayed sensor response [35]. Also, conventional sensors lack high sensitivity and selectivity [36] and hence, cancer/tumour cannot be detected in their earlier stages and treated in time.

In recent years, various researchers employed nanomaterials for early stage detection of cancer owing to its intrinsic size depended properties such as enhanced efficiency, specificity, selectivity, etc.

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Table 1
Conventional existing cancer screening techniques.

Sl. No.	Test method	Type of cancer	Ref.
1	Papanicolaou test	Cervical cancer	[13]
2	Mammography	Breast cancer	[14]
3	Prostate specific antigen level detection	Prostate cancer	[15]
4	Occult blood detection	Colon cancer	[16]
5	Endoscopy	Oral cancer, colon cancer, gastric cancer, etc.	[17,18,19]
6	Computed tomography	Prostate cancer, lung cancer, breast cancer, etc.	[20,21,22]
7	X-ray	Lung cancer, colorectal cancer, etc.	[23,24]
8	Ultrasound imaging	Breast cancer, Prostate cancer, etc.	[25,26]
9	Magnetic resonance imaging	Gastro-intestinal cancer, brain cancer, prostate cancer, etc.	[27,28,29]
10	Biopsy	Prostate cancer, breast cancer, etc.	[30,31,32]

Table 2
Nanotechnology-based techniques for the detection of cancer.

Sl. No	Techniques	Nanomaterials used	Cancer type	Ref.
1.	Surface enhanced Raman spectroscopy	Silver nanoparticles	Gastric cancer	[37]
2.	Molecular photoacoustic and photothermal flow cytometry method	Metallic nanoparticle: Magnetic nano-particle	Human breast cancer	[38]
3.	Near-Infrared fluorescent Imaging Techniques	Quantum dots & dye containing nanoparticles	All types of cancer	[39]
4.	Nanopore based sensor	Probed nanoparticle	Lung caner	[40]
5.	Surface plasmon resonance based Immunosensor	Gold nanoparticles	Prostate cancer	[41]
6.	Magnetic resonance property	Iron-oxide Nanoparticles	Prostate cancer	[42]
7.	Electrocatalytic method	Gold nanopores	Colorectal adenocarcinomas cancer	[43]
8.	Optical detection	Gold nano-shells	Prostate cancer	[44]
9.	Colorimetric sensor	Oval shaped gold nanoparticle	Lung cancer, Breast cancer	[45]
10.	Green-fluorescence techniques	Gold nanoparticles	Cervical, liver, breast, testis cancer	[46]
11.	Polymer sensor array technique	Cationic gold-nanoparticles	Metastatic human breast cells	[47]
12.	Bio-barcode based detection	Magnetic nanoparticles	Prostate cancer	[48]
13.	Micro array techniques	Nano-sensors based array	Breast, Lung, & Prostate cancer	[49]

Various types of nanoparticle and the analytical tools used so far in the detection of cancer are summarized in Table 2.

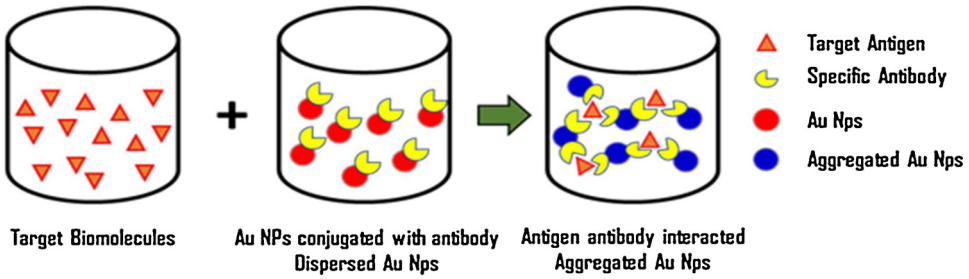
From these data, it is clear that the nanomaterials have proved to be an excellent sensor material which can enable early stage diagnose of cancer. The major drawbacks that set aside in the use of nano based sensor to the common public is its high cost and the technology is still only under research [50]. However, among these techniques, colorimetric sensor is one of the techniques found to be considerably cost effective with high sensitivity, less complexity and have high commercial potential owing to its less complex procedure which can be utilized by any common public [51]. A colorimetric sensor is a technique adapted to detect the analyte of interest (cancer cells) rapidly by providing a visual colour change [51]. In colorimetric sensor applications, metallic nanoparticles are most widely used since it possesses remarkable inherent surface plasmon resonance property which can be made utilized for a visual color change termed as colorimetric method which are elaborated in the upcoming section.

Table 3
Nanoparticles possessing surface plasmon resonance used for colorimetric detection.

Sl. No.	Nanoparticles	Description	Ref.
1	NiO	Detection of the breast cancer cell line MCF-7	[61]
2	Cu	Detection of DNA in femtomolar-level	[62]
3	Pt	Selective detection of mercuric ions in water	[63]
4	WO_3	Bioimaging	[64]
5	Au − Cu_9S_5	Photothermal therapy in the second near-infrared window	[65]
6	Ag/Au bimetallic	Optical glucose sensing	[66]
7	Ag	Detection of glucose	[67]
8	Bi_2Se_3 decorated Au	Detection of cancer biomarker	[68]
9	Au	Detection of spermine and spermidine	[69]
10	TiO_2/SnO_x-Au	Colorimetric immunoassay sensor for tumour marker	[70]

2. Mechanism of colorimetric detection

In fact, in the case of metallic nanoparticles, the free electrons are confined in its finite space due to the size confinement and will naturally have a frequency of oscillation. On irradiating the nanometallic particles at a frequency which matches the inbound natural frequency of electron oscillations, absorption occurs and induce non-propagating oscillation termed as localised surface plasmon resonance (LSPR) effect [52]. Predominantly, the LSPR effect is displayed by metallic nano particles. Besides the pristine metallic nano particles, bimetallic type nano particles, composites and metal oxides also exhibit LSPR effect. The literature that dealt with the LSPR effect for colorimetric detection is summarized in Table 3. Apart from the various kinds of NPs exhibiting LSPR effect, Au Nps is most preferred since it poses many desirable characteristics which make them a potential candidate for sensing. The primary requirement for the colorimetric detection is the high SPR activity which determines the sensitivity of the colorimetric sensor. From the literature, it is clear that the Au Nps is best in this category with highest SPR sensitivity [53], which is more advantageous regarding the detection of biomolecules present in very low levels likely in picomolar concentrations [54]. Usually metal Nps such as Cu, Ag, Au, Pt, etc. possess SPR activity where Cu Nps is the cheapest, whereas it may undergo oxidation easily especially at nano size [55]. Ag Nps is a class of material which has been utilized in many applications. The cytotoxicity and ecotoxicity of Ag Nps is well explored by many researchers [56,57]. Therefore, with the increase in the use of Ag Nps results in the inclined toxicity level to the ecosystem [58]. The research community wants a material which should be more bio-compatible. In



Scheme 1. Schematic representation explaining the aggregation of Au Nps.

contrast of Ag Nps, the Au Nps are more bio-compatible and non-cytogenic to normal cells [59,60]. Even though, the Au Nps is expensive in contrast to Ag Nps, owing to the environmental concern among the research community Au Nps is a more opt candidate for detecting the biomolecules by colorimetric technique.

The colorimetric sensing ability of Au Nps is followed by a colour change from red to purple caused due to the coupling of LSPR facilitated by the aggregation of Au Nps. LSPR coupling is usually occurred when particles with plasmonic characteristic comes closer where the distance should be considerably below the diameter of particles. When this phenomenon occurs, the resonances from the adjacent particles are blended, resulting in a redshift of wavelength. The scale of redshift generally depends on the reduced interparticle distance facilitated by higher degree of agglomeration. The LSPR depends on the local environment so that a change in the local refractive index leads to a LSPR spectral shift which in turn results in colour variation of the colloidal solution. Thus, a visible sensing mechanism is developed without the usage of fluorescent or radio isotope labels. Colorimetric studies possess various advantages such as high sensitivity and specificity, facile, convenience, time saving as well as low detection of limits or limit of detection (LOD) [51,71]. Generally, in biological detection systems, the Au Nps are made to aggregate in the presence of analyte leading to the colorimetric detection. The Au Nps aggregation can be facilitated by means of the most widely used technique via. antigen – antibody (Ag-Ab) interaction. To understand the use of Au Nps as colorimetric sensor, it is advisable to have a look at its different applications.

3. Gold nanoparticles as colorimetric sensor

Colorimetric Au Nps assays are widely used to detect bio-molecules and evaluate enzyme activity. Au Nps suspension with size ranging in ~ 15 nm stabilized with citrate is wine red in colour which has a absorption maximum wavelength at 520 nm [72]. When there is an interaction between citrate-coated Au Nps having anionic surface charge with cationic bio-molecules, the Au Nps will tend to aggregate, leads to plasmon coupling and corresponding red shift of absorption wavelength is visualised [73]. However, the specificity and sensitivity cannot be expected from this method since all the cationic bio-molecules will facilitate Au Nps aggregation which displays false positive results. Therefore, Au Nps should be functionalized by a particular ligand that binds to a selective analyte of interest. When the target analytes are attached to a large number of Au Nps through ligand, Au Nps tends to aggregate and causes change in the colour of solution. These surface ligands act as the charged groups or functional groups attached to the surface of Au Nps that provides conditions for aggregation [74].

Colorimetric sensor is a two-way approach where during aggregation the change in colour from red to blue/purple and during re-dispersion the colour can be changed from blue/purple to red. Such a color response effects are extensively used in the many applications like detection of melamine in milk, paracetamol measurement in plasma, heavy metal detection, glucose detection, cancer detection, etc. [45,75–78]. Of those claims, detecting the presence of cancer analytes is found to be most needed application where number of lives can be saved with early detection. Therefore, numerous literature and reports are found with respect to the use of Au Nps as colorimetric sensor for cancer detection.

4. Cancer detection by colorimetric method using Au Nps

The detection of cancer by the colorimetric studies is less expensive when compared to conventional techniques as stated in Table 2. Au Nps based colorimetric method for the detection of cancerous cells is primarily based on the color change facilitated by its aggregation or dispersion. As a simple example, when human breast cancer cells and normal human breast cells are dispersed separately in a solution containing Au Nps conjugated with antibody specific to cancer breast cells, the solution turns bluish while adding cancer cells but found unchanged (red colour from Au Nps) for normal cells Scheme 1.

Likewise, there are many reports that uses different pathways to achieve colorimetric detection. Even though, the majority of the literature is focused on antigen-antibody interaction based detection, as an attempt to enhance the sensitivity and selectivity, new miscellaneous pathways have been developed using aptamer, magnetic particles, peptide, pH, etc. In this report, we have compiled some of the important results from literature globally for better understanding.

El-Sayed et al. [79] diagnosed malignant oral epithelial cell lines (HOC 313 clone 8 and HSC 3) using Au Nps conjugated with monoclonal anti-epidermal growth factor receptor (anti-EGFR). They show SPR absorption spectra when they are incubated with two malignant oral cancer cell lines with 600 % greater efficiency than the normal cells (HaCaT- normal keratinocyte cell line) with maximum red shift of wavelength. Despite of using specific antibody for the target analyte, reports are available for aptamer and peptide based detection systems. Borghei *et al.* [80] diagnosed MCF-7 cells (human breast cancer cell lines) based on aptamer–cell interaction. The MCF-7 cells are capable of capturing nucleolin aptamers (AS 1411) owing to the over expressed nucleolin receptors in cancer cells. If all the nucleolin aptamers are bind to the nucleolin receptors, while adding complementary ssDNA-Au Nps there will be no aptamer remains to bind. Therefore, no aggregation of Au Nps is noticed displaying red color. In contrast, for normal cells ssDNA-AuNps binds with excessive unbounded aptamer which facilitates aggregation giving purple color [Fig. 1]. This phenomenon is followed spectrophotometrically to ensure accurate colorimetric response for cancer and non-cancer cells and displays a detection limit of 10 cells. Therefore, this study can effectively detect early stage cancer.

By using cell-triggered cyclic enzymatic signal amplification (CTCESA) Zhang *et al.* [81] detected CCRF-CEM cells (lymphoblastic leukemia). Hairpin aptamers probe (HAPs) and linker DNA is co-existed in a solution where the target cells are introduced. HAPs bind specifically to cancer cells, trigger a conformational switch leading to linker DNA hybridization and successively cleaved by nicking endonuclease-strand scission cycles. In the presence of DNA-Au Nps, the cleaved linker DNA cannot assemble into the DNA-Au Nps and thus, the solution is found red in color as a result of no aggregation. In the absence of cancer cells, there won't be any role for HAPs and therefore, the linker

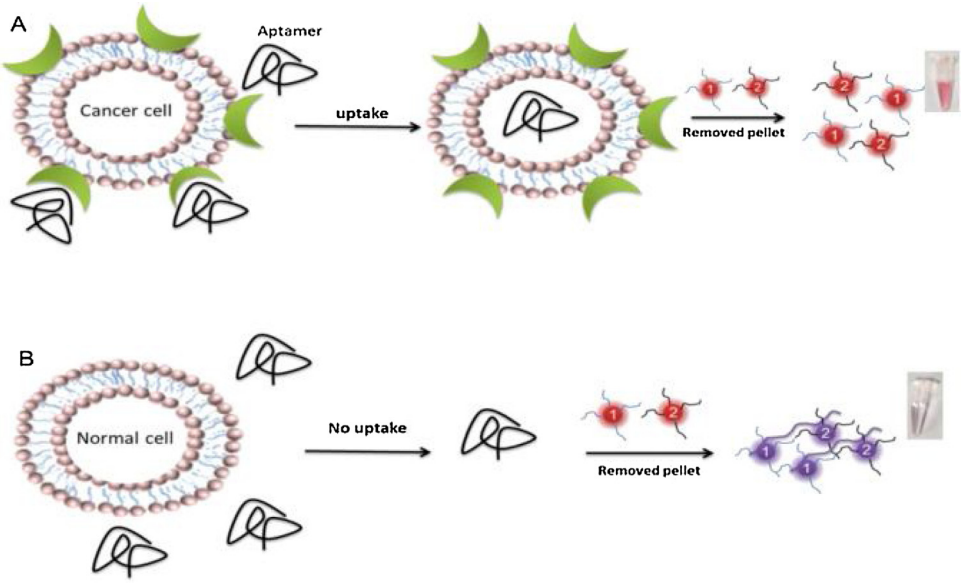


Fig. 1. Schematic representation of selective colorimetric method for detection of cancer cells by employing DNA probe 1,2 -functionalized gold nanoparticles and AS1411 aptamer (Reproduced from Borghei et al. [80] with permission from the Elsevier).

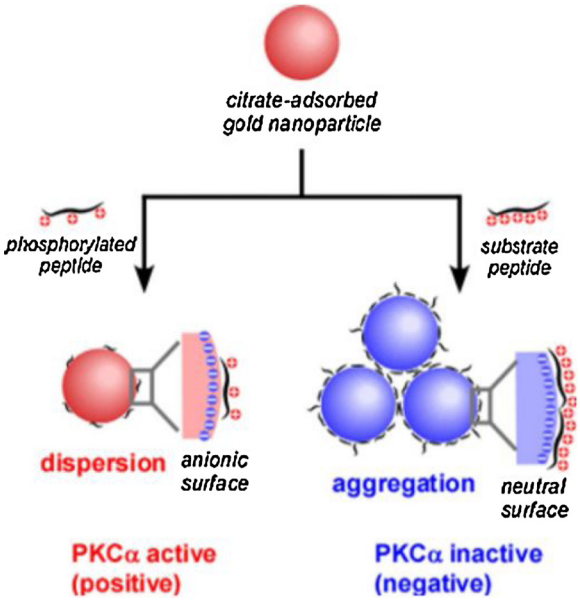


Fig. 2. Schematic of the GNP-based assay for cancer diagnosis. This system is based on the noncrosslinking aggregation mechanism and a cationic PKCα-specific substrate peptide is used as a coagulant of citrate-coated GNPs with anionic surface charges (Reproduced from Kang et al. [82] with permission from the Elsevier).

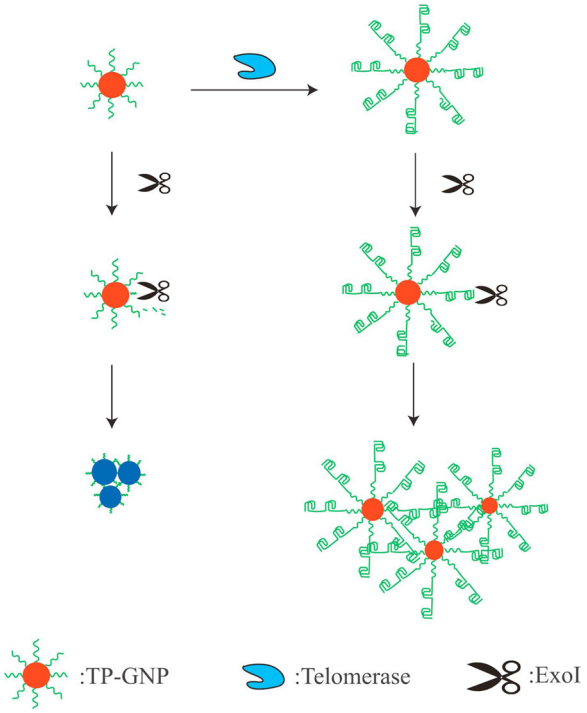


Fig. 3. Schematic representation of Exo I-based method for analyzing the telomerase activity (Reproduced from Zhang et al. [84] with permission from the Elsevier).

DNA assemble between the DNA-Au Nps facilitating aggregation turning the solution purple. The method has high sensitivity and specificity with the detection limit of 40 cells.

Kang et al. [82] developed a colorimetric assay used for the diagnosis of cancer using anionic citrate coated Au Nps with average diameter of 20 nm. In that, the anionic citrate coated Au Nps had tendency to aggregate in presence of cationic protein kinase C (PKC) α-specific peptide through non-crosslinking route. The aggregation is caused due to the +5 cationic charge of PKC α-specific peptide. However, phosphorylation of PKC α-specific peptide by the addition of PKC α reduces its cationic charge to +3 and hence, decline the tendency of Au Nps aggregation [Fig. 2]. This principle is used to detect the presence of cancer cells since PKC α is known to be hyperactivated in many of the cancer cells [83] and are found limited in normal tissues. In this context, the lysates of cancer cell lines and normal tissue are added to Au Nps with PKC α-specific peptide. While adding lysates of cancer cell lines, there won't be any aggregation due to the fact that the over expressed PKC α which phosphorylate PKC α-specific peptide reduces its cationic charge and therefore, no aggregation happens where the solution will be in same color (red). In contrast, while adding lysates from normal tissue, the Au Nps tend to aggregate because of the presence of free-standing PKC α-specific peptide with higher cationic charge resulting in the color change from red to blue. The aggregation and dispersion of Au Nps results in negative and positive responses, which are

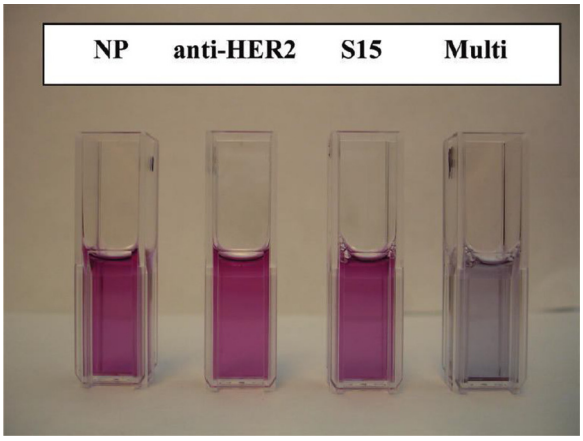


Fig. 4. Photograph showing colorimetric change only when multifunctional oval shape gold nanoparticle has been used (Reproduced from Lu et al. [45] with permission from the American Chemical Society).

schematically, represented in Fig. 2.

Zhang et al. [84] developed a modified Au Nps with telomerase primer on its surface and it is treated along with human leukemia cells (HL-60, K562), human hepatocellular carcinoma cell (HepG2), human embryonic kidney cell (293 T), and human normal skin fibroblast (HSF). Then to terminate the telomerase reaction, RNase is added which is followed by the addition of ExoI (exonuclease 1). It is already known that telomerase is a widely accepted biomarker for cancer. Hence, in the presence of telomerase, it will add the telomeric tandem repeats (T T A G G G) in to telomeric primers. The telomerase extended products are folded into G-quadruplex and making it resistant towards enzymatic cleavage by ExoI and therefore, Au Nps are found to be stable (red in color). But in the absence of telomerase, the primer is cleaved by ExoI leading to the destabilization of Au Nps resulting in rapid aggregation. In this case, the color of the Au Nps suspension changes from red to blue owing to the LSPR coupling facilitated by declined inter-particle distance [Fig. 3].

In order to improve the sensitivity and selectivity of detection, Au Nps can be conjugated with both aptamer and antibody. A highly efficient detection of breast cancer SK-BR-3 cell line employing two photon scattering and simple colorimetric assay is developed by Lu et al. [45]. For this purpose, they used a multi-functional oval shaped Au Nps. The multi-functional Au Nps are prepared by conjugating s6 RNA aptamer and monoclonal anti-HER2/c-erb-2 antibody over its surface. It is clear from the Fig. 4 that only multi-functional Au Nps display colorimetric detection of SK-BR-3 cell line validating its sensitivity. Further, the selectivity of the designed system is authenticated by checking its sensitivity towards MDA-MB-231 breast cancer cell line and HaCaT non-cancerous cell line and showed that multi-functional Au Nps are only sensitive to SK-BR-3.

As the research communities start to realize the efficiency and scope of colorimetric detection of cancer, they have taken a step ahead to improve the sensitivity and selectivity. There are reports which displays excellent results where the target analytes are separated using magnetic particles which are used for colorimetric detection. Liu et al. [85] worked on novel colorimetric enzyme immunoassay for detecting carcinoembryonic antigen (CEA). In this method they coated Au Nps with anti-CEA antibody and labelled with biotin having binding affinity for streptavidin-horseradish peroxidase (HRP), through which 12 HRP molecules are coated to each Au Nps. For sandwich type immunoreaction, Au Nps-anti CEA-HRP complex is brought in close proximity to the antigen interacted antibody coated magnetic microparticle (MMP) where both the complexes are adhered by means of antigen [Fig. 5] resulting a change in optical signal. Here, the amount of capturing antibody on MMP and Au Nps complex will severely affect the signal response.

Apart from the aggregation and dispersion induced colorimetric detection, reports are available which uses miscellaneous techniques. Ye hu et al. [86] developed an aptasensor to detect Anterior gradient homolog 2 (AGR2) protein which is highly expressed in adenocarcinomas with the help of LSPR of Au Nps and magnetic property of magnetic particles. Magnetic bead is conjugated with analyte specific aptamer which have affinity towards DNA probes attached to Au Nps. The aptamer conjugated magnetic beads are treated with the target analyte and therefore, the aptamer binds to AGR2 leaving only a limited unbounded aptamer tail. After which the DNA probe attached Au Nps are added where the DNA probes binds with the unbounded aptamer, magnetic separation is performed and therefore, the Au Nps which are bounded to the magnetic beads are removed showing only a small color change. If the target analytes are not present, most of the Au Nps is bounded to magnetic particles and while magnetic separation of almost all Au Nps are removed resulting in faded red color [Fig. 6]. This technique is spectrophotometrically followed and display a detection limit of 6.6 pM. This can be practically used for the detection of AGR2 protein level in urine sample of cancer patient.

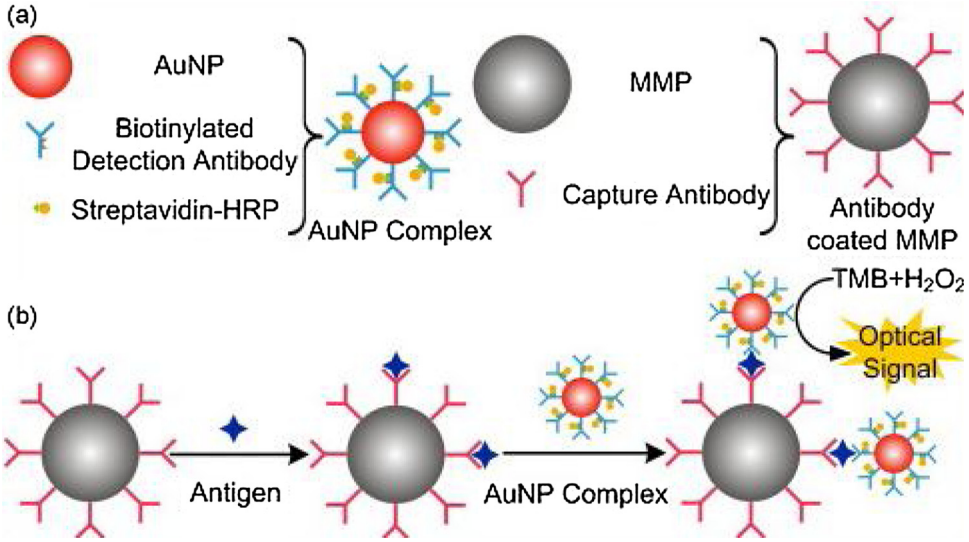


Fig. 5. Schematic diagrams of the experimental system (a) Preparation of the AuNP–anti-CEA–HRP complex and the antibody-coated MMP (b) The colorimetric enzyme immunoassay processes based on the AuNP complex and MMP (Reproduced from Liu et al. [85] with permission from the Elsevier).

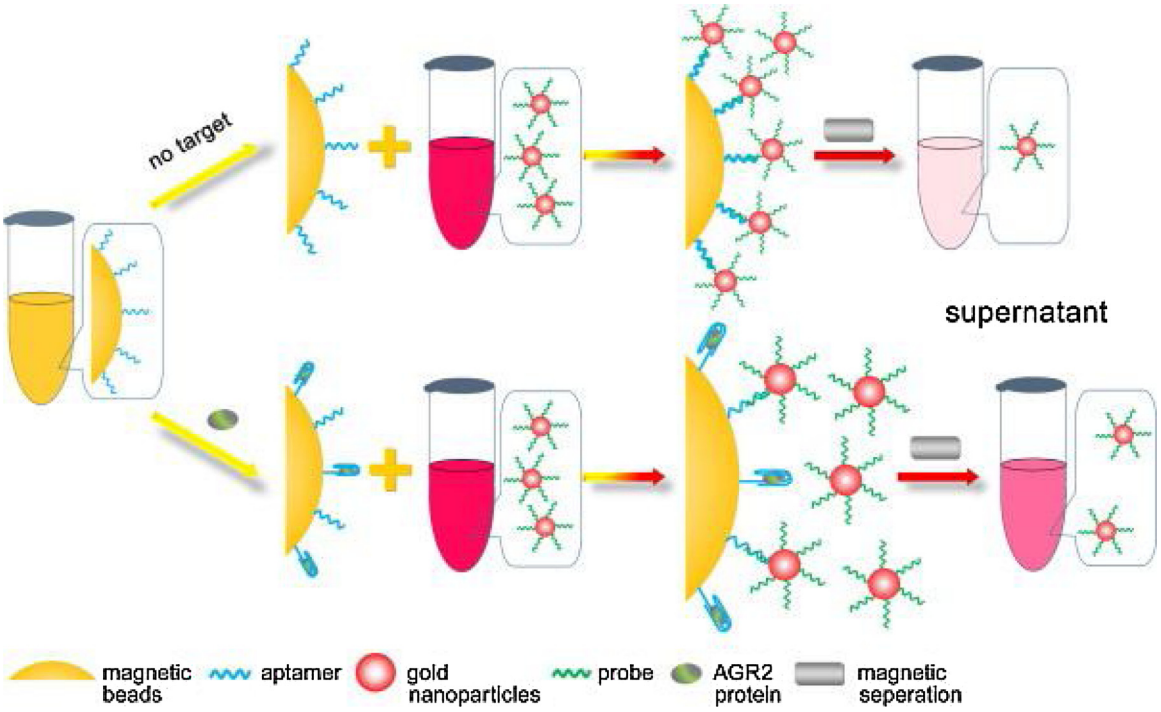


Fig. 6. Schematic representation of AGR2 protein detection procedure (Reproduced from Ye hu et al. [86] with permission from the Elsevier).

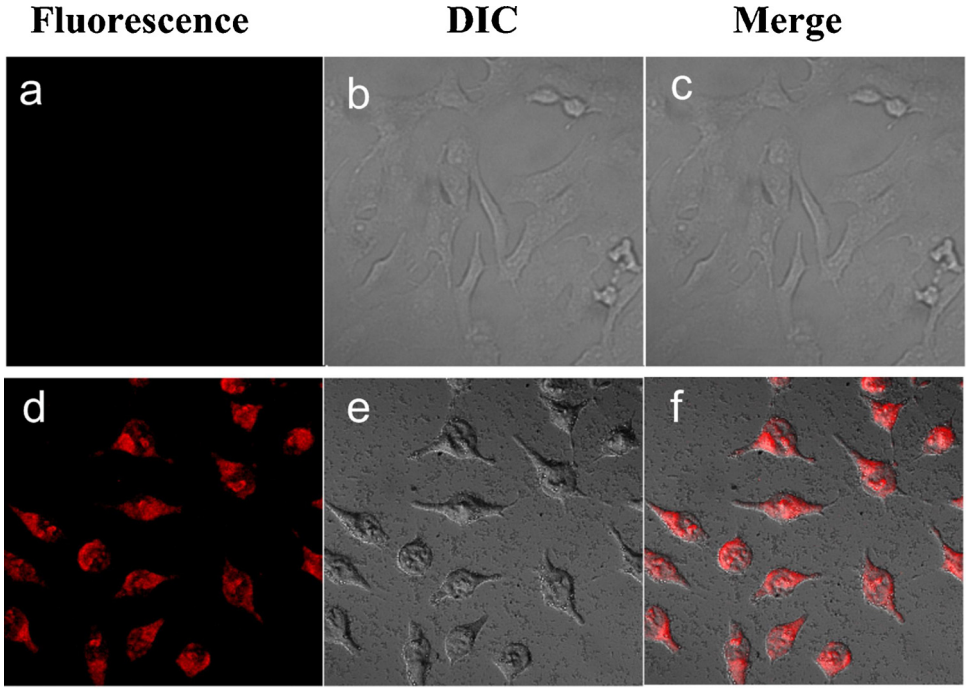


Fig. 7. LSCM images of Vero cells (a-c) and HeLa cells (d-f) after incubated with F-GNRs (Reproduced from Guo et al. [87] with permission from the Elsevier).

Guo et al. [87] developed an optical detecting probe with fluorescence and LSPR absorption property to identify and diagnose cancer cells by conjugating folic acid to Au nanorods (FGNRs). For elucidating its colorimetric performance, human cervical cancer (HeLa) cells and African green monkey kidney (Vero) cells are taken as model. Fig. 7a-f display the LSCM images of Vero cells (a–c) and HeLa cells (d–f) after incubated along with F-GNRs where the fluorescence is absent in Vero cells and shows red fluorescence in HeLa cells. This fact implies that the Vero cells didn't responded to FGNRs whenever the FGNRs have good affinity towards cytoplasm and cell membrane of HeLa cells. Also, they reported about its aggregation on adding into HeLa cells owing to the interaction of folate molecules with the cells, in turn change the color of the solution from red to blue.

Chu et al. [88] performed series of experiments to detect a prostate specific antigen (PSA) based on change in color of the solution with respect to change in pH. Fe_3O_4 Nps is coated with dopamine to immobilize primary anti-PSA antibody and is treated with known quantity of PSA. Magnetic separation is performed and the supernatant is discarded. The above mixture is allowed to assemble with glutathione functionalized Au Nps conjugated with secondary anti-PSA antibody to

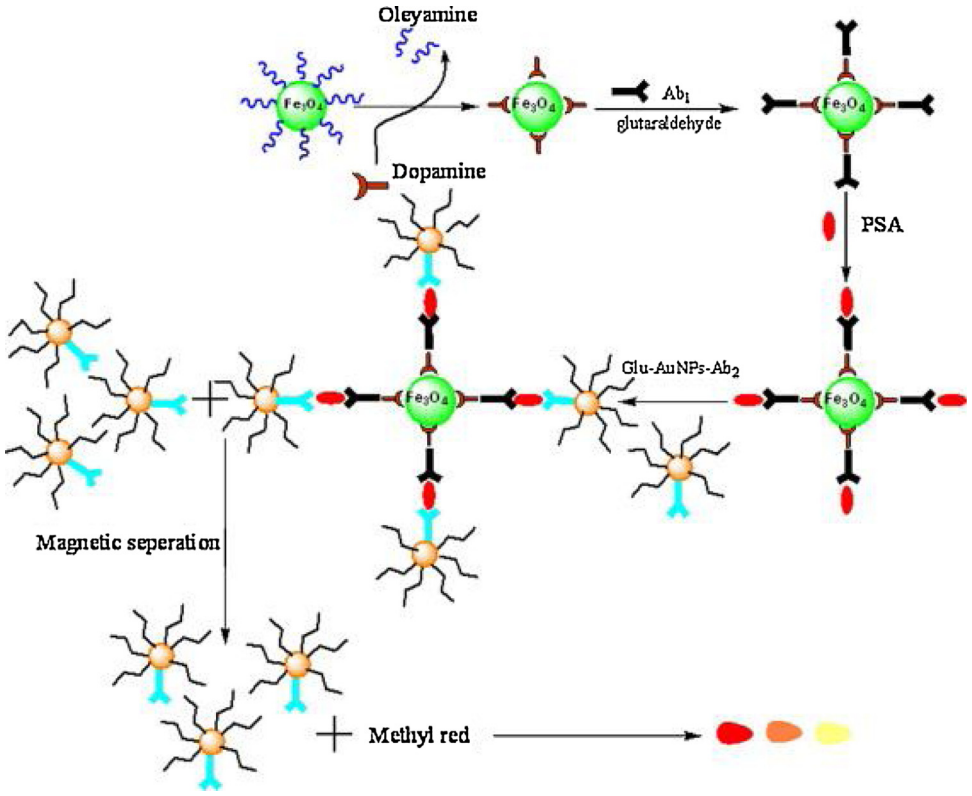


Fig. 8. Schematic for the detection of PSA using immune-complex colorimetric assay (Reproduced from Chu et al [88] with permission from the Elsevier).

Table 4
Bio-conjugated Au Nps as colorimetric sensor for Au Nps.

Sl. No.	Ligand used	Type of cancer	Ref.
1	Aptamer	Cancers like lymphomas and leukaemia	[89]
2	Carcinoembryonic antigen aptamer	Cancers such as colorectal, gastric, pancreatic and cervical	[90]
3	Dual aptamer- MUC1 and VEGF	Breast cancer	[91]
4	DNA conjugated for KRAS gene optimum functionalization	Pancreas cancers, Non-small cell lung cancer, and metastatic colorectal cancers	[92]
5	In Situ hybridization of DNA aptamers	Prostate cancer	[93]
6	DNA or protein as specific ligand	Nasopharyngeal carcinoma (HK-1 cell)	[94]
7	mDNAs-Apt-MBs (messenger DNA modified on magnetic beads)	Leukemia cancer (HL-60 cells)	[95]
8	EGFR biomarkers c-DNA & C-C-DNA complementary strand	Lung cancer (NSCLC)	[96]
9	hnRNPB1 biomarker thiol linked ss-DNA probe	Lung cancer	[97]
10	Nucleic acid	Breast cancer (MDA-MB-231 and Hs578 T cell)	[98]
11	ER-alfa RNA aptamer biomarker ER probe	Breast and ovarian tumour	[99]
12	Lysosome DNA Aptamer	Cancers such as colon, brain, and lungs.	[100]
13	Alpha-fetoprotein	Liver cancer	[101]
14	Cationic peptide probe	Lung and pancreatic cancer	[102]
15	Ag Nps and Kaposi sarcoma associated Herps virus DNA	Kaposi's sarcoma	[103]
16	Human fibronectin antibody (anti-hFN)	Non- small cell lung cancer	[104]
17	PSA monoclonal antibody biomarker binding with streptavidin coated Au Nps	Prostate cancer	[105]
18	PAX1 GENE biomarker methylation specific primer	Cervical cancer	[106]
19	HELA biomarker folic acid ligand conjugated with -NH functional group	Cervical cancer	[107]
20	Magnetic microparticles which are conjugated with biotinylated antibodies	Colon cancer	[108]
21	Magnetic bioconjugates particles containing 7500 horseradish peroxidase (HRP) labels along with detection antibodies (Ab2)	Prostate cancer	[109]
22	Immunoassay based on glucose oxidase (GOx)-catalysed	Prostate cancer	[110]
23	Fluorescein isothiocyanate	Cervical cancer (HeLa cell line)	[111]
24	Platelets derived growth factor	Ovarian cancer	[112]
25	Folic acid	Chronic myelogenous leukemia1 (K-562 cells)	[113]

form an immune-complex. Magnetic separation is done to remove the un-bound Nps and are mixed with known concentration of methyl red. The final solution changes color with respect to the increase in concentration of PSA owing to the presence of glutathione which alters the pH of the solution. The idea is based on glutathione on the Au Nps can cause the pH change, which will result in the color change of the methyl red solution based on the concentration of PSA [Fig. 8].

Likewise, there are many literatures that dealt with the study of biomolecule conjugated Au Nps as colorimetric sensor for the detection of different types of cancer which are compiled in Table 4 for better understanding.

5. Challenges

- The prediction of interactions of bio molecules with Au Nps with at most accuracy is very challenging.
- In case of Metastatic cancer, it is tough to diagnose the origin of the cancer owing to its rapid multiplicity.
- One of the major disadvantages of cancer diagnostic is that a particular cancer has many antigens resulted due to uncontrolled cell multiplication. These antigens can't be detected efficiently with the help of single antibody conjugated to Au Nps. Therefore, multi-modelling of the Nps conjugated with multiple antigen specific antibody should be studied.
- Type of cancer cannot be validated with the help of antigens since different types of cancer may proliferate same antigens or biomarker.
- From the literature data it is clear that most of the prepared Au Nps are spherical in shape. The preparation of Au Nps other than spherical shape is little bit difficult. So, change in morphology of Au Nps may enhance or deprive its property and hence, new methodologies for facile fabrication of Au Nps is required.
- New techniques should be developed in order to improve the sensitivity and specificity of Au Nps for efficiently target particular antigens.

Therefore, extensive research is required to obtain a real time practical use diagnostic tool based on colorimetric property of Au Nps.

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