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Optical Bio-barcode Nanobiosensors

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Abstract

Nanobiosensors are at the core of multidisciplinary research worldwide, from textiles to medicine, from space research to marine. The field of optical nanobiosensors has a special importance within this growing area over the last quarter of the century. Various forms of optical detection methods have been used in a wide spectrum of applications. Practical applications are intentionally given to help clinicians and laboratory employees in terms of materials, compositions, and protocols of use. This tutorial review includes recent efforts in the use of nanoparticle-based bio-barcode analysis to detect a target molecule by focusing on optical techniques.The optical sensing part defines fluorescence, real-time PCR, colorimetric, luminescence, surface plasmon and electrophoresis resonance systems. Finally, applications have been summarized in the detection of pathogenic microorganisms, clinical analysis, pesticides and toxicants in the environmental area and in food products.

Key Words

"Optic, Biobarcode, Nanobiosensor''

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1. INTRODUCTION

Nanotechnology is the study of extremely small structures with a size between 0.1 and 100 nm. Nanotechnology literally means any technology that is a nanometer with real-world applications. Nanotechnology is probable to have a major impact on semiconductor technology, information technology and our economy and society, or cellular and molecular biology in the early 21st century. Nanotechnology promises breakthroughs in science and technology research, materials and production, pharmaceutical and health, nanoelectronic and energy, information technology, biotechnology, biosensors and national security. Nanotechnology is widely felt to be the next Industrial Revolution (Bhushan B., 2010) Nanoparticle based materials offer excellent expectations for biological and chemical detection due to their distinctive electrical properties (Zhu et al., 2004). In recent years, metal nanoparticles have been applied for detect of protein (Jie et al., 2007), and DNA (Hansen et al., 2006a,b), with sensitivities in the picomolar and femtomolar range. Nanoparticle-on-a-biobarcode is one more selectivity of nanobiosensor technology, Magnetic and gold nanoparticles, bound to a suitable antibody or complementary DNA, are used to label specific molecules, target DNA, structures or microorganisms. Bio-barcode has recently emerged as a new bioassay technique with excellent ability for multiplexing (Hill. H.D., Mirkin C.A. 2006), reaching also high sensitivity. Bio-barcode analyzes are some of the few non-enzyme amplification assays that can provide sensitivity comparable to PCR that does not contain enzymes and specific instrumentation. The most frequently used detection methods are given as follows with special emphasis on their nanobiosensors applications.

1.1. Fluorescence Detection

Optical and Fluorescence is the most frequently used method and it has a variety of schemes. The most commonly used block diagram approach of an optical biosensor with fluorescence detection is as follows:

Optical Biosensor =	Ligand-binding target molecule (high selectivity)	+	Fluorescence detection (high sensitivity)

Zang et al, have shown that a very small amount of small molecules can be detected by competitive bio-barcode immunoassay. To do that, properly modified gold nanoparticles with monoclonal antibody (McAb) and 6-carboxyfluoresce in the labeled single stranded thiol oligonucleotides (FAM-SH-ssDNA) have been used (Fig. 1A). The fluorescence of 6-FAM was quenched by gold nanoparticle, when adding the small molecule and modified AuNPs to Ovalbumin linked haptens(OVA-hapten) were coated on the bottom of the microplate, between a hapten and small molecule would be a competitive reaction (Fig. 1B). The hapten-McAb-Au NPs probe was formed at the bottom of the microplate, the AuNPs labeled with small molecule can be removed by washing. After washing the free AuNPs, DTT has been used to release of 6-FAM-SH-ss DNA from the surface of labeled AuNPs on microplate and hence fluorescence signal can be detected (Zhang C. et al, 2017). The steps need to realized are given as follows:

$$\text{AuNPs} + \text{McAb} + \text{6-FAM-ssDNA} \longrightarrow \text{Capture Probe}$$

$$\text{Target Protein} + \text{Capture Probe} + \text{OVA-hapten} \longrightarrow \text{Hapten-McAb-AuNPs-FAM-ssDNA} + \text{Target protein-McAb-AuNPs}$$

$$\xrightarrow{\text{wash}} \text{Hapten-McAb-AuNPs-FAM-ssDNA}$$

$$\text{Hapten-McAb-AuNPs-FAM-ssDNA} + \text{DTT} \longrightarrow \text{FAM-ssDNA} \longrightarrow \text{signal}$$

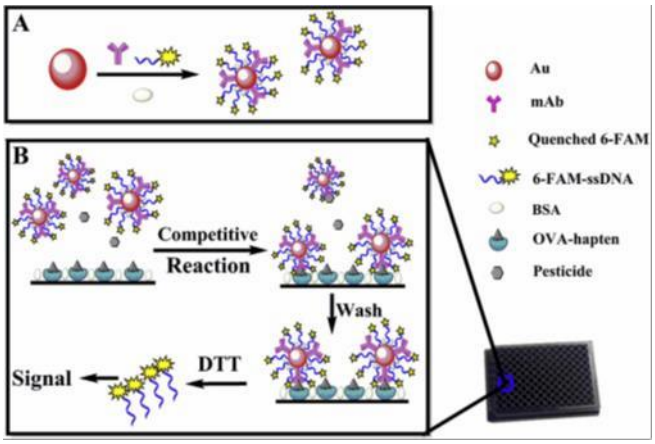

Fig. 1. (A) preparation of modified AuNPs with McAb and barcode DNA, (B) formed of hapten-McAb-AuNP probe complex and detection fluorescence signal (Zhang C. et al, 2017).

Amini et al, developed a new optical fluorescence bio-barcode technique to detect Exotoxin A by bio-barcode DNA (BBC-DNA) assay, Exotoxin A is the most virulent virulence factor of P. aeruginosa. Gold nanoparticle (AuNP) and magnetic nanoparticle (MNP) probes have been used, the AuNPs modified by first probe DNA (1pDNA) and fluorescence marker bio-barcode DNA (Fig. 2A) and the MNPs modified by a second probe DNA (2pDNA) see (Fig. 2B). When added target DNA, the target DNA can hybridize with 1pDNA and 2pDNA. The conjugation of probes with nanoparticles and hybridization with target

DNA resulted in the following sandwich structure: MNP 2pDNA-tDNA-AuNP 1pDNA-BBC-DNA (Fig. 2C). Free AuNPs and MNPs were removed by sample magnetic separation, the sandwich complex remain constant in the tube. After released total DNAs by dithiothreitol (DTT). Finally, the fluorescent signal can be measured by fluorescence spectrophotometer and hence detect of Exotoxin A (Fig. 2D) (Amini B., et al 2016).

$$\text{AuNPs} + \text{1pDNA} + \text{Mark BBC-DNA} \longrightarrow \text{1CP (First Camture Probe)}$$
$$\text{MNPs} + \text{2pDNA} \longrightarrow \text{2CP (Second Capture Probe)}$$

$$\text{1CP} + \text{2CP} + \text{Target DNA} \xrightarrow{\text{Hybridization}} \text{Sandwich Probes} + \text{non-binding probes} \xrightarrow{\text{magnetic separation}} \text{Sandwich Probes} \xrightarrow{\text{DTT}}$$
$$\text{Marker BBC-DNA} \longrightarrow \text{Signal}$$

Zhou et al, developed a new method to detection of a known piece of DNA, using silver nanoparticles and magnetic nanoparticles. Silver nanoparticles were functionalized with labeled ssDNA (single-strand DNA) and fluorescently barcode dsDNA (double-strand DNA). The MNP was modified with capture DNA. The target DNA has two complementary DNAs, one half with labeled DNA and the other half with capture DNA. Having bounded target DNA to nanoprobes, the complex sandwich was formed and can be separated by the magnetic field and then spectrofluorometric measurements were carried out directly (Zhou Z. et al, 2014).

$$\text{AgNPs} + \text{1.Capture DNA} + \text{fluorescently BBC-dsDNA} \longrightarrow \text{First Capture Probe}$$
$$\text{MNPs} + \text{2.Capture DNA} \longrightarrow \text{Second Capture Probe}$$
$$\text{1.CP} + \text{2.CP} + \text{Target DNA} \longrightarrow \text{Sandwich Probes} + \text{Free Probes} \xrightarrow{\text{magnetic separation}} \text{Sandwich probes} \xrightarrow{\text{Heat}} \text{fluorescently BBC-ssDNA} \longrightarrow \text{signal}$$

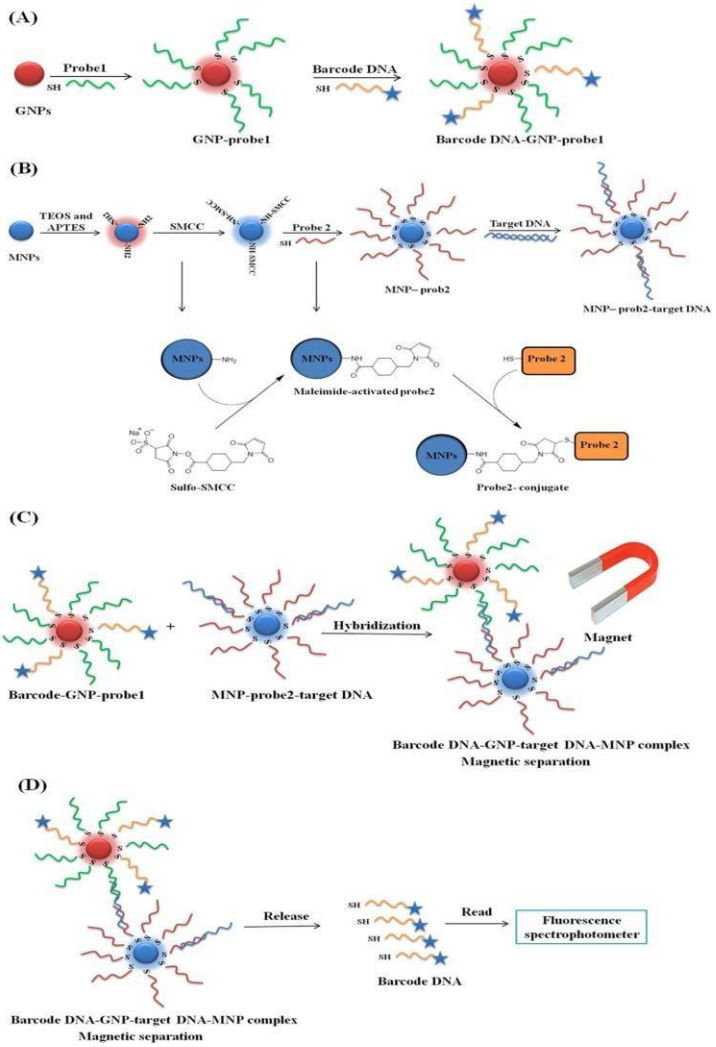

Fig. 2. (A) preparation of AuNP and coated by probe-1 DNA and bio-barcode DNA, (B) Modified MNP by probe-2 DNA, (C) binding target DNA with 2pDNA and 1pDNA and formed the sandwich, (D) magnetic separation, DNAs release and read the fluorescence signal (Amini B., et al 2016).

Dong et al, developed a highly sensitive and selective biosensor for the detection of microRNAs using bio-barcode DNA assay with catalytic hairpin assembly via multiple probes. In the designed system, two nanoprobes of gold nanoparticles functionalized

with locked nucleic acid (LNA) and bio-barcode DNA and the magnetic nanoparticles modified with DNA probe were prepared (Fig. 3A). When adding the target miRNA and reported probe (RP), the target miRNA hybridized between AuNP-LNA and MNP-DNA, and the reported probe hybridized with BBC-DNA (Fig 3B). After separating the sandwich by a magnetic field, the reported probe can be released under high temperature. The RP-DNA can trigger an nicking enzyme-assisted (Nb,BbvcI) strand cycle, which produces an amplified signal selectivity and sensitive miRNA detection (Fig. 3C) (Dong H., et al, 2015)

AuNPs + BBC-DNA + LNA ⟶ AuNPs-ssDNA

MNPs + LNA ⟶ MNPs-ssDNA

AuNPs-DNA + MNPs-DNA + Target miRNA + Reported probe —Hybridization⟶ Sandwich Probes + Free Probes —magnetic separation⟶

Sandwich Probes —Heat⟶ Reported probes ⟶ Quantitative measurement by nicking enzyme-assisted strand cycle assay

Broto et al, reported for the first time an NP-based bio-barcode for detection of C reactive protein (CRP) in plasma samples. This assay uses polystyrene particles modified with BBC-DNA and capture antibody, magnetic beads modified with specific antibody and a fluorescence DNA microarray. The MBs were added to plasma sample, the target protein in plasma sample labeled with the first antibody on the surface of the MBs to form immunocomplex that will be isolated, then add the BBC-DNA modified particles to form the sandwich complex. The Sandwich complex isolated by magnetic field, the release of the modified oligonucleotide occurs which is finally hybridized in a fluorescent DNA microarray and the fluorescent signal can be detected. (Fig. 4) (Broto M., et al 2017).

Polystyrene NPs + BBC-DNA + Ab ⟶ Immunocomplex probes

MNPs + Ab ⟶ Magnetic Probes

Immunocomplex + MNPs-Ab + Target protein ⟶ Immunosandwiches + Free Probes —magnetic separation⟶ Immunosandwiches

—release⟶ BBC-DNA —hybridization on microarray⟶ Signal

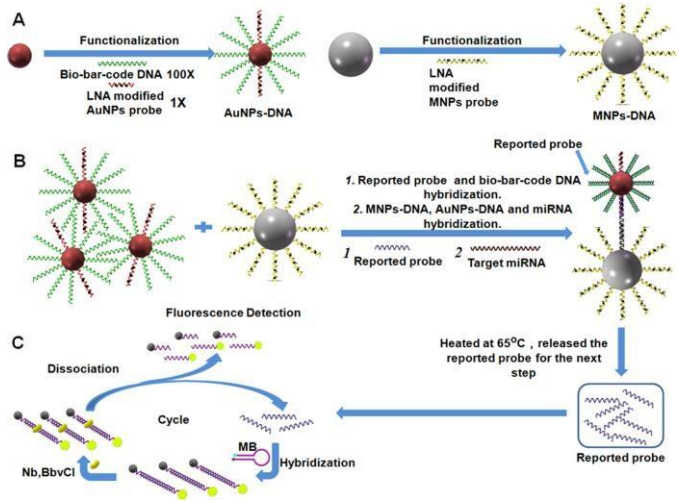

Fig. 3. (A) proportion of modified AuNPs and MNPs, (B) formed of AuNP LNA-miRNA-DNA MNP and BBC-DNA-RP, (C) released RP detection by enzyme-Assisted Strand Cycle (Nb,BbvcI) and Exponential Signal Amplification (Dong H., et al, 2015)

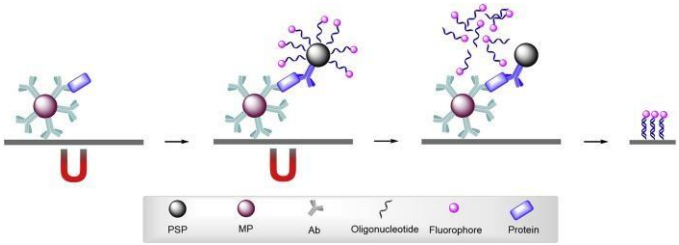

Fig. 4. Diagram of the detection of a small molecule by the sandwich nanoparticle-based bio-barcode assay (Broto M., et al 2017).

Trévisan et al, developed a new type of BBC biosensor to resolve problem encountered in detecting of poor biological samples. The method uses evanescent wave fluorescence, magnetic beads (MB) and nonmagnetic beads (latex beads LB), both functionalized with oligonucleotides (Fig. 5a,b). The LB probe modified with two type oligonucleotides (ODN), the first ODN complementary to fluorescently bio-barcode DNA (BBC-ODN), the second ODN can hybridize with half of target DNA, another half of target DNA is complementary to ODN onto the surface of MB. When added the target DNA to probes, ‘’MB-tDNA-LB-BCB’’ sandwiches were formed. After magnetic separation of sandwich from excess non-hybridized BBC, the fluorescent BBC-ODN dehybridize with high temperature (Fig. 5c). The sensor detector the fluorescent of BBC-ODN onto the surface of Eva chip by measuring the kinetics of fluorescence evolution. (Trévisan M., et al 2010)

LB + cBBC-ODN + Capture ODN ⟶ Latex Probe (LP)

MB + ODN with aminolink ⟶ Magnetic Probe (MP)

LP + MP + Target nucleic acid + Fluorescent BBC ⟶ LP-tDNA-MP Sandwich+ Free Pro $\xrightarrow{\text{magnetic separation}}$ Target

Sandwiches $\xrightarrow{\text{Heat}}$ Fluorescent BBC $\xrightarrow{\text{Eva Chip Well}}$ Signal

1.2. Light absorption (colorimetric)

Specific antibodies modified nanoparticles interact with the target molecule, the resulting nanoparticle aggregation or separated DNA can be measured by light absorption. *Zhou et al*, have shown that specific enzymes can be detected by DNAzyme for the detection of protein cancer biomarkers. Two nanoprobes were used, the first one is a MMPs (magnetic microparticles) were functionalized with McAb anti-AFP (α-fetoprotein), the second nanoprobe is a AuNPs functionalized with polyclonal antibody (PcAb) anti-AFP and dsDNA, only one of the double strand was labeled with AuNPs and another strand can be hybridized with the first strand, was the peroxidase-mimicking DNAzyme. Thus, magnetic beads are added to the sample, AFP was sandwiched between AuNP and MMP (Fig. 6). After isolating the sandwiches by a magnetic field, the DNAzyme hybridized from the other strand into the supernatant, the released DNAzyme then reacted with substrate solution, producing a green color and can be detected by absorption light with a peak at 410 nm (Zhou. W.H. et al, 2009).

MMP + McAb ⟶ First Capture Probe

AuNPs + PcAb + Thiolated DNA + DNAzyme ⟶ Second Capture Probe

1.Probe +2.Probe +Target protein (AFP) ⟶ Sandwich Probe + Free Probes $\xrightarrow{\text{magnetic separation}}$ Sandwich Probes $\xrightarrow{\text{Heat}}$ DNAzyme

DNAzyme + Substrate ⟶ change of color $\xrightarrow{\text{VIS-absorption}}$ Signal

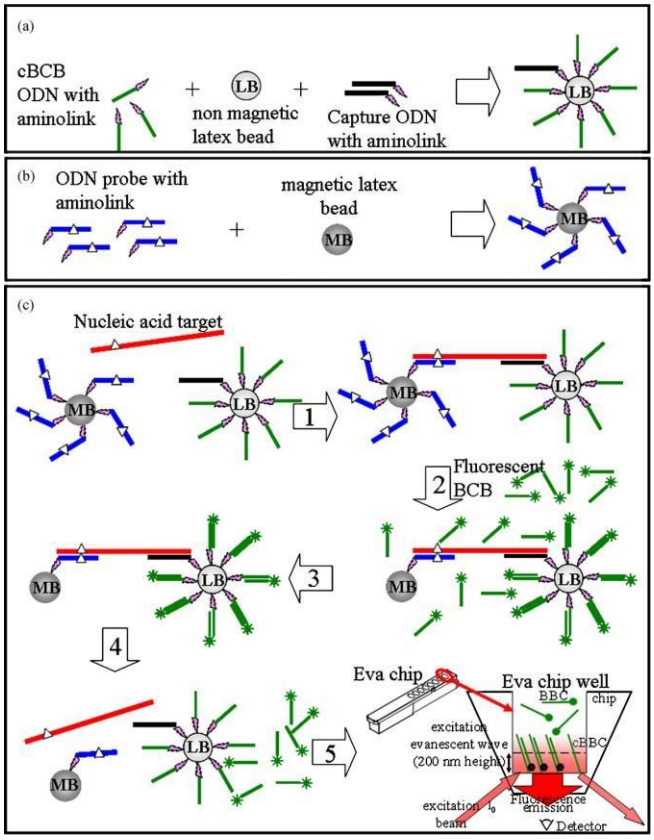

Fig. 5. (a) Preparation of modified latex beads with BBC ODN, (b) Preparation of magnetic beads modified with ODN probe, (c) schematic diagram of the bio-barcode assay. (1) hybridization of target DNA with modified Latex Bead and MB, (2) labeled of fluorescent BBC with BBC-ODN onto the surface of LB, (3) magnetic separation of MB, (4) released of fluorescent BBC, (5) detection of fluorescent BBC-ODN in EVA chip with EWF sensor (Zhou. W.H., et al, 2009).

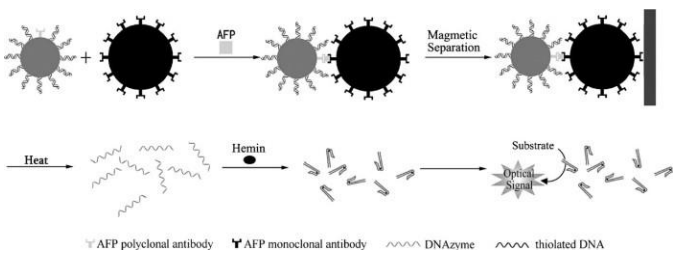

Fig. 6. Schematic illustration of the immunocomplex assay for detection of cancer biomarker (Zhou. W.H. et al, 2009).

Nam and co-workers, developed an ultrasensitive colorimetric bio barcode amplification method for detection of interleukin-2 (IL-2). The IL-2 is a cytokine signaling molecule in the immune system. In order to detect IL-2, the functionalized silica beads with McAb Anti-interleukin-2 and bio-barcode ssDNA, thus hybridize with complement BBC-DNA. The other particle is magnetic bead. The magnetic beads were modified with seconder Anti-interleukin. When added IL-2 to probes, the first and second antibody are bonded with IL-2 and formed the complex sandwiches ''BBC-DNA/SiB/IL-2/MB'' (Fig 7A). After separated the nonbonded probe by magnetic field the barcode DNA released from SiB by high heat and hybridized with modified AuNPs with barcode capture probes. The bonded AuNPs with barcode DNA can give a less reddish and the other free particles gives more reddish color, for the separation of two nanoparticles they used thin-layer-chromatography (TLC) plate. (Fig. 7B) (Nam J.M., et al 2005, 2007)

Si beads + Anti-IL-2 + BBC-dsDNA ⟶ Barcode Probe

Magnetic Beads + Anti-IL-2 ⟶ Magnetic Probe

Barcode Probe + Magnetic Probe + IL-2 ⟶ Sandwich Probes + Free Probes $\xrightarrow{\text{Magnetic separation}}$ Sandwich probes $\xrightarrow{\text{Heat}}$ BBC-ssDNA

BBC-ssDNA + BBC capture AuNPs $\xrightarrow{\text{Hybridization}}$ BBC-dsDNA-AuNPs $\xrightarrow{\text{Spotting on a TLC Plate}}$ Signal (Colorimetric detection method)

1.3. Light scattering

The principle is simple, metal nanoparticles, such as AuNPs or silver nanoparticle, can be used to spread light of certain wavelengths. *Du et al,* developed a novel bio barcode competitive amplification immunoassay for detection of small molecule pesticide residue based on gold nanoparticles labeling silver staining method in a microwell plate. To detect small molecule, such as, Triazophos (TAP), two types of probes were used, the first one is MMPs coated with ovalbumin coupled with the pesticide hapten, and the second probe is gold nanoparticles (AuNPs). The nanoparticles were coated with McAb and BBC-ssDNA. After labeling TAP with gold nanoprobes, the non-bonded gold nanoprobes labeled with ovalbumin onto the surface of the magnetic microparticle and released free AuNPs by magnetic separation (Fig. 8A). The bonded of AuNPs with magnetic particles were treated with DTT to release barcode DNA and then was measured by a simple method based on microwell plate. The barcode added to the plate via the method. The plate has a biotinylated DNA and modified gold nanoparticles with capture DNA. The barcode DNA has two half-complementaries, one with biotinylated DNA and the other with capture DNA. These surrogate barcode targets are then hybridized to microarrays and detected with silver amplified gold nanoparticle probes. (Fig. 8B) (Du P. et al, 2017)

AuNPs + McAb + BBC-ssDNA ⟶ Capture Probes

MMPs + OVA-hapten ⟶ Magnetic Probes

Capture Probes + Magnetic Probes + TAP ⟶ AuNP-McAb/hapten-MMP + AuNP-McAb/TAP $\xrightarrow{\text{Magnetic separation}}$ AuNP-McAb/hapten-MMP Probes $\xrightarrow{\text{DTT}}$ BBC-ssDNA ⟶ Measurement by silver-amplified method on microwell plate

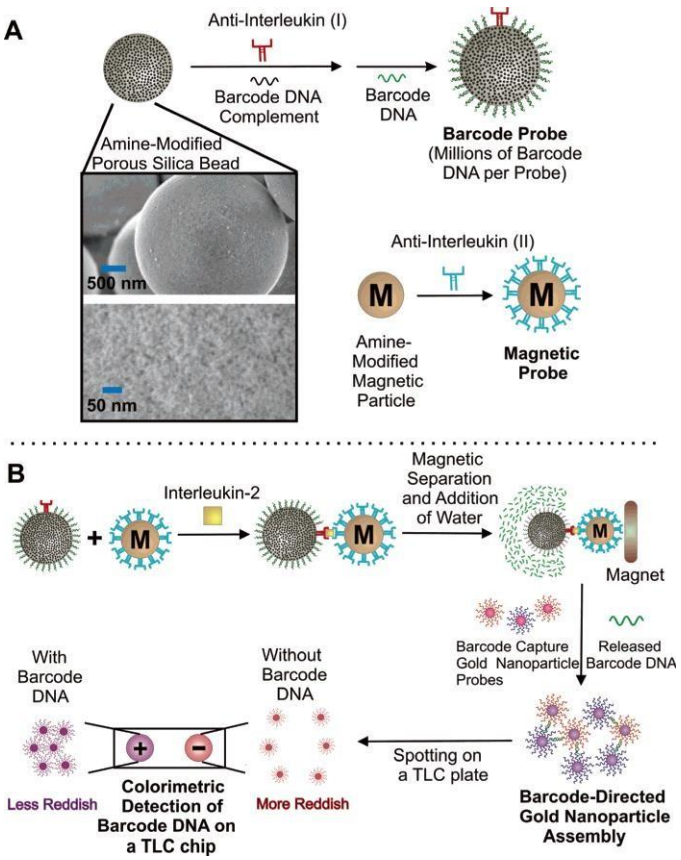

Fig. 7. (A) Preparation of modified silica beads and magnetic beads, (B) formed of sandwich complex and quantified of barcode DNA by TLC plate. (Nam J.M., et al, 2007)

Bao et al, reported barcode immunoassay method for the detection of PSA (prostate-specific antigen). In this work, they used a magnetic nanoparticle, gold nanoparticle and ssDNA barcode. In the first step, target protein labeled with the first antibody onto a surface of magnetic particle and in the second step antibody labeled onto a surface of gold nanoparticle was used to form sandwich probes. After magnetic separation, the bonded gold nanoparticle released from magnetic nanoparticle and the barcode DNA released from gold nanoparticle by Dithiothreitol (DTT). The released DNA can hybridize with modified AuNPs by capture DNA and surface of biotinylated DNA - streptavidin-coated microwell plate, finally the signal was amplified by silver enhancement. (Bao T.P. el al, 2006). Another work, by *Nam et al*, used gold nanoparticles modified by ssDNA and complementary barcode DNA, after magnetic separation, the BBC-DNA released by high temperature and signal amplified by a silver enhancement in a microwell plate (Nam J.M., el al 2003)

AuNPs + First Antibody + BBC-dsDNA ⟶ Capture Probes
MMPs + Second Antibody ⟶ Magnetic Probes
Capture Probes + Magnetic Probes + PSA ⟶ AuNP-1.Ab/PSA/2.Ab-MMP + Free Probes —Magnetic separation→ Sandwich Probes —Heat→ BBC-ssDNA ⟶ Measurement was carried out by silver-amplified method on microwell plate.

1.4. Real-Time PCR

When bio-barcode conjugated with modified nanoparticles or target RNA, after release operation, bio-barcode can be measured by real-time PCR. *Du et al*, reported a new bio-barcode immunoassay competitive amplification method for detecting a small molecule (Mw < 5000) like triazophos (TAP) pesticide. In this work they used gold and magnetic nanoparticles, the gold nanoparticle modified with McAB and ssDNA, ssDNA can hybridize with barcode DNA. A magnetic nanoparticle (MNPs) was developed by conjugation of magnetic nanoparticles and OVA-coupled with hapten. When added a target molecule, the target molecule bonded with McAb at gold nanoprobes and free gold nanoprobes bonded with hapten-OVA onto the surface of MNPs and both together formed the sandwich (AuNP-McAB-OVA-MNP). After magnetic separation of probes by magnetic field, the bonded gold nanoprobes with target protein were removed, and then the bonded gold nanoprobes with magnetic probes remained in the tube (Fig. 9). The barcode DNA isolated from AuNPs in the tube and detected by real-time PCR (Du P. et al, 2016)

AuNPs + McAb + SH-ssDNA ⟶ GNP Probes
GNP probes + BBC-ssDNA —Hybridization→ Capture Probes
MNPs + OVA-hapten ⟶ MNP Probes
Capture Probes + MNP probes + TAP ⟶ dsDNA-SH-AuNP-McAb/hapten-OVA-MNPs Sandwich Probes + AuNP-Ab/TAP —Magnetic separation→ Sandwich Probes —Heat→ ssDNA-SH-AuNP-McAb/hapten-OVA-MNPs Sandwich Probes + BBC-ssDNA —DNA Isolation→ BBC-ssDNA ⟶ Quantitative Detection was done by real-time PCR.

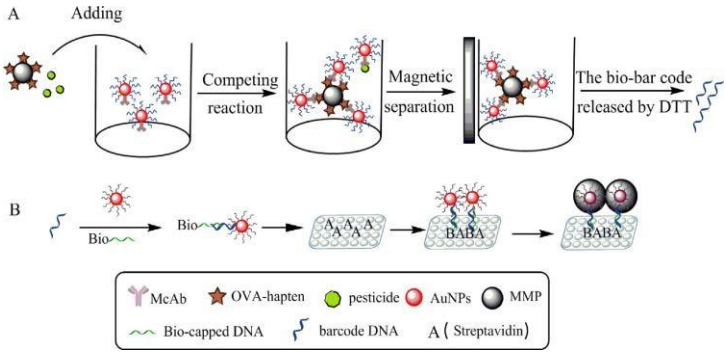

Fig. 8. Schematic illustration of the immunocomplex assay with microwell plate for detection pesticide (Du P. et al, 2017).

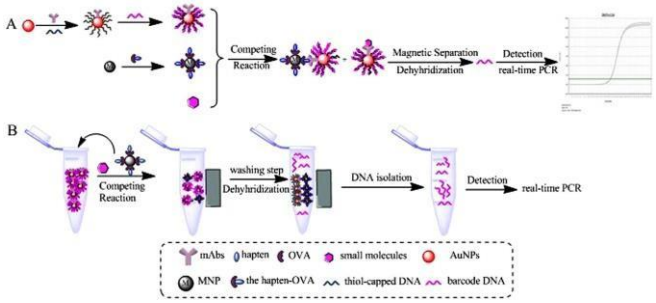

Fig. 9. Schematic illustration of competitive bio barcode immunoassay nanobiosensor (Du P. el al, 2016).

Yang et al, reported a novel bio-barcode immunoassay to detection of polychlorinated biphenyls (PCBs) in hairtail, to simplify the technique further and improve the sensitivity of the previously developed bio barcode immunoassay. This work combines bio barcode DNA assay and immune rt-PCR. The gold nanoparticles were modified with a thiol-capped DNA and antibody for the proportion of a capture probe. The Real-Time PCR tubes functionalized with ovalbumin coating antigen. The target protein in the sample conjugation with PcAb onto the surface of AuNPs and the non-bonded of capture probes fixed on the wall through immunoreaction of coating antigen onto the rt-PCR tube. The target protein with capture probes was removed by washing, the

barcode DNA onto a surface of fixed AuNPs released by high temperature and directly quantify the barcode DNA in the tube by real-time PCR (Fig. 10) (Yang G. et al, 2015).

rt-PCR tube + OVA-antigen → Fixed probes

AuNPs + SH-dsDNA + PcAb → Capture Probes

Fixed Probes + Capture Probes + PBCs → Sandwich Probes + Free Probes —Wash→ Sandwich Probes —Heat→ Dehybridization of dsDNA and Detection of BBC-ssDNA by rt-PCR

Yang and co-workers also developed an immunosandwich assay for the determination of 3,4,3',4'-tetrachlorobiphenyl (PCB77), using PcAb for conjugation with the target protein and coating antigen in PCR tube, the gold nanoparticles functionalized with thiol-capped dsDNA and goat anti-rabbit IgG. IgG was conjugated with Fc region of polyclonal antibody by immunoreaction in PCR tube and formed the sandwich immuno-complex (Fig. 11). The signal-DNA was released from the probes by the initial heating procedure of real-time PCR and was quantified by real-time PCR (Yang G.X., et al, 2013)

rt-PCR tube + OVA-antigen → Fixed Probes

AuNPs + SH-dsDNA + Goat anti-rabbit IgG → GNP Probes

PcAb + PCB77 —Conjugation→ PcAb-PCB77 + Free PcAb

PcAb-PCB77 + Free PcAb + Fixed Probes —Conjugation→ PcAb-PCB77 + Conjugate Probes —Wash→ Conjugate Probes

Conjugate Probes + GNP Probes —Conjugation→ Sandwich Probes + Free GNP Probes —Wash→ Sandwich Probes —Heat→ Dehybridization of dsDNA and Detection of BBC-ssDNA by rt-PCR

1.5. Electrophoresis

Lee et al, developed a new type of bio barcode gel assay for determination of different miRNA levels from lung and breast cancer cells with high selectivity and sensitivity. Sandwiching target miRNA with a gold-nanoprobe (AuNPs-DNA) functionalized with a different signal component oligonucleotide and magnetic nanoprobe (MNPs-DNA) functionalized with signal component oligonucleotide to make the AuNPs-DNA/miRNA/MNP-DNA sandwiches. Then, separated from the solution by a magnetic field (Fig. 12). Finally, dissolved the AuNPs by potassium cyanide (KCN), to completely release BBC-DNA in a very short time and to further increase the signal intensity detected during gel electrophoresis of double helix BBC-DNA sequences (Lee H., et al, 2013).

AuNPs + BBC-ssDNA → GNP Probes

MNPs + cBBC-ssDNA → Magnetic Probes

GNP probes + Magnetic Probes + Target miRNA —Hybridization→ Sandwich Probes + Free Probes —Magnetic Separation→ Sandwich Probes —Dehybridization by Heat→ GNP Probes +Magnetic Probes

GNP probe —Dissolve AuNPs by KCN→ BBC-ssDNA → Detection signal density during the gel electrophoresis of double helix barcode-DNA

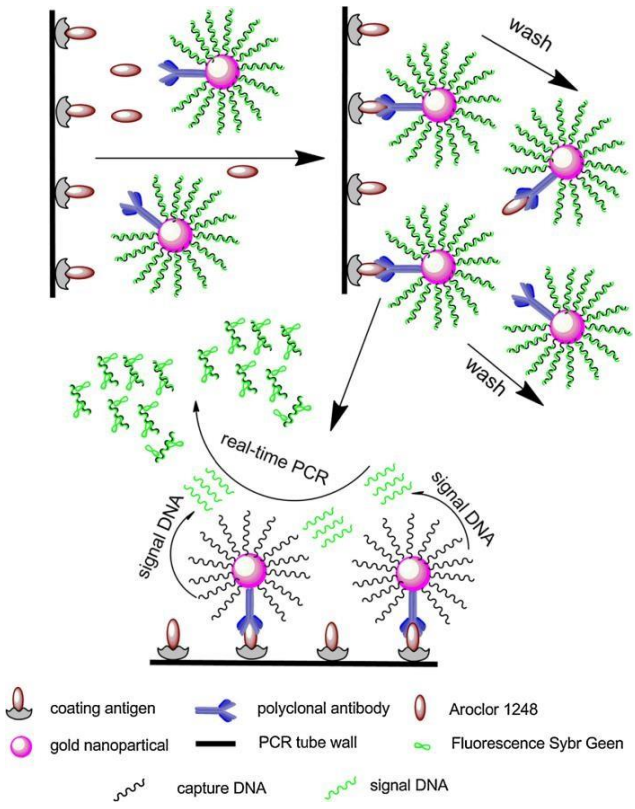

Fig. 10. Schematic illustration of detection of Arcelor 1248 by barcode immunoassay used Real-Time PCR (Yang G. et al, 2015).

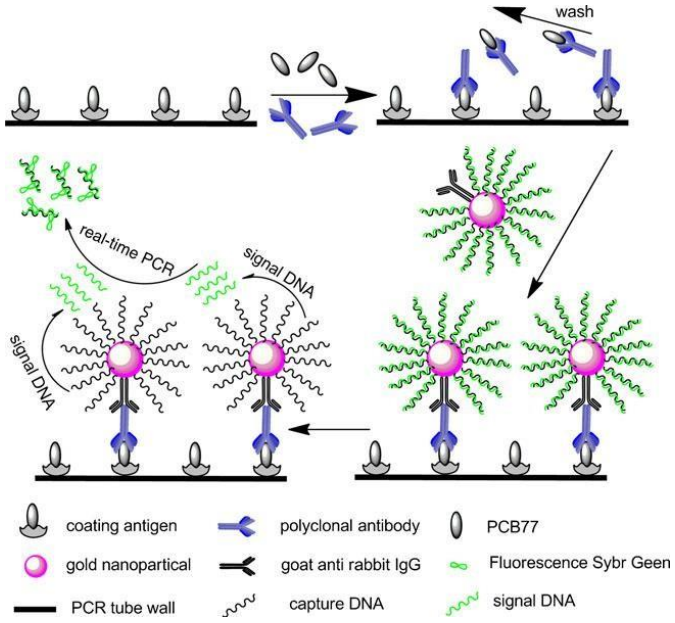

Fig. 11. Schematic illustration of immunosorbent bio barcode assay (Yang G.X., et al, 2013).

Dong et al, developed a new type of bio-barcode nano-biosensor for detection of HIV-1 p24 antigen. A pair of anti-p24 mAb was used in BBC analyzes to capture p24 antigen in the form of a sandwich and measure p24 capture used gel electrophoresis and PCR amplification. in this work they compare between nanoparticle based BBC assay and normal fluorescence microplate and bio-barcode based microplate. The first 1G12 mAb was coated on microplate wells (Figure 13A) or MMPs to capture free p24 antigens. The captured p24 captured 1D4 mAb coated AuNP probes having dsDNA oligonucleotides. While an oligonucleotide sequence is covalently immobilized, the unbound free bio barcode DNA strand can be released by high heat. The released BBC-DNA was amplified by PCR, electrophoresed on the agarose gel and quantified. (Fig. 13C) (Chen L., et al, 2009). In another paper authors used a G12 antibody, coated on microplate wells to capture free P24 antigen and labeling with the second mAb onto the surface of AuNPs (Fig. 13B) (Dong. H. et al, 2012).
Hee An and co-workers also used a mAb immobilized microplate method based on bio-barcode to detect tyrosinehydroxylase (An J.H., et al, 2013).

$$\text{AuNPs} + 1.\text{McAb} + \text{BBC-dsDNA} \longrightarrow \text{Capture Probes}$$
$$\text{MNPs} + 2.\text{McAb} \longrightarrow \text{Magnetic Probes}$$
$$\text{Magnetic Probes} + \text{Capture Probes} + \text{Target Protein} \longrightarrow \text{Sandwich Probes} + \text{Free Probes} \xrightarrow{\text{Magnetic Separation}} \text{Sandwich Probes}$$
$$\xrightarrow{\text{Heat}} \text{BBC-ssDNA} \longrightarrow \text{Detection by Gel Electrophoresis Analysis}$$

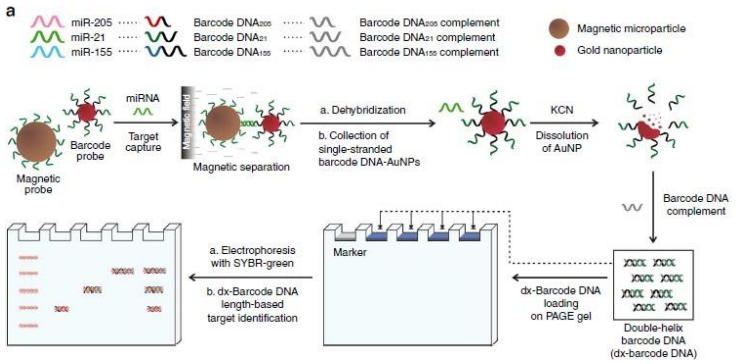

Fig. 12. The schematic diagram of the bio barcode nanobiosensor gel assay for detection of miRNA (Lee H., et al, 2013).

1.6. Surface Plasmon Resonance (SPR):

SPR is an optical detection method that detects that the molecular adsorption-induced dielectric constant occurs on the surface of a noble metal such as gold or on a semiconductor surface. *Loo et al*, used SPR sensing to detect cytochrome-c (Fig. 14). For this work, they developed a new generation aptamer-based BBC assay. MMPs were functionalized with cyt-c Ab and aptamer to form sandwich ``MMP-Ab/cyt-c/aptamer''. After washing unbonded probes by magnetic field, aptamer released by high heat from the sandwich and hybridized with the SPR probe. The SPR probe was prepared for RNase H for SPR sensing. RNase H is used to specifically digest RNA in a probe. After hydrolysis of the RNA probe with RNase H, the unspoilt aptamer was released from the RNA-DNA hybrid and ligated to a new RNA probe for another enzymatic reaction cycle to amplify the signal by gold nano rods (Au-NRs) (Loo J.F.C., el al, 2017)

MMPs + cyt-c Ab → Magnetic Probes

Magnetic Probes + cyt-c —Conjugation→ Cyt-c Probes

Cyt-c Probes + Aptamer —Conjugation→ MMP-Ab/Cyt-c/Aptamer Sandwich Probes + Free Aptamer —Magnetic Separation→ Sandwich Probes —Heat→ release Aptamer

Aptamer + SPR probe + RNase H → Digestion bonded probes → signal

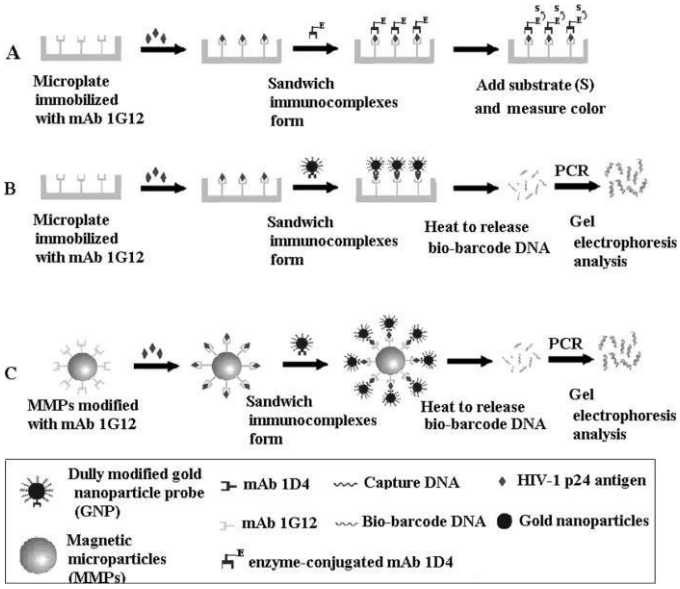

Fig. 13. (A) General ELISA assay to detect an HIV-1 P24 antigen, (B) microplate method for detection HIV-1 P24 antigen by PCR and electrophoresis, (C) Detection of HIV-1 P24 by magnetic nanoparticles and gold nanoparticles-based bio-barcdoe assay method (Dong. H. et al, 2012)

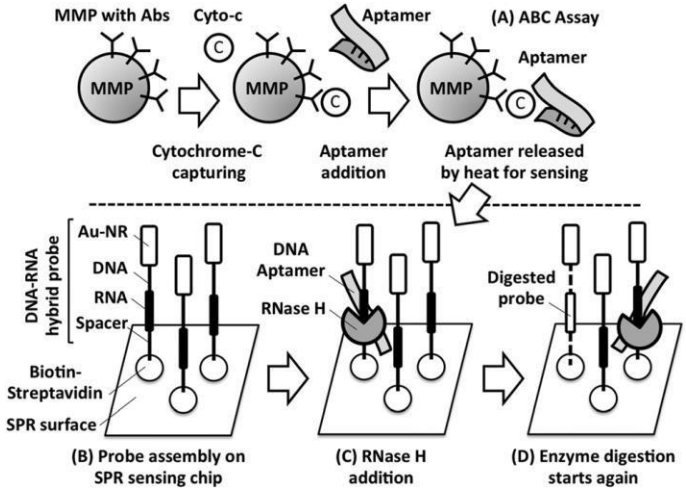

Fig. 14. The BBC assay showing the design and workflow for cytochrome-c sensing. (A) form a sandwich ``MMP-Ab/cyt-c/aptamer'' and separated by magnetic field, (B) released aptamer by heat and adding to SPR probe, (C) adding RNase H enzyme to specifically hydrolyze RNA in the probe, (D) amplify signal by a next enzymatic reaction cycle (Loo J.F.C., el al, 2017)

2. CONCLUSION

This review has summarized recent challenges, trends and advances in the quickly evolving field of bio barcode optical biosensors supported by nanoparticles. An overview of the techniques reported, the liner range, the role of nanoparticles, the limit of detection of biosensor and the detection techniques used are summarized in Table 1. This study showed that nanoparticle-based bio-barcode ensure very good results with promising sensitivity and selectivity; It offers an appealing analytical approach for accessible, fast and low-cost for detection of biomolecules, toxins, environmental pollutants and pathogens. The major advantages of bio-barcode biosensors are exceptionally small; portability, high sensitivity, acceptable analysis costs, simplified use and direct interpretation of results.

Table 1: General data on nanoparticle-based bio-barcode sensing

Marker Sample matrix	LOD	Liner range	NP	Role of NP	Detection technique	Reference
triazophos	*6 ng L^{-1}*	0.01-20 µg L^{-1}	Au NP	Label	fluorescence	(Zhang C. et al, 2017)
tDNA	1 pM		Ag NP	Transducer modifier	fluorescence	(Zhou Z. et al, 2014)
miRNA	52.2 zM	0.3 pM to 3 aM	Au NP	Probe capture	fluorescence	(Dong H., et al, 2015)
tDNA	2 pM		Latex bead	Probe capture	fluorescence	(Trévisan M., et al 2010)
AFP	0.1 ng	0.2 to 20 ng	Au NP	Catalytic label	Light absorption	(Zhou. W.H. et al, 2009)
İnterleukin-2	30 aM	-	Si NP	Label	Light absorption	(Nam J.M., et al 2005)
Triazophos	$1.96x10^{-2}$ ng ml^{-1}	$2.5x10^{-2}$ to 40 ng ml^{-1}	Siliver enhancement Au NP	Scatter light	Light scattering	(Du P. et al, 2017)
triazophos	0.02 ng ml^{-1}	0.04 to 10 ng ml^{-1}	Au NP	Label	rt PCR	(Du P. et al, 2016)
miRNA	10 pM	1 aM to 10 nM	Au NP	Label	Electrophoresis	(Lee H., et al, 2013)
HIV-1 P24	0.1 pg ml^{-1}	0.1 to 1000 pg ml^{-1}	Au NP	Label and Probe capture	Electrophoresis	(Dong. H. et al, 2012).
Cyt-c	80 pM		MMP	Probe capture	SPR	(Loo J.F.C., et al, 2017)

3. ABBREVIATIONS

Ab	Antibody	miRNA	Micro ribonucleic acid
AFP	α-fetoprotein	MMPs	Magnetic microparticles
Au NPs	Gold nanoparticles	MNPs	magnetic nanoparticles
Au NRs	Gold nanorods	MP	magnetic probe
BBC	Bio-barcode	NPs	nanoparticles
CP	Capture probe	ODN	Oligonucleotides
Cyt-c	Cytochrom c	OVA	Ovalbumin
DNA	Deoxyribonucleic acid	PcAb	polyclonal antibody
dsDNA	Double-stranded Deoxyribonucleic acid	PCBs	polychlorinated biphenyls
DTT	Dithiothreitol	PCR	Polymerase chain reaction
EWF	Evanescent wave fluorescence	PSA	Prostate-specific antigen
FAM	Carboxyfluoresce	RNA	Ribonucleic acid
HIV	Human immunodeficiency virus	RP	Reported probe
IgG	Immunoglobulin G	rt-PCR	Real-time PCR
IL	Interleukin	SH-ssDNA	single-stranded thiol-oligonucleotides
LB	latex beads	SiB	Silica beads
LNA	Locked nucleic acid	SPR	Surface plazmon resonance
LOD	Limit of detection	ssDNA	single-stranded Deoxyribonucleic acid
LP	Latex probe	TAP	Triazophos
MB	Magnetic beads	tDNA	Target DNA
McAb	monoclonal antibody		

REFERENCES

Amini B., Kamali M., Salouti M., Yaghmaei P., (2016), Fluorescence bio-barcode DNA assay based on gold and magnetic nanoparticles for detection of Exotoxin A gene sequence., Doi: j.bios.2016.10.030

An j.H., Oh B.K., Choi J.W., (2013), Detection of Tyrosine Hydroxylase in Dopaminergic Neuron Cell Using Gold Nanoparticles-Based Barcode DNA, DOI: 10.1166/jbn.2013.1525

Bao Y.P., Wei T.F., Lefebvre P.A., An H., He L., Kunkel G.T., Muller U.R., (2006), Detection of Protein Analytes via Nanoparticle-Based Bio Bar Code Technology, DOI: 10.1021/ac051798d

Bhushan B., (2010), springer handbook of nanotechnology (1-11) (3rd Edition). Springer Heidelberg Dordrecht London New York. DOI 10.1007/978-3-642-02525-9

Broto M., Galve R., Marco M.P., (2017), Sandwich NP-based biobarcode assay for quantification C-reactive protein in plasma samples, DOI: 10.1016/j.aca.2017.09.007

Chen L., Wei H., Guo Y., Cui Z., Zhang Z., Zhang X.E., (2009), Gold nanoparticle enhanced immuno-PCR for ultrasensitive detection of Hantaan virus nucleocapsid protein, DOI: 10.1016/j.jim.2009.05.007

Dong H., Liu J., Zhu H., Ou C.Y., Xing W., Qiu M., Zhang G., Xiao Y., Yao J., Pan P., Jiang Y., (2012), Two types of nanoparticle-based bio-barcode amplification assays to detect HIV-1 p24 antigen, DOI: 10.1186/1743-422X-9-180

Dong H., Meng X., Dai W., Cao Y., Lu H., Zhou S., Zhang X., (2015), Highly Sensitive and Selective MicroRNA Detection Based on DNABio- Bar-Code and Enzyme-Assisted Strand Cycle Exponential Signal Amplification, DOI: 10.1021/acs.analchem.5b00029

Du P., Jin M., Chen G., Zhang C., Jiang Z., Zhang Y., Zou P., She Y., Jin F., Shao H., Wang S., Zheng L., Wang J., (2016), A Competitive Bio-Barcode Amplification Immunoassay for Small Molecules Based on Nanoparticles, DOI: 10.1038/srep38114

Du P., Jin M., Zhang C., Chen G., Cui x., Zhang Y., Zhang Y., Zou P., Jiang Z., Cao X., She Y., Jin F., Wang J., (2017), Highly sensitive detection of triazophos pesticide using a novelbio-bar-code amplification competitive immunoassay in a micro wellplate-based platform, DOI: 10.1016/j.snb.2017.10.075

H.D. Hill, C.A. Mirkin, (2006), The bio-barcode assay for the detection of protein and nucleic acid targets using DTT-induced ligand exchange, Nat. Protoc. 1 324e336.

Hansen, J.A., Mukhopadhyay, R., Hansen, J.O., Gothelf, K.V., 2006a. J. Am. Chem. Soc. 128, 3860–3861.

Hansen, J.A.,Wang, J., Kawde, A.-N., Xiang, Y., Gothelf, K.V., Collins, G., 2006b., Quantum-Dot/Aptamer-Based Ultrasensitive Multi-Analyte Electrochemical Biosensor, J. Am. Chem. Soc. 128, 2228–2229.

Jie, G., Liu, B., Pan, H., Zhu, J.J., Chen, H.Y., 2007, CdS Nanocrystal-Based Electrochemiluminescence Biosensor for the Detection of Low-Density Lipoprotein by Increasing Sensitivity with Gold Nanoparticle Amplification, Anal. Chem. 79, 5574–5581.

Lee H., Park J.E., Nam J.M., (2013), Bio-barcode gel assay for microRNA, DOI: 10.1038/ncomms4367

Loo J.F.C., Yang C., Tsang H.L., Lau P.M., Yong K.T., Ho H.P., Kong S.K., (2017), An Aptamer Bio-barCode (ABC) assay using SPR, RNase H, and probes with RNA and gold-nanorods for anti-cancer drug screening, DOI: 10.1039/c7an01026e

Nam J.M. Jang K.J. Groves J.T., (2007), Detection of proteins using a colorimetric bio-barcode assay, DOI: 10.1038/nprot.2007.201

Nam J.M., Thaxton C.S., Mirkin C.A. (2003), Nanoparticles-based bio-barcodes for the ultrasensitive detection of proteins, DOI: 10.1126/science.1088755

Nam J.M., Wise A.R., Groves J.T., (2005), Colorimetric Bio-Barcode Amplification Assay for Cytokines, DOI: 10.1021/ac0513764

S.I. Stoeva, J.S. Lee, C.S. Thaxton, C.A. Mirkin, Multiplexed DNA detection with biobarcoded nanoparticle probes, Angew. Chem. Int. Ed. Engl. 45 (2006) 3303e3306.

Trévisan M., Schawaller M., Quapil G., Souteyrand E., Mérieux Y., 2010, Evanescent wave fluorescence biosensor combined with DNA bio-barcode assay for platelet genotyping, DOI: 10.1016/j.bios.2010.08.038

Yang G., Zhuang H., Chen H., Ping X., Bu D., (2015), A gold nanoparticle based immunosorbent bio-barcode assaycombined with real-time immuno-PCR for the detection ofpolychlorinated biphenyls, DOI: 10.1016/j.snb.2015.02.128

Yang G.X., Zhuang H.S., Chen H.Y., Ping X.Y., Bu D., (2013), A sensitive immunosorbent bio-barcode assay based on real-time immuno-PCR for detecting 3,4,3',4'-tetrachlorobiphenyl, DOI: 10.1007/s00216-013-7583-9

Zhang C., Du P., Jiang Z., Jin M., Chaen g., Cao X., Cui X., Zhang Y., Li R., Abd El-aty A.M., Wang J. (2017), A simple and sensitive competitive bio-barcode immunoassay for triazophos based on multi-modified gold nanoparticles and fluorescent signal amplification, Doi: J.ACA.2017.10.032.

Zhou W.H., Zhu C.L., Lu C.H., Guo X., Chen F., Yang H.H., Wang X., (2009), Amplified detection of protein cancer biomarkers using DNAzyme functionalized nanoprobesw, DOI: 10.1039/b916217h

Zhou Z., Li T., Huang H., Chen Y., Liu F., Huang C., Li N., (2014), A dual amplification strategy for DNA detection combining bio-barcode assay and metal-enhanced fluorescence modality, Doi: 10.1039/c4cc05554c

Zhu, N. N., Zhang, A. P., Wang, Q. J., He, P. G. and Fang, Y. Z. 2004b. Electrochemical detection of DNA hybridization using methylene blue and electro‐deposited zirconia thin films on gold electrodes. Anal. Chim. Acta, 510: 163–168