Prospects of Biosensors based on Functionalized and Nanostructured Solitary: Detection of Viral Infections and Other Risks

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SI 1. Brief on Different Applications

Advances in nanotechnology over the past decade have emerged as a substitute for conventional therapies and facilitated the development of economically viable biosensors. Next-generation biosensors could play a significant role in biological sciences.¹ Notably, they could provide a new dimension for new therapeutic approaches and expedite the detection process of various biomolecules like DNAs, RNAs and others.²⁻³ Furthermore, they may be used for a variety of environmental changes, such as the detection of environmental pollutants such as heavy metals, toxins, pesticides, antibiotics, organic pollutants, and so on.

SI 1.1. Drug Discovery

Drug discovery is about the investigation of new therapeutic or biological potential candidates. It provides huge potential for monitoring drugs and would lead to innovation in precision medicine. Recent advances in pharmaceutical research have strengthened the applicability of biosensors. Biosensor friendliness has increased the number of small molecules which could have potential therapeutic.² Biosensors can enhance high-throughput screening of drug-like molecules.³ Furthermore, the sensitivity and efficacy of biosensors in pharmaceutical applications could be taken advantage for developing various pharmaceutical products.¹⁻⁴

SI 1.2. Disease Detection

Methods for early detection and diagnosis were critical in halting the spread of rapid transmission diseases and reducing morbidity and mortality in those conditions. Because conventional procedures have their limits, new ways of diagnosing might be more accurate and specific.⁵ Viruses such as Zika, Ebola, SARS-CoV, MERS-CoV and others have posed a constant threat to humanity over the last several decades. Thousands of people have died as a result of various types of microbial infections in humans over the last several years. Recently, humanity has been afflicted by the coronavirus infection very badly and the disease is known as COVID-19 and later, it is declared as pandemic by World Health Organization (WHO).⁶⁻¹¹
For example, the invention of iron-based magnetic nanoparticles (IMNPs) targets organs infected by COVID-19. Lately, biosensors based on field-effect transistors (FET) have been reported, constructed by immobilizing an antibody to spike HCoV-2 onto graphene via a probe linker, i.e., 1-pyrenebutyric acid N-hydroxysuccinimide ester (PBASE) and reported to have a detection limit of 1 fg/ml.

**SI 1.3. Cancer Therapy**

Early prognosis of cancer improves the chances of its cure. Recently, several types of cancer have been diagnosed at a later stage and have metastasized throughout the body. Therefore, there is a dire need for accurate and effective diagnosis and treatment. Over the past years, biosensor-based approaches have emerged to be effective in the detection of cancer biomarkers, the design of anti-cancerous therapeutics and drug efficiency. Based on the available literature, cancer biomarkers have been a very useful tools for detection. Hence, biomarker detection via biosensors could remarkably improve the detection. Furthermore, point-of-care biosensors have the potential to provide robust, reliable and accurate therapeutic monitoring, cancer imaging, and drug discovery and delivery. Few examples of cancer biomarkers such as RNA, DNA or proteins are illustrated (Figure SI.1).

**SI 1.4. Delivery System**

Disease management is a crucial step followed by prognosis. Therapeutic intervention for disease management necessitates a targeted drug delivery approach. Adopting an advanced approach for drug delivery would improve the drug’s bioavailability, diminish side effects, etc. Nanobiosensor-based drug delivery models would improve the pharmacodynamics and pharmacokinetics of modern drugs. Biosensor integration would provide effective management, controlled drug release, and many more advantages.

**SI 1.5. Molecular or Optical Imaging**
Molecular or cellular imaging is crucial to study the biochemical changes at the cellular or molecular level. In order to study the inside of the cell, fluorescent or FRET based biosensors have been reported. These biosensors use labelled probes, which can efficiently be used in situ or in vivo detection. Therefore, biosensor application in imaging techniques would enhance the investigation of movement of ions, protein localization, and other metabolites.\textsuperscript{1,20}

In a nutshell, the development of next-generation biosensors has an immense role in various disciplines of science. Therefore, the NM-functionalized biosensors could revolutionize research. The combination of biological sensing elements with NM provides recognition of biological or chemical molecules and has resulted in the development of NM-based biosensors.\textsuperscript{21}

SI 2. Optical Biosensor

SI 2.1. Colorimetric Detection

Colorimetric biosensor was one of the most popular method due to its simple and instant detection with a change in the colour of the solution by the naked eye. For example, the Au NPs in the sensor change the colour from red to purple after aggregation. The aggregated, complex-based sensor was joined with a cell phone camera to quantitatively detect \textit{E. coli}\.\textsuperscript{22} For HCoV-2 detection, Au NPs capped with thiol-modified antisense oligonucleotides, which was N-gene specific encoded nucleocapsid protein. Li \textit{et al.} have used Au NPs to prepare lateral flow immunoassays that can be used simultaneously for IgM and IgG antibodies of HCoV-2 detection.\textsuperscript{23-27}

SI 2.2. Plasmonic Biosensor

Plasmonic biosensors are classified based on the technology used as; (1) SPR and (2) Surface Enhanced Raman Spectroscopy (SERS). SPR is the milestone of label-free nanophotonic
biosensors. In contrast, SERS is a promising and powerful tool with high sensitivity. Due to the sensitivity of single molecules, specificity for molecules, and insensitivity to freezing, SERS was used to detect bacteria or viruses. To enhance sensing and miniaturization, incorporating nanostructures such as nanorods, nanodimers, or complex geometries can be an alternative for ultrasensitive label-free biosensors using conventional SPR systems as point-of-care devices. These also facilitate the invention of 2D microarrays for multiplexed analysis.

A smartphone was converted into real-time SPR biosensor on an intensity interrogation mechanism by attaching it with an optical device (Figure SI.2). Collimated light passed through a linear polarizer filter becomes transverse magnetic polarized. This polarized beam passed through a beam splitter plate directed towards the sensor at normal incidence after reflection. The reflected beam from the sensor surface passed through a splitter plate that focused on the camera sensor of a smartphone through an external lens that forms an image. The key advantages of the plasmonic biosensor are highly sensitive, label-free sensor, multiplexing capability, quantification detection, and much more characterized details of an analyte with the disadvantages of limited LOD and quantification capability.

**SI. 3. SWCNTs-based Biosensor**

Kam et al. established the modification with the help of PL-PEG having a chain and terminal maleimide and amine (NH$_2$) groups which bind SWCNTs by van der Waals and hydrophobic interactions (Figure SI.6). In modifying with PEG, PL-PEG, and phospholipid molecules, non-covalently adsorbs on SWCNTs. Then, PL-PEG binds strongly with SWCNTs and herein, the sidewall of SWCNTs interacts with two PL alkyl chains leads to enhancing the solubility of f-SWCNTs in the water. The f-SWCNTs have terminal amine or maleimide used to conjugate various biomolecules such as DNA oligonucleotides and siRNA. Singh et al. demonstrated the presence of positive charge on SWCNTs was due to ammonium and lysine groups:
SWCNTs-NH$_3^+$ (1) and SWCNTs-Lys-NH$_3^+$ (2) respectively, (Figure SI.7). These positively charged f-SWCNTs play a crucial role in gene delivery as well as in plasmid DNA. Both f-SWCNTs were condensed DNA in different degrees and depends on the surface area of SWCNTs and the charge density ratio of SWCNTs and DNA. In both f-SWCNTs, 2 showed the higher condensation of DNA than 1 because of larger surface area. The experimental data shows that a large surface area condenses more DNA and can enhance the gene transfer.$^{38}$ Chen et al. reported the tumour-targeted drug delivery with the help of biotin, which covalently binds with the end and sidewall of SWCNTs.$^{39}$

**SI. 4. Au NPs-based Biosensors**

Zhou et al. demonstrated aptamer-engineered Au NPs for the sensing of adenosine via the colorimetric method using the E-eye system. The principle of sensing of adenosine was that aptamer controls the change in the colour of Au NPs by binding with it. In the sensing of adenosine, one aptamer was bound with two adenosines leading to prevent the aptamer from adsorbing on Au NPs. E-eye system detected the change in colour from red to purple when unmodified Au NPs with aptamer was mixed in a high salt solution (Figure SI.10).$^{40}$ Steinmetz et al. demonstrated silsesquioxane f-Au NPs as label-free DNA biosensor based on oxidized GCE for Zika Virus detection. The f-Au NPs were synthesized via the layer-by-layer deposition method.$^{41}$ Bai et al. proposed modification with DNA with immobilization on the electrode for amplified electrogenerated chemiluminescence biosensing for thymine DNA glycosylase detection. To synthesize DNA-Au NPs, a suitable amount of ssDNA was activated with phosphine hydrochloride and acetate buffer followed by mixing of prepared Au NPs solution. After that, tris-acetate buffer and NaCl solution were dropwise added to the above mixture.$^{42}$ Huang et al. synthesized PEG-engineered Au NPs. Dicarboxylic PEG and chloroauric acid were mixed with continuous stirring followed by the addition of NaBH$_4$ mixture via chemical reduction method, which was used to detect ssDNA (Figure SI.11). The use of PEG prevents
the aggregation of Au NPs after target DNA addition, reduces non-specific binding on NPs, and increases the chemical stability of NPs in a complex solution. Moreover, PEG was used to increase the ability to capture target DNA on Au NPs surface.\textsuperscript{43} Mohammed \textit{et al.} proposed citrate-activated Au NPs to show the effect of unevenly ends in ssDNA and dsDNA in a colorimetric biosensor to sense the Hepatitis C RNA virus. Activated Au NPs were synthesized via the citrate reduction method.\textsuperscript{44} Wang \textit{et al.} synthesized core-shell Fe\textsubscript{3}O\textsubscript{4}-Au NPs modified with peptide nucleic acid (PNA), used for miRNA detection. In the modified NPs, one PNA molecule was bound to only one Au NP. The NPs act as a molecular carrier that passes through a nanopore electrochemical sensing system to bind with target miRNA selectively.\textsuperscript{45}

\textbf{SI.5. UCNPs-based biosensors}

Chen \textit{et al.} proposed the mechanism for engineering of NaYF\textsubscript{4}:Yb,Er/Tm upconversion (UC) NPs with carboxylic acid groups on the outer part and further bound with streptavidin. Firstly, oleic acid present on the outer part of NPs get oxidized using Lemieux-von Rudloff reagent into azelaic acid, which leads to reactive carboxylic acid generated on its surface. The TEM image reveals that the aggregation was prevented by the presence of long-chain oleic acid ligands on the surface (Figure SI.14A), while oxidized ligands affect the interaction and thus prevent the formation of nanoarrays and consist of single nanocubes (Figure SI.14B). The particle size distribution was quite similar in both cases, suggesting no significant effect on the size and shape of UCNPs due to oxidation, but the arrays were different. Due to reactive carboxylic acid on the surface, it had excellent solubility in water. Also, it binds with streptavidin to form an amide bond with the help of EDC and NHS as cross-linkers, as shown in Figure SI.15. Further, this streptavidin-bounded UCNPs material was used to prepare a high sensitivity DNA sensor with various biological applications.\textsuperscript{46} Wilhelm \textit{et al.} proposed the activation of Si-coated UCNPs with PEG as a spacer with N-hydroxysuccinimide ester. Firstly, oleic acid-capped UCNPs were coated with silica via the reverse-microemulsion method.
Further, Si-coated UCNPs were functionalized using silanization reagent having reactive amino groups. In silanization reagent, triethoxysilane molecule conjugated with PEG and NHS ester having activated carboxylic group and they were covalently bonded to Si-coated UCNPs surface. PEG can prevent the UCNPs from agglomeration, enhances specific binding and solubility in aqueous media. In contrast, NHS ester group enhances the binding property to proteins such as streptavidin and BSA (Figure SI.16).\textsuperscript{47}

Nagarajan \textit{et al.} proposed Si-coated UCNPs modifications with the help of amino-ethoxy silane. The UCNPs were coated with silica via the Stober process. The average particle diameter was less before silica coating and was higher after functionalization. Further, the coated UCNPs were modified with the amine group with the help of amino-ethoxy silane having application in bio-imaging. These UCNPs were conjugated with the anti-Cx43 and antibody via the glutaraldehyde spacer method. The UCNPs describe the bio-imaging applications by labelling gap junction between live cardiac cells, responsible for forming communication channels.\textsuperscript{48}

\textbf{SI.6 Other Materials-based Biosensors}

Rohilla \textit{et al.} synthesized the functionalization of CuO NPs (f-CuO) with dopamine via the microwave-assisted method for colorimetric biosensor L-cysteine detection in human urine and serum.\textsuperscript{49} Chauhan \textit{et al.} synthesized aspartic acid-engineered Gd\textsubscript{2}O\textsubscript{3} nanorods immobilized on indium doped tin dioxide (ITO) via an electrophoretic deposition process for Vitamin-D\textsubscript{3} detection. Gd\textsubscript{2}O\textsubscript{3} was synthesized via the precipitation method.\textsuperscript{50} Ou \textit{et al.} synthesized DNA-modified PtCo mesoporous nanosphere (MNS) for electrochemical immunodetection of N\textsuperscript{6}-Methyladenosine (m\textsuperscript{6}A) RNA and synthesized PtCo MNS via slow reduction reaction by Pluronic®F-127, KBr, H\textsubscript{2}PtCl\textsubscript{6}, and CoCl\textsubscript{2} in an aqueous solution of ascorbic acid with heating in a water bath. The colour of the solution is turned from light yellow to black. After that, the prepared PtCo MNS is mixed with 100 μM thiol-modified m\textsuperscript{6}A-DNA to get the desired
The NWs having hierarchical structure helps in facile ion diffusion and fast electron-transport path that is responsible for excellent performance of biosensor. Yang et al. proposed streptavidin-engineered CuO NPs as a lateral flow strip biosensor for sensing human papillomavirus (HPV) type 16 DNA. As per the author's knowledge, the vivid colour of CuO NP was first used in the biosensor as coloured tags. Firstly, CuO NPs were reacted with streptavidin and then biotin-modified DNA probe to yield CuO capture probe. CuO NPs were synthesized via the quick-precipitation method.

SI.7 Utilization of Biosensors in Detection of COVID-19

Another method was CT scan, wherein X-ray measurements are taken from different viewpoints to obtain a 3D representation to analyze the abnormal features. In addition, a scan of patients in early infection resembles a normal chest radiogram. Therefore, it was used as a prognosis tool for COVID-19. Also, contact tracing was the use of the smartphone-based application to determine active cases and it had been successful in controlling transmission of HCoV-2. Another approach for the COVID-19 diagnosis was gene sequencing using an automated software, SmartXGene. However, the innovation of ultrasensitive biosensors is the solution.
Figure SI.1. Schematic representation of the working principle of biosensors for the detection of cancer biomarkers. Reprinted with permission from ref 18. Copyright 2021 Elsevier.

Figure SI.2. Representation of optical biosensor with smartphone integration. Reprinted with permission from ref 35. Copyright 2016 Elsevier B.V.
Figure SI.3. Schematic diagram of PEG-modified SWCNTs.

Figure SI.4. Schematic diagram of CTAB-functionalized SWCNTs.

Figure SI.5. Schematic diagram of (a) HMDA-SWCNTs and (b) PDDA-SWCNTs.
Figure SI.6. Schematic diagram of PL-PEG-modified SWCNTs.

Figure SI.7. Schematic diagram of (a) SWCNTs-NH$_3^+$ and (b) SWCNTs-Lys-NH$_3^+$. 

Figure SI.8. Schematic diagram of MWCNTs-NH$_3^+$. 
**Figure SI.9.** TEM images of (A) CTAB-Au NRs, (B) PDDAC-Au NRs, and (C) PEI-Au NRs. Reprinted with permission from ref \(^56\). Copyright 2012 American Chemical Society.

**Figure SI.10.** Schematic mechanism for the colorimetric detection of adenosine using aptamer engineered Au NPs.

**Figure SI.11.** Schematic diagram of attachment of PEG on the surface of Au NPs.
Figure SI.12. TEM images of functionalized monodisperse silica colloids in cyclohexane. (a) SNP, (b) AP-SNP, (c) MP-SNP, (d) P-SNP and (e) V-SNP. Reprinted with permission from ref 57. Copyright 2010 Elsevier.

Figure SI.13. Schematic diagram of bio labelling of HeLa cells with Fe₃O₄/UCNP nanocomposites using EDC/NHS.
Figure SI.14. TEM images of (A) the as-prepared and (B) oxidized NaYF₄:Yb,Er samples. Reprinted with permission from ref 46. Copyright 2008 American Chemical Society.

Figure SI.15

Figure SI.15. Schematic diagram of binding of streptavidin with carboxylic acid-engineered UCNP.
Figure SI.16. Schematic diagram of PEG-activated SiO$_2$@UCNP conjugate with protein.

Figure SI.17. SEM images of PPy nanowires on pre-treated GCE at different magnifications (A), (B) at 1 μM and (c), (D) at 100nM. Reprinted with permission from ref$^{58}$. Copyright 2019 Elsevier B. V.
Figure SI.18. Photographs and schematics of our smartphone-based fluorescence microscope.

The cell phone screen in (a) shows the fluorescence image. (b) A back view of the same cell phone attachment, and (c) its schematic illustration. Reprinted with permission from ref 59. Copyright 2013 American Chemical Society.
Figure SI.19. (a) Proposed mobile health system (b) Proposed future society. Reprinted with permission from. (a) Proposed mobile health system. Reprinted with permission from ref \(^\text{60}\) Copyright 2020 The Science and Information Organization and (b) Proposed future society. Reprinted with permission from ref\(^\text{61}\) Copyright 2020 Wiley-VCH GmbH.

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