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Mini Review

Nano-Technological Approaches to Improve the Efficiency of Bio-Assays

Mini Review

One of the biggest issues in today's healthcare industry is to find a very fast yet effective diagnostic platform, which is suitable for our busy lifestyle without compromising the detection efficiency. The major requirements of an efficient diagnostic platform can be summarized as minimum sample requirement, least reagent requirement, having options of multiple tests in a single platform, high through put analysis and last but never the least a non-expensive sample run. The largest contributor of the bio-assay industry is protein based chromogenic bio-assays, which depends on strong antigen-antibody interaction and high emissive properties of reporter dye molecule attached to the antigen. In reality, this apparently simple looking reaction system has to face several difficulties before an appreciable signal is received by the photo-detector to give an analysable dataset. With the rapid emergence of nanotechnology during last few decades, some of the critical problems have been solved [1-5]. However, a large number of unresolved issues still remain there. This editorial will briefly address some of those critical issues and how they have been tackled by nanotechnology. The two-most tunable variables of a bio-assay platform are the reporter molecules and the sensing platform as described by the Figure 1. We will describe both the issues separately in the next sections.

Optical efficiency of the reporter molecule

The optical efficiency of a reporter molecule suffers from two major issues, firstly the biological auto-fluorescence and secondly the fluorescence quenching of the reporter dye by the aqueous environment. The biological autofluorescence originates from the
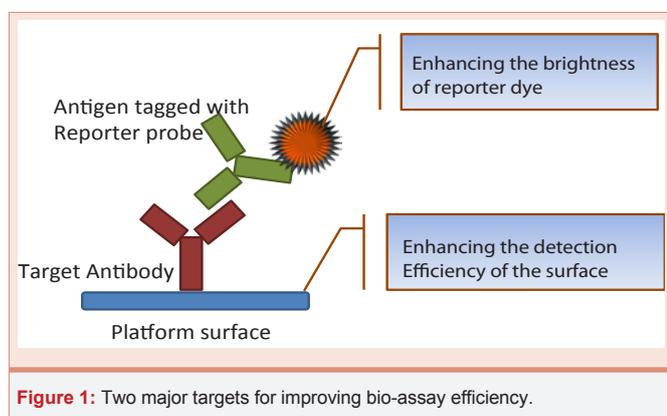
scattering surface of biomolecules and/or biological membranes functioning as a background for the target molecules [6]. This apparently weak fluorescence signal emitting from the biological surrounding mainly covers the UV/visible part of the spectrum. Hence, the auto-fluorescence significantly increases the noise in the system; and thus reduces the signal/noise ratio. This not only results in a very poor fluorescence signal weakening the detection efficiency of the bio-assay, it also suggests to use reporter dye molecule with red shifted fluorescence maximum to avoid the interference from auto-fluorescence. In addition, the fluorescence intensity of the reporter dye molecule also suffers from the quenching by its surrounding that includes the biomolecules as well as the aqueous solvent. These two major deadlocks have significantly restricted the choice of suitable dyes for bio-assays. Easily available dyes with very high quantum efficiencies (QE) are either very much hydrophobic or their emission spectrum are not well shifted towards the red region of the spectrum. Thus the dyes, which are stable in aqueous environment with appreciably high quantum efficiency having fluorescence maximum in the far red region are very few and expensive as well.

Nanotechnology has provided a smart solution to this problem by replacing the reporter dye molecules with a dye-doped core/shell nanoparticle, where high QE hydrophobic dyes can be entrapped within the hydrophobic core [7]. This strategy has several advantages over the conventional dye based assay system as described below.

a. Hydrophobic dyes, which are not otherwise usable as free dye in the aqueous environment, are now eligible for selection.

b. One single core/shell nanoparticle can accommodate hundreds to thousands of dye molecules inside its core; thus increasing the brightness factor of the fluorophore [8]. Brightness factor, B_F is defined as

$$BF = \frac{\text{No of Dye molecules inside core}}{\text{QE of the single dye}} \times \text{Residual QE of the entrapped dye}$$

Here, one needs to remember that, though the residual QE of the entrapped dye molecules is significantly lower than the free dye molecule due to self-quenching (say around 10 fold), the very large number of dye molecules (say around 1000 fold) more than cancel that effect and increases the B_F by around 100 fold (Figure 2).

Several research groups, including us, have used silica based core/shell nano architecture to improve the detection efficiency of fluorescence probes [9,10]. The main challenges to establish high brightness nanoparticle as a feasible substitute for free dye molecule is the issue of stability. Special cares are warranted to stabilize the nanoparticles (10nm to few hundred nm in size) in aqueous
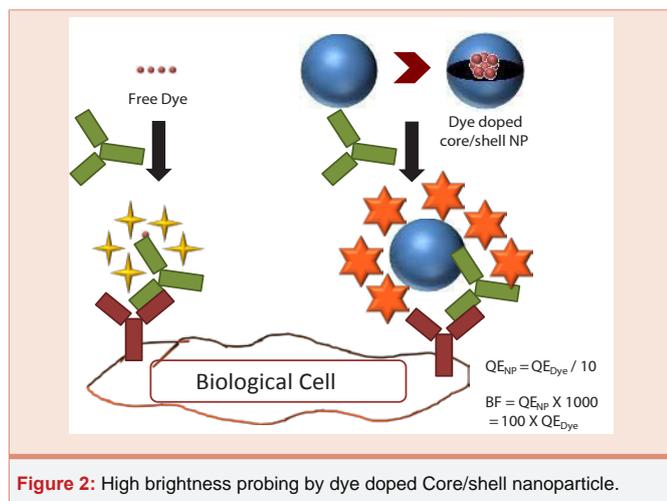

Figure 1: Two major targets for improving bio-assay efficiency.

Figure 2: High brightness probing by dye doped Core/shell nanoparticle.

environment using specialized surface chemistry including various silanes, dendrimers, linker molecules etc.

However, a further improvement of the luminescence property of the dye molecule is also possible. The concept of metal enhanced fluorescence (MEF) or plasmonic enhancement of fluorescence was primarily introduced by the pioneering research group of Lackwicz and Geddes, who proposed that a noble metal nanocore, if placed within a critical distance (10 to 20 nm) to the dye molecule, can actually enhance the fluorescence QE [11,12]. The empirically showed that the enhancement factor for this process is inversely proportional to the QE of the dye molecule. Several hybrid nanostructures including Au and/or Ag nanoforms have demonstrated the significant improvement of the QE for the dye molecules ranging up to thousand fold for very low QE (< 0.001) dyes [13].

Besides the mentioned hybridization strategies, there are several classes of nanomaterials, which have improved the optical detection efficiency in bio-diagnostics. Some of these special classes of nanoforms are described here.

Quantum Dots

The exceptional photophysical properties of colloidal nanoforms quantum dots(QD) have strongly attracted the bioanalytical community over the last approximately 20 y. Particularly, the integration of QDs in the bio-analytical methodologies have significantly contributed to the generation of Förster resonance energy transfer (FRET), based diagnostic platforms [14]. So et al., have introduced Self-illuminating QD conjugates for *in vivo* imaging [15]. However, to effectively apply photo dynamic therapy on malignant cells there are few more difficulties to overcome. For breast cancer treatment several organic dyes and radiocolloid materials are used. However, these methods have significant shortfalls as patients get exposed to ionizing radiation and due to their instability, local tissue damage is imminent. Radenkovic and his group have shown the potential of Cadmium free semiconductor quantum dots in biocompatible Sentinel lymph node (SLN) biopsy during cancer treatment. They have shown that, optimally functionalised near infrared emitting QDs are highly photo stable, efficient image-guided

tumor resection agent with the capability of deep tissue penetration [16].

The state of the art personal healthcare industry has put significant emphasis on the development of easy to use portable diagnostic platforms like Integrated quantum dot barcode smartphone optical device for wireless multiplexed diagnosis [17], camera-based ratio metric fluorescence transduction on a paper-based platform using immobilized quantum dots as FRET donors [18]. Algar et al., showed QDs as simultaneous acceptors and donors in time gated FRET relay events and their application in biosensing [19]. In the similar line, Freeman et al., have demonstrated an amplified multiplexed analysis of DNA by the exonuclease III catalyzed regeneration of the target DNA in the presence of functionalized semiconductor QDs [20]. Algar et al., has also demonstrated the multiplexed tracking of protease activity using a single color of QD vector and a time-gated FRET mechanisms [21]. The steady state fluorescence based diagnostic methods have lately been complemented by their time resolved counterparts as Geißler and co-workers have shown a. Six-color time-resolved FRET for ultrasensitive multiplexed biosensing [22]. To establish a strong theoretical basis to this kind of platforms, Claussenet et al., have constructed complex logic functions implemented with QD bionanophotonic circuits [23].

Carbon Dots

The emergence of Carbon quantum dots or C-Dots as bio-compatible optical nanoprobes has been a significant development of nano-biodiagnostic industry. Several advantages like higher bio-compatibility, tunable luminescence emission and ease of surface functionalization have made this genre of nanoforms a highly sought-after alternative for expensive hydrophilic dyes. Loo et al., have demonstrated carboxylic C-Dots as a Fluorescent Sensing Platform for DNA Detection [24]. Guo and co-workers have demonstrated a color switchable, emission-enhanced fluorescence realized by engineering C-dot@C-dot nanoparticles [25]. These C-Dots have also shown potential as a two-photon visible nanocarriers for safe and highly efficient delivery of siRNA and DNA [26]. Application specific functional surface engineering of C-Dots are gradually emerging as a very popular agent for fluorescent biosensing and *in vivo* bioimaging [27].

Upconversion nanoparticles

Besides quantum dots, C-Dots and other conventional luminescent nanoparticles, a unique branch of photophysical platform has emerged as photon upconversion technology. This upconversion of photon is resulted due to the occurrence of a series of successive electronic transitions within complex energy levels of lanthanide ions - embedded in the crystal lattice. In a lanthanide-doped upconversion nanoparticles (UCNP), the dopant ions are homogeneously distributed within the host lattice. After being readily accessible to surface quenchers, these UCNPs lose their excitation energy and produces weak and susceptible emissions. Current studies on UCNPs are primarily focused on core-shell type nano architecture dopant ions are spatially confined. Upconverting lanthanide ions are doped inside of the interior of a core-shell nanoparticle. The two most useful properties of UCNPs are that the upconversion emission can be

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tuned and thus substantially enhanced, and their optical integrity can be largely preserved [28]. Lanthanide-doped UCNPs have generated a lot of interest due to some interesting physicochemical properties like large anti-Stokes shifts, low toxicity, low auto-fluorescence background along with and high penetration depth making them an efficient downshifting luminescence bioprobes with various biological applications [29]. Within several modes of applications, UCNPs are showing potential as photodynamic anti-cancer agents, bio-imaging agents, multifunctional MRI contrast agents, drug delivery agents [30-32].

Electro chemo iuminescent nanoparticles

Another important mode of photophysical properties exploited by nanoparticle based diagnostics is elctro-chemiluminescence. Berg and co-workers have shown the potential of AlGaInP based nanowire system as a precursor for next-generation light-emitting diodes as indicated by the electro-optical properties measured by injection luminescence measurements [33]. In a similar line, Cheng et al., have achieved atomically thin transition metal dichalcogenides p-n diodes with distinct layer-number dependent emission characteristics to produce a highest external quantum efficiency up to 12% [34]. Quantum chemical calculations through DFT were reported by Wawrzynczyk et al., who predicted significant changes in luminescence spectra shapes as well as luminescence lifetime values by changing the local chemical environment of very small $\alpha NaYF_4$:4 % Eu^{3+} colloidal nanoparticles [35]. However, by using polymer-dispersed liquid crystal technology based on 50 μm-thick PDLC layer formed between a transparent electrode and a ZnS:Cu phosphor layer, Song et al., have improved the luminescence efficiency by more than 15%. [36]. Xie group has used layer-by-layer (LBL) technology to develop a gold nanoparticle and toluidine blue-graphene based label-free electrochemical aptasensor for highly sensitive thrombin detection with appreciably high signal/noise ratio [37]. Su et al., have improved conventional immune-assay methods by developing a multiple amplification immunoassay for alpha-fetoprotein (AFP) detection with the detection limit of 1.7 pg/mL. [38] Similarly, another ultrasensitive protein detection strategy was developed by Mao et al., who utilized silver catalysis for Ru (bpy)(3) (2+) electrochemiluminescence (ECL) signal [39].

Improvement of nanosurface property (Surface plasmon resonance)

Last three decades have witnessed a significant surge in the research on the biomedical applications of surface plasmon resonance (SPR) and localised surface plasmon resonance (LSPR) originated from noble metal surface. Propagating surface plasmon polaritons or plasmon waves are produced in various illumination configurations from grating coupling to near-field excitation. The fundamental optical configuration to demonstrate SPR was demonstrated by Kretschmann geometry where a thin noble metal film is covered on a prism. However, drawbacks like being a bulky system and having low spectral resolution has limited its application [40,41]. On the other hand, LSPR, which is a coupling between electromagnetic field and spatially confined free-electrons, has shown significant potential for improving the optical resolution. LSPR sensors are significantly advantageous compared to SPR sensors due to their capability of

optimizing the sensing performance through variations of the size and shapes of nanostructures. The extremely intense and highly confined electromagnetic fields induced by the LSPR can realize a highly sensitive probe to detect small changes in the dielectric environment around the nanostructures. However, the primary mode of LSPR detection platform is based on surface enhanced Raman scattering (SERS).

When the biomolecular binding events get close to the surface of a noble metal nanostructure, the refractive index of immediate environment surrounding the nanostructure is increased. Thus, biomolecular interactions at the surface of the nanostructures directly lead to local refractive index changes; these changes can then be monitored via the LSPR peak wavelength shift. Das et al., has successfully detected Attomole levels of the protein myoglobin on a SERS active gold nanograin aggregate array with interspacial distances down to 10 nm [42]. Similarly, Tamiya's group was capable of detecting changes in refractive index reporting specific biomolecular reactions like biotin-avidin interaction [43]. Similar methods were employed by Lim et al., who have sensed DNA at a single molecule level by using SERS active nanoodumbells by engineering the gap between two nanoparticles, Raman-dye position and environment [44]. This platform got further geometrically extended Ginger et al., introduced dimers of plasmonic nanoparticles to target DNA with elevated sensitivity [45].

The LSPR technology has further been improved by the introduction of multiple modes of plasmonic resonance bands during the first decade of the 21st century produced by noble metal nanoforms with asymmetric geometry. The spherical or semi-spherical geometry of the nanoforms have produced only one mode of vibration. Fundamentally, a nanosphere exhibits dipolar resonance with degenerated longitudinal and transverse modes due to the spherical symmetry. However, by the increase of aspect ratio at a nanoparticle, both transverse and longitudinal modes are split leading to multimodal vibration. The introduction of nanorods, nanostars, nanoplatlets and nanoprisms have demonstrated new plasmonic modes like dipole, qudrupole and octapole modes with both in-plane and out-of-plane vibrations. In the last decade, the seminal research by the group of G C Schatz has adequately established the theoretical background of the attractive spectroscopic properties of the noble metal nanoplanar geometry including nanotriangles and nanoprisms [46-48]. Although the expectations are very high from various multimodal-LSPR (mLSPR) vibrations of the nanoin biomedical fields due to their higher level of resolution, the current state of research lies in a very nascent stage. Some of the notable contributions are mentioned here.

Nguyen. et. al. has demonstrated a smart and highly (surface enhanced Raman spectroscopy) SERS-active plasmonic platform that was designed by coupling regular arrays of nanotriangles to colloidal gold nanorods via a thermoresponsive polymer spacer made of (poly(N-isopropylacrylamide) [49]. Fletcher et al., have used silver nanotriangle as nanoantenna to excite dark-mode plasmon resonances to couple a planar incident wave-front into a virtual point source [50]. Luo and co-workers have prepared a composite sol with reduced graphene oxide/silver nanotriangle (rGO/AgNT)

with SERS activity [51]. Kuhler et al., have embedded nanoantenna array constituted by nanotriangles with a supported phospholipid membrane to create a detection "hot-spot" which is SERS active [52]. Li and co-workers have demonstrated the potential of two-dimensional array of silver nanotriangles as a highperformance platform of bioassay. They have clearly shown on an antigen-antibody detection platform that the interaction between fluorophores and antibodies have been appreciably modulated (more than 3 times) by the plasmonic enhancement demonstrated by polystyrene mediated templating of Ag nanotriangles [53]. Kannadorai et al., has recently described the fabrication of silver nanotriangle array using angle resolved nanosphere lithography and utilizing the same for enhancing fluorescence [54]. Boca-Farcau has demonstrated another approach, where they have used silver nanotriangles which were biocompatibilized with chitosan (bio) polymer, labeled with Raman active para-aminothiophenol (pATP), and conjugated with folic acid [55]. They applied this approach by targeting the folate receptor of NIH:OVCAR-3 human ovary cancer cell line. Hence, integrating the advantages of multimodal optical imaging and SERS detection with hyperthermia capabilities through site specificity, these nanoparticles can represent a real candidate for personalized medicine. With several novel surface modification techniques by using various nano-patterning, generating nano hole arrays with various nanofabrication tools, a whole new generation of nanopatterned bio-sensing platform is emerging to take the diagnostic efficiency to the next level. The limit of detection (LOD) for these patterned nano-surface based biosensing platform is expected to surpass the current state of the art by many fold within next decade.

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