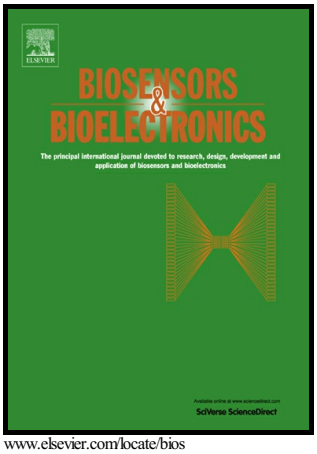

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PII: S0956-5663(18)30411-1
DOI: https://doi.org/10.1016/j.bios.2018.05.057
Reference: BIOS10515

To appear in: *Biosensors and Bioelectronic*

Received date: 10 April 2018
Revised date: 19 May 2018
Accepted date: 29 May 2018

Cite this article as: Rahim Nosrati, Sadegh Dehghani, Bahareh Karimi, Meysam Yousefi, Seyed Mohammad Taghdisi, Khalil Abnous, Mona Alibolandi and Mohammad Ramezani, Siderophore-based biosensors and nanosensors; new approach on the development of diagnostic systems, *Biosensors and Bioelectronic,* https://doi.org/10.1016/j.bios.2018.05.057

Siderophore-based biosensors and nanosensors; new approach on the development of diagnostic systems

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Abstract

Siderophores are small organic compounds secreted by microorganisms under iron-depleted conditions which enhance the uptake of iron. Siderophores can play vital roles in ecology, agriculture, bioremediation, biosensor, and medicine. In recent years, the concept of siderophore-based biosensing devices has opened new horizons in high precision detection of various metal ions especially the iron, microorganisms, phosphopeptides, antibiotics as well pesticides. Once combined with nanomaterials, nano-scale siderophore systems provide powerful analytical platforms for detection of low concentration of metal ions and numerous pathogens. In this article, a brief overview of general aspects of siderophore is firstly discussed. In addition, a clear and concise review of recent advances of siderophore-based biosensors (siderosensor) and nanosensors are mainly discussed herein. Subsequently, future perspectives and challenges of siderophore-based sensors are discussed briefly.

Keywords: Siderophore, Biosensors, Nanosensors, Bacteria, Iron, Metal ion

1. Introduction

Siderophores are low-molecular-weight organic compounds secreted by microorganisms further down iron-depleted conditions which promote the process of iron uptake (Saha et al. 2015; Sandy and Butler 2009). Siderophores strongly bind the insoluble ferric form of iron ion (Fe^{3+}) outside the cell. Fe(III)-siderophore complexes are subsequently recognized by outer membrane siderophore receptors or siderophore binding proteins. The complexes cross the membrane to cytosol through siderophore-mediated Fe transport systems. Inside the cell, Fe(III) gets reduced into soluble ferrous iron (Fe^{2+}) which is accessible to microorganism followed by the siderophore release (Ahmed and Holmström 2014; Hider and Kong 2010; Saha et al. 2015).

Based on the chemical nature of their coordination sites with iron, siderophores typically can be categorized into three main classes, viz., hydroxamates, catecholates (as well known as phenolates), and carboxylates (Fig. 1A) (Pérez-Miranda et al. 2007; Raymond and Dertz 2004). Siderophores have two or more functional groups which are considered as ‘‘mixed type’’ siderophores (Holden and Bachman 2015). In binding sites, oxygen donor ligands are used for Fe(III) coordination (Johnstone and Nolan 2015; Schalk et al. 2011). Hydroxamate type consisted of a widespread group of siderophores are produced by both fungi and bacteria (Winkelmann 2007). Most of the hydroxamate siderophores contain C (=O) N-(OH) R, where R is either an amino acid or its derivative. Two oxygen molecules from each hydroxamate group form a bidentate ligand with iron (Fig. 1A). Therefore, a hexadentate octahedral complex with Fe^{3+} results from each siderophore (Saha et al. 2015). Catecholate (phenolate) type of siderophores is mostly produced by some bacteria. Each catecholate group supplies two oxygen atoms for chelation with iron in order to form a hexadentate octahedral complex (Fig. 1A) (Dave et al. 2006). Carboxylates are produced by a group of *Zygomycetes* fungi (mucorales) and mostly by bacteria such as *Rhizobium* and *Staphylococcus*. This type coordinates iron through hydroxyl and carboxyl groups (Fig. 1A) (Baakza et al. 2004; Dave and Dube 2000).

Recently, new insight about siderophore has drawn much attention due to its potential roles in diverse sectors including ecology, agriculture, bioremediation, biosensor, and medicine (Górska et al. 2014). In microbial ecology, siderophores change the microbial communities by enhancing the growth of unculturable microorganisms (Lewis et al. 2010). Siderophores act as agents to help plants to uptake the Fe and to promote the growth of several plants and subsequent increase of their yield, which explicate their role in agriculture (Vejan et al. 2016). Siderophores play a pivotal role in biological control against phyto-pathogens and as a substitute for hazardous pesticides (Haas and Défago 2005). In the field of bioremediation, different types of siderophores can be used as an efficient agent in detoxifying heavy-metal-contaminated samples (Khan et al. 2017). In the medical application, siderophores are used in the treatment of many pathologic conditions including infectious diseases and cancers. In drug delivery systems, siderophore uses the “Trojan horse strategy” to form siderophore–antibiotic complexes and supports the selective delivery of antibiotics into the antibiotic-resistant bacteria (Chu et al. 2010; Górska et al. 2014; Miethke and Marahiel 2007). Other medical applications of siderophores consist of treatment of iron overload diseases (for example sickle cell anemia), antimalarial activity, removal of transuranic elements from the body (Nagoba and Vedpathak 2011), molecular imaging (Petrik et al. 2017) and anticancer activity (Miethke and Marahiel 2007). Recently, siderophores have been used as biosensor and nanosensor platforms for the detection of several metal ions especially the iron in different environments and detection of microorganisms as well. Figure 1B depicts the schematic diagram of siderophore-based biosensor operations and functions.

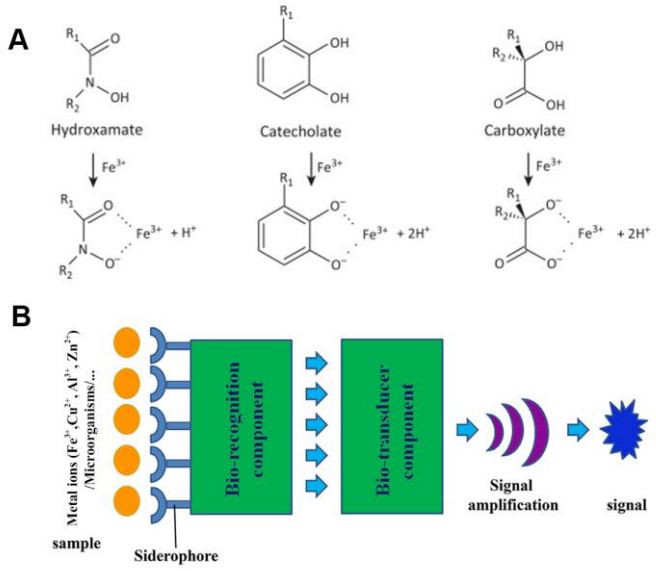

Fig. 1 (A) The main structural classes of siderophores and iron coordination complexes; (B) Schematic diagram of a siderophore-based biosensor. Reprinted with permission from (Górska et al. 2014) and reproduce from published paper (Saha et al. 2015).

Biosensor is a simple and compact analytical device capable of generating specific quantitative or semi-quantitative analytical information using a biological recognition element coupled to a signal conversion unit (a transducer) (Mokhtarzadeh et al. 2015; Nosrati et al. 2017). Biosensors are classified by their method of signal transduction into electrochemical, optical, electronic, piezoelectric, gravimetric and pyroelectric (Damborský et al. 2016). Optical and electrochemical platforms are two commonly used types of biosensors (Vigneshvar et al. 2016). Optical-based biosensors are usually non-destructive to an analyte to be detected, and can be fabricated and manipulated relatively in an easy and rapid fashion (Perumal and Hashim 2014; Shahdordizadeh et al. 2017). Typically, electrochemical biosensors operate through detection of output electrical signal generated following specific binding or catalytic reactions of surface modifier biomaterials such as aptamer, enzyme, antibody, or nucleic acids on the surface of a metal or carbon electrode (Luo and Davis 2013; Zhu et al. 2014). Nanomaterials have opened new options for designing biosensors and immunosensors (Dehghani et al. 2018; Jalalian et al. 2018). The hybrid of nanomaterials (NMs) and biosensing platforms (nano-biosensors) provides synergetic and versatile strategies for more simple, swift, and sensitive detection (Vigneshvar et al. 2016) and enhancing the ability of single molecule monitoring (Charbgoo et al. 2018; Mokhtarzadeh et al. 2015; Turner 2013).

In recent years, scientists have employed a variety of siderophore-based biosensors and nanosensors for the detection of a ranging of compounds from various metal ions (Chung Chun Lam et al. 2006; Orcutt et al. 2010; Phillips et al. 2015; Sharma and Gohil 2010; Yin et al. 2016; Yoder and Kisaalita 2011), proteins (e.g. phosphopeptides) (Bossé et al. 2014), antibiotics (Pawar et al. 2016), pesticides (Yin et al. 2014) to the detection of microorganisms (Doorneweerd et al. 2010; Inomata et al. 2014; Pahlow et al. 2016) and nucleic acid amplification and sequencing (Eason 2013). In this review, we have paid special attention to the recent advances regarding the roles and applications of siderophores on the development of biosensing detection methods.

2. Approaches for metal ions detection

Rapid and high precision detection of metal ions in biological samples is of great interest owing to diverse and important roles in lots of crucial biological processes (Hood and Skaar 2012). Metal ions

play remarkable role in metabolic processes such as transport of oxygen, muscular contraction, regulation of cell activity, photosynthesis, nitrogen fixation, nerve impulses and signal transmission (Carter et al. 2014). They also serve as co-factors or structural elements of enzymes (metalloenzyme) (Zhu et al. 2015). The proper concentration, no more, no less, of metal ions is essential for correct outcome but when present in excess, they are toxic (Fones and Preston 2013). Furthermore, some metal ions that are not biologically relevant such as mercury, lead, and cadmium are known to be toxic for organisms due to their bioaccumulation properties (Saidur et al. 2017). The presence of heavy metals in food chains poses a serious threat on the environment and thus human health. Therefore, early detection and monitoring of heavy metals contamination in the environment is becoming one of the main requirements for society (Priyadarshini and Pradhan 2017; Schalk et al. 2011).

A various chemical and analytic techniques including colorimetry, flame photometry, UV–vis spectrophotometry, atomic absorption spectrometry (AAS), electron microprobe analysis (Yang et al. 2016), ion-sensitive electrodes (ISEs) (Li et al. 2017), neutron activation analysis (Smichowski and Londonio 2018), secondary ion mass spectrometry (SIMS) (Penner-Hahn 2013), Synchrotron X-ray fluorescence microscopy (SXRF) (Fahrni 2007) and inductively coupled plasma-mass spectrometry (ICP-MS) (Carter et al. 2014) have been used for the quantitative detection of metal ions. However, these methods often require sophisticated instrumentations with complicated protocols facing with certain shortcomings. These methods are often very expensive, labor-intensive, time-consuming, tedious and require large amount of sample volumes and can only be handled by experienced personnel (Saidur et al. 2017).

The biosensing platforms for metal ions detection has recently developed because of their advantages such as high sensitivity and selectivity, rapid response, cost-effectiveness, non-toxicity and suitability of handling (Vigneshvar et al. 2016). In recent years, nanomaterials such as AuNPs (Priyadarshini and Pradhan 2017), magnetic nanoparticles, graphene and nanocomposite materials have been applied for the development of electrochemical and optical biosensors to investigate metal ions, in particular, transition-metals (Liu et al. 2017). The transition metals (e. g. Fe, Zn, Cu, Mn, Co, Ni, Mo, V, and Se), often referred as trace elements, which are essential for all forms of life (Palmer and Skaar 2016; Zhu et al. 2015). The precious specificity and high affinity of siderophores for numerous metal ions or their receptor provide the basis for using these molecules as sensors or probes. Nowadays, several siderophore-based biosensors and nanosensors have introduced with considerable success for various metal ions detection such as iron (Chung Chun Lam et al. 2006; Orcutt et al. 2010; Phillips et al. 2015; Sharma and Gohil 2010; Yoder and Kisaalita 2011), copper (Yin et al. 2016), molybdate (Duhme-Klair et al. 2003; Duhme-Klair 2009; Jedner et al. 2003) and aluminum (Raju et al. 2017a; Raju et al. 2018b; Raju et al. 2017b).

Among various siderophore-based methods developed for the estimation of metal ions, especially iron, fluorescent probes combined with siderophores (or analogues) or fluorescent siderophores have been considered owing to their rapid response rates and high sensitivity, which allow the detection of low concentrations of analyte. Sensors make use of different electrochemical properties of the siderophores as fluorescent probes to detect the metal content.

2.1. Detection of iron ions

Iron is a crucial micronutrient for variety of important processes in metabolism due to its diverse roles in chlorophyll biosynthesis, redox reactions and distinct physiological activities (Omidvari et al. 2010)., Iron also is perhaps the most important micronutrient used by bacteria which is required as a cofactor for a large number of enzymes and iron-containing proteins (Rachid and Ahmed 2005). It is

relevant to note that the accurate sense of Fe(III) is of key importance to assess, e.g. effective diagnosis of certain disease states.

Fluorescent siderophores have emerged as potent receptors for the remarkable progress in developing fluorophore molecules for iron ions detection. Iron, like many transition metal ions, has a desire to quench fluorophore emission and afford fluorescence quenching or ‘‘turn-off’’ following Fe(III) recognition. Both naturally fluorescent emissive siderophores and synthetic fluorophore siderophores have been employed for the detection of Fe(III) (Palanché et al. 1999).

Among natural fluorescent siderophores, the pyoverdines (PVDs) have been the most employed for the detection of Fe(III). Pyoverdines are diffusible yellow-green fluorescent siderophores produced by all fluorescent pseudomonads, especially *Pseudomonas aeruginosa* and *Pseudomonas fluorescens* (Visca et al. 2007). The PVD gene cluster is involved in the biosynthesis and excretion of these siderophores (Ravel and Cornelis 2003). All PVDs are composed of three parts comprising a conserved fluorescent dihydroxyquinoline-type chromophore, an acyl side chain (either dicarboxylic acid or amide) bound to NH_2-group of the chromophore; and a variable strain-specific peptide chain linked by an amide group bound to the carboxyl group of the chromophore (Lamont et al. 2006; Visca et al. 2007). The peptide arm contain 6 to 12 amino-acids and based on their sequence, different siderotype of PVDs have been recognized (Meyer et al. 2008). Pyoverdines form hexa-coordinate Fe(III) complexes and bind to iron by using both hydroxamate and catecholate groups. The binding of hydroxamates with ferric iron has very high stability constant approximately in the range of 10^{22} to 10^{32} M^{-1} (Winkelmann 2007). This strong binding between ferric iron and siderophore protects the complexes against hydrolysis and enzymatic degradation in the environment (Winkelmann 2007). Pyoverdines afford a fluorescence quenching response to Fe(III) (Zheng and Nolan 2012). These characteristics make pyoverdine a promising agent for the construction of optical biosensors. For this purpose, several studies have reported detection of iron using this siderophore.

In early 1990s, for the first time, it was reported that a natural fluorescent pyoverdine can act as a new sensitive, robust, and specific Fe^{3+} biosensor. In this work, PVD was immobilized on a controlled pore glass (CPG) and was packed into a flow cell. This system exhibited a linear range (LR) 10–200 ng mL^{-1} iron(III) with a modest detection limit of 10 ng mL^{-1} in solution and 3 ng mL^{-1} in immobilized form. The sensor was successfully applied to evaluate iron concentrations in tap and mineral waters. The biosensor possessed good stability and could be used over a period for at least 3 months or equivalent to about 1000 determinations. However, a significant difference was not shown between this siderophore-based monitoring with the inductively coupled plasma atomic emission spectroscopy (ICPAES) reference method (Barrero et al. 1993). In another study conducted by the same group, they developed a new strategy for the determination of trace amounts of iron(III). To implement this system, they entrapped PVD in sol–gel glass and used as a reactive solid phase. In comparison to CPG, the PVD was more stable in sol–gel glass and leaching or bleaching of the trapped reagent was not observed. Iron(III) was determined by two sampling systems, continuous flow and flow injection (FI) methods. Both methods provided a fast response with the limit of detections (LOD) of 3 ng ml^{-1} and 20 ng ml^{-1} for the continuous and FI (sample injection 1 ml) systems, respectively. The selective sensor successfully determined iron in tap waters (continuous system) and human serum (FI system) (Barrero et al. 1995). The response of PVD immobilized on a sol-gel thin film is faster to analytes owing to a much faster rate of diffusion (Gupta and Chaudhury 2007). Furthermore, it was demonstrated that no significant loss of fluorescence signal were observed in siderophore encapsulation in sol–gel matrices (Sharma and Gohil 2010).

Another pyoverdine-based biosensor in which PVD was immobilized on CPG, was described by Pulido-Tofino et al. (2000). The developed method allowed the determination of Fe(III) in the 3–200 g l^{-1} range in synthetic, tap and well waters and wines. Kadam et al. (2012) designed an optical fluorescence quenching biosensor based on pyoverdine–CPG composites for iron detection. In this platform, pyoverdine secreted by *Pseudomonas monteilii* was immobilized on amino alkylated CPG and cross linked with glutaraldehyde (2.5%, 28°C, 30 min). The immobilization complex was confirmed using fluorescence microscopic images (excitation range, 465–495 nm) for bright green fluorescence and by FTIR spectrum showing peak at 3406.4 cm^{-1} corresponding to stretching of amine group. Changes in fluorescence intensity on spectrofluorimeter was used for quantitative rating of biosensing activity at concentrations 0-100 μg mL^{-1} of ferric iron ($FeCl_3$, $7H_2O$) (Kadam et al. 2012).

Gupta et al. investigated crude culture broth supernatant of *P. fluorescens* as biosensors for online detection of ionic forms of iron. They also tested the effects of pH, buffers, different ferric salts and possible interference by ferrous ions under different solution conditions. The result of this investigation demonstrated that this structure is very specific to ferric ions and can sense Fe(III) ≥10 μM in solutions. The presence of Fe^{2+}, different pH or different buffer conditions did not affect the specificity of biosensor for Fe^{3+}. This study demonstrated that the siderophore-based optical biosensor was cheap, user-friendly, and simple as it relied only on using a spectrophotometer (Gupta et al. 2008). However, this whole culture broth assay is not suitable and reliable method, possibly due to lower signal to noise ratio and existence of multiple siderophores which secreted by *Pseudomonas* spp. into cultures medium. It is well established fact that purified siderophores are better for accurate detection.

On the basis of immobilization of pyoverdine in sol-gel glass, a biosensor was developed for specific detection of Fe(III). In this study, the most specific and linear response for pyoverdine binding to Fe(II and III) was assayed in three formulations of porous sol-gel glass (A, B and C). The formulations, A, B, and C, varied in the amount of water added, resulting in respective R values (molar ratio of water:silicon) of 5.6, 8.2, and 10.8, respectively. Pyoverdine-doped sol-gel pellets were placed in a flow cell in a fluorometer and the fluorescence quenching was measured as pellets were exposed to 0.28-0.56 mM iron (II or III). After 10 minutes, a greater quenching (65-88% of the initial fluorescence) was observed for ferric ion compared with a small fluorescence quenching (89-97%) of ferrous ion. The most specific and linear response was observed for pyoverdine immobilized in sol-gel C (Yoder and Kisaalita 2011). Either encapsulation or immobilization of pyoverdine in large-pore micelle-templated silica (MTS) have also been employed for the fabrication of the optical detection of Fe(III) and other metal ions in solution based on the fluorescence properties of pyoverdine (Mureseanu et al. 2003; Panadda et al. 2009; Renard et al. 2005).

Azotobactin (Az) is a pyoverdine-type siderophore produced under iron limiting conditions by the nitrogen-fixing soil bacteria *Azotobacter vinelandii* (Kraepiel et al. 2009; Yoneyama et al. 2011). Similar to pyoverdine, it is structurally made of a derivative of dihydroxyquinoline fluorescent chromophore, bound *via* a carboxylic acid group to the N terminal of an oligopeptide of ten amino acids producing a yellow-green fluorescence. Quenching of this fluorescence as a result of Fe(III) complexation is taken as the analytical potential considered as Fe(III) biosensors. In this aspect, Sharma and Gohil used azotobactin as an optical biosensor for the detection of concentration of 0.1 to 2.0 mmol L^{-1} Fe(III) in biological fluids, particularly in human serum by a modified design based on the encapsulation of Az in sol-gel matrix. The lowest estimated value of Fe was 0.14±0.018 μmol L^{-1} (Sharma and Gohil 2010). In another study, a fluorescence method employing azotobactin as an

Fe(III) reporter was subsequently devised for quantifying nontransferrin-bound iron (NTBI or NTB-Fe) in the serum of thalassemia patients which could measure NTBI levels in a range from 0.07 to 3.24 μM (Sharma et al. 2009). Overload of transfusional iron associated with some diseases including thalassemia, sickle cell anemia, aplastic anemia, and myelodysplastic syndromes could lead to the appearance of excess iron in the serum known as NTBI (Ganz and Nemeth 2015; Marsella and Borgna-Pignatti 2014). NTBI is toxic because generates free radical and causes morbidity and mortality *via* tissue damage (Brissot et al. 2012).

Palanche et al. (1999), for the first time, suggested the application of fluorescent siderophores as chemical sensors for the detection of trace levels of iron(III). In this study, the iron detection potential of azotobactin δ as natural siderophore was compared with three fluorescent synthetic derivatives of desferrioxamine B (DFB) (NBD-, MA-, NCP-desferrioxamine B) and one anthryl-desferrichrome biomimetic analogue. Desferrioxamines and desferrichromes are tris-hydroxamate siderophores (Butler and Theisen 2010). Desferrioxamine is a well-known linear siderophore comprised of three functional hydroxamic acids. DFB is an FDA-approved iron chelator for the treatment of iron overload diseases (Saha et al. 2015) and is produced by *Streptomyces* especially *Streptomyces pilosus* and marine *Actinomycetes* (Codd et al. 2018). Desferrichrome is a cyclic hexapeptide composed of three glycine and three hydroxylated and acetylated ornithine residues, excreted by diverse fungi of the genera *Aspergillus, Ustilago* (*U. sphaerogena*) and *Penicillium* (Butler and Theisen 2010). The semisynthetic DFBs possess new properties and broad range of functions and become of interest in recent approaches (Codd et al. 2018). In this report, azotobactin δ was the most talented chemosensor of ferric traces in water, more sensitive than the NBD-DFB. Under more lipophilic conditions, the anthryl-desferrichrome analogue showed more sensitivity than the lipophilic MA-DFB and NCP-DFB. The calculated detection limits for azotobactin δ (in water) and the artificial chelator (lipophilic conditions) were 0.5 ng ml^{-1} and 0.6 ng mL^{-1}, respectively. Using this method, they detected 0-95 ng mL^{-1} of Fe(III) by azotobactin δ and 0-180 ng mL^{-1} of Fe(III) with desferrichrome analogue. The interaction of other cations revealed that only Cu(II) and Al(III) interfere with the iron analysis when present at similar concentrations (Palanché et al. 1999).

A novel optical chemosensor for ultrasensitive detection of Fe^{3+} in aquatic systems was reported by Orcutt et al. (2010) based on an indicator displacement assay (IDA) and combination of time-resolved fluorescence (TRF) and fluorescent resonance energy transfer (FRET) (Fig. 2A). IDAs are now a common technique for converting most of synthetic receptors into an optical sensor (Nguyen and Anslyn 2006). Iron is one of the most important elements for oceanic primary productivity and accumulations of microbial community. In this approach, a fluorescent siderophore, *N*-methyanthranyl desferrioxamine B (MA-DFB) as sensitizer (antenna) and lanthanide (Ln) ion as indicator were used. Because Ln ions absorb light poorly, the absorbed light by the sensitizer molecule would be transfered as energy to the Ln ion generating luminescence. In the presence of Fe, Fe(III) coordination by siderophore led to lanthanide displacement from the siderophore and subsequent loss of lanthanide luminescence allowed for the detection. Using this strategy, they detected Fe^{3+} ion concentrations as low as 5 nM (Orcutt et al. 2010). Despite the widespread use of FRET-based reporters, unfortunately, FRET approaches are associated with numerous restrictions. The low signal-to-noise ratio (SNR) (Leavesley and Rich 2016) and close physical proximity between donor and acceptor probes are the largest limitations of FRET models (Taghdisi et al. 2014; Zadran et al. 2012). Moreover, many fluorescent proteins are sensitive to changes in pH, ionic concentrations, oxidation, temperature, and refractive index (Leavesley and Rich 2016). The combination of IDA and lanthanide resonance energy transfer (LRET) as a powerful technology offers many technical benefits

including greater accuracy in farther measurable distances, insensitivity to incomplete labeling, and the ability to use generic relatively large labels (Selvin 2002).

Nanometer-scale engineered liposomes offer an influential platform for developing chemical sensors of trace metals in marine systems. A nano-scale liposome-based device was designed to sequester iron from Fe(III)-DFB complexes to estimate the level of Fe that is biologically available to phytoplankton. Liposomes were fabricated by a bilayer membrane incorporating polymerizable diacetylene lipid covering an aqueous and low pH core. A carrier molecule, lasalocid, was placed on the bilayer membrane for the specific Fe-DFB transport. Iron uptake was measured when the lasalocid was incorporated into the liposome membranes. This procedure can only assess the amount of transported Fe into nano-liposome which is associated with the interactions between Fe and carrier molecule and it does not represent the actual amount of iron in the samples and are remained as important challenge for this work (Orcutt and Wells 2007).

Su et al. designed fluorescent siderophore-based nanobiosensor for Fe(III) ion determination using fluorescein-desferrioxamine (Fl-DFO) conjugate. Combination of fluorescein molecules with DFO component produced a photo-induced electron transfer (PET) phenomenon because of the close proximity of fluorescein fluorophore (the acceptor) and the DFO (the donor). According to the PET mechanism, the fluorescence of a fluorophore is quenched by electron transfer from the donor to the acceptor. In the absence of Fe ions, a high fluorescence emission is produced by fluorescein molecules. The binding of DFO receptor unit to Fe(III) ions, caused the quenching of fluorescein molecules. This work clearly identified that among two different Fl-DFO isomers (Isomers 5 and 6, defined by the attachment of DFO at the 5- or 6-position of the benzene ring of Fl), only 5-FlDFO was able to undergo a quenching of emitted light after Fe complexation. During successive Fe ion complexation, the fluorescence of 5-FlDFO decreased proportional to the ion concentration. No significant effect on fluorescence emission of Fl-DFO was observed in present of Ca^{2+}, Ni^{2+}, and Al^{3+} ions in the solution, although they all formed complex with DFO. This fluoroionophore nanosensor molecule detected a very low concentration of Fe ion down to 2.16×10^{-2} μM (Su et al. 2010).

In another study, the concentration of bioavailable Fe in ocean has been quantified by using a siderophore parabactin. The purified parabactin, secreted from *Paracoccus denitrificans*, was encapsulated within a spin-coated sol-gel thin film onto a quartz substrate, which was subsequently incorporated in a flow cell system. The LOD of the fabricated biosensor was 40 pM without any interference from cations and anions present in oceanic waters (Chung Chun Lam et al. 2006).

A new synthetic fluorescent siderophore named as probe 3, has been developed for the detection of Fe(III) in water samples. The probe was consisted of two Schiff base receptors connected to a mesitylene platform. The recognition was based on the quenching of the fluorescent intensity of receptor upon addition of Fe ions. The dipodal sensor displayed good selectivity for Fe(III) compared with other metal ions, in HEPES buffered solution at pH 7.0 (Singh et al. 2009). Recently, a siderophore-inspired nanoparticle-based colorimetric nano-biosensor was established for the selective detection of Fe(III) (Fig. 2B). In this study, AuNPs are functionalized with phenyl or catechol moiety at the a-chain-end. In the presence of Fe(III) in sample, the catechol group bind Fe^{3+} and formed catechol-Fe^{3+} complexes. Assembly of AuNPs led to the hybridization process which rise to a purple color that was colorimetrically detected (Robati et al. 2016). On the contrary, for the unbound Fe^{2+}, a red color of separated AuNPs was observed. Therefore, a strong red-to-purple colorimetric response occurred in the presence of Fe^{3+} at serum concentrations ranging from 8 to 25 mM in saline solution (Phillips et al. 2015).

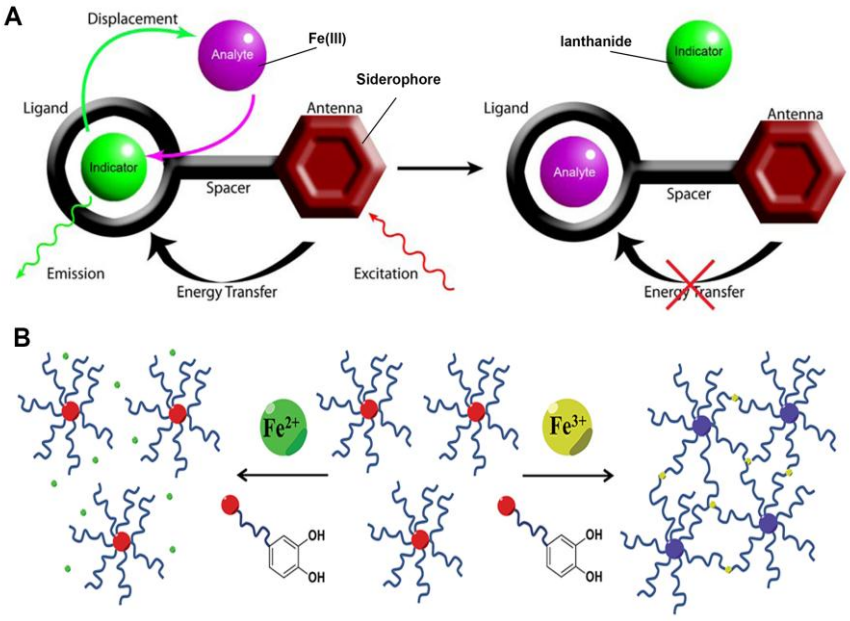

Fig. 2 (A) A FRET-based optical chemosensor for ultrasensitive detection of Fe^{3+} based on the indicator displace assay. Reprinted with permission from (Orcutt et al. 2010); (B) A siderophore-inspired nanoparticle-based colorimetric nano-biosensor for the selective detection of Fe(III). Reproduced from (Phillips et al. 2015) with permission from the Royal Society of Chemistry.

Acquired results of siderophores-based biosensors and nanosensors for iron detection at the ng mL^{-1} or pM level are well competitive with other methods previously described. UV-visible spectrophotometry, colorimetry and AAS as common analytical methods that are mostly used for iron determination allow detecting of iron at the range of µg to ng mL^{-1} levels (Lunvongsa et al. 2006; Riemer et al. 2004). However, ICP-MS/MS as a highly sensitive method shows ng mL^{-1} detection limit for iron (Jackson et al. 2018). Moreover, the Rhodamine-based sensors senses µM to nM levels of Fe(III) in aqueous solution (Ding et al. 2013; Kamal et al. 2014). In comparison with traditional methods, recent method does not require a pre-concentration step and can measure Fe(III) in the nanomolar and subnanomolar concentration range without any interference from cations and anions present in the sample. In addition, the siderophore-based biosensing platforms that are low-cost and suitable to handle are considered for metal ions detection owing to the rapid response rates and high sensitivity and selectivity, which allow the detection of low concentrations of metal.

2.2. Detection of other metal ions

Bacterial siderophores are able to bind metals other than iron and thus enhance their bioavailability in the rhizosphere of plants (Rajkumar et al. 2010). To date, different kinds of siderophore-based biosensing methods have been used effectively for the monitoring of other metal ions. For example, Jedner et al. (2003) fabricated a siderophore-based luminescent sensor for molybdate (Mo) detection. In this platform, a synthetic derivative, aminochelin, as the receptor unit was combined with a luminescent tris(2,2′-bipyridyl)ruthenium(II) $[Ru(bpy)3]^{2+}$ unit which provided an electron transfer quenching mechanism. When Mo(VI) was added to the system, the fluorescence intensity ratio changed. Aminochelin is a catecholamine siderophore, produced by *A. vinelandii* (Khodr et al. 2002).

A simple and sensitive fluorescent pyoverdine-based biosensor was developed for the selective detection of copper ion (Cu^{2+}). Detection of copper ion is very important because environmental copper pollution seriously threatens the health of organisms and the safety of ecosystem. In this study,

the fluorescence of pyoverdine was quenched significantly after binding to Cu^{2+} (Fig. 3A). The established biosensor was a reliable method to detect copper ion with linearity within the range of 0.2–10 μM and the LOD of 50 nM and 1 μM. Cu^{2+} could be distinguished directly by naked eyes under UV light. The biosensor had been successfully employed for the detection of copper ion in drinking water, seawater and biological samples without any interference with the quenching efficiency of copper ion by the coexisting common cations and anions. Therefore, this platform can be considered as a powerful tool to monitor copper pollution in the environment (Yin et al. 2016).

Aluminum contamination is largely associated with bauxite mining and food-additives/food packaging borne. Raised-up levels of Al^{3+} alters the physiology of cells thus leading to several human disorders such as dementia, anemia, and bone diseases (Krewski et al. 2007). Therefore, the design of Al(III)-selective receptors is vital for monitoring the Al^{3+} levels. In this respect, Raju et al. (2017b) fabricated a novel nanobiosensor relied on siderophore-coated magnetic iron nanoparticles (Fe_3O_4-NPs) for practical applications and *in vivo* imaging of Al^{3+} in live organism (Fig. 3B) (Raju et al. 2017b). A catechol-derived siderophore, 2,3-dihydroxybenzoylglycine (H_3L), produced by the gram-positive bacterium *Bacillus subtilis* NRRL B-1471 was conjugated to the surfaces of bare FeNPs (HL-FeNPs complexes). In the presence of aqueous solution of Al^{3+}, a strong emission from the solution mixture was observed. The LOD of biosensor HL-FeNPs was 20 nM. *In vivo* bio-imaging in live brine shrimp Artemia confirmed that HL-FeNPs could be used as fluorescent biomarker for Al(III) in live whole organisms. In comparison with previous sensors, this is the first report on the surface functionalization of iron nanoparticles by siderophore. This strategy resulted in easy removal of excess Al^{3+} in aqueous solution *via* external magnet. Moreover, the low solubility in water is one of the posing serious limitations of earlier chemosensor probes for the practical detection of Al(III) while lots of siderophores and nanoparticle-based probes are completely soluble in water and are not challenged by the solubility problem.

In another study conducted by the same group, they revealed imaging of Zn^{2+} in Artemia as a living whole organism, by aeruginic acid (H_2L) as a natural intermediate fluorimetric siderophore with 49 nM limit of detection (Raju et al. 2017a). Simultaneous detection of Cu^{2+} and Zn^{2+} in environmental water samples was accomplished by integrating Rhodamine 6G hydrazide (Rg_6NHNH_2) with H_2L, named as HL2 (Raju et al. 2018a). In recent study, two different optical techniques including 1) colorimetric change due to the complexation between HL2 and Cu^{2+} and 2) fluorimetric change of the "pre-treated HL2 solution" and subsequent binding with Zn^{2+} were employed (Fig. 3C). The maximum measurable concentration of Cu^{2+} and Zn^{2+} in Cu^{2+}-Zn^{2+} mixture was 120 μM and 100 μM, respectively, whereas in the case of Cu^{2+} alone in solution, the maximum measurable concentration was 37 nM.

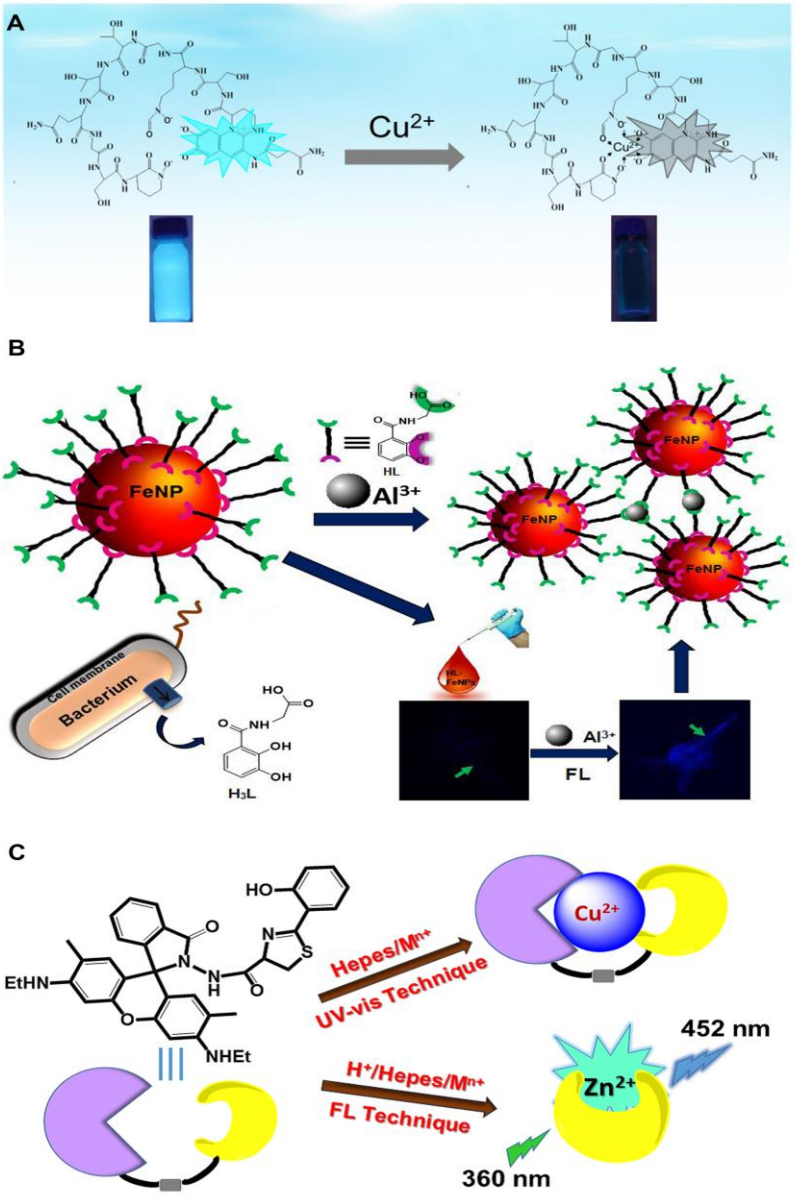

Fig. 3 (A) The detection of copper ion by an optical fluorescence pyoverdine quenching biosensor; (B) *In vivo* imaging of Al^{3+} in live organism by a nanobiosensor based on siderophore-coated Fe_3O_4-NPs; (C) Simultaneous detection of Cu^{2+} and Zn^{2+} in environmental water samples based on colorimetric and fluorimetric change. Reprinted with permission from (Yin et al. 2016), (Raju et al. 2017b) and (Raju et al. 2018a).

In another study, a new model for online biosensing of metal toxicity in environment based on PVD obtained from *P. fluorescens* was introduced (Chiadò et al. 2013). It was found that PVD production was influenced by the concentration of Fe^{3+}, Cu^{2+} and Zn^{2+} ions. The concept of critical metal concentrations for pyoverdine (CMCP) could be useful for constructing a biosensor that would be able to detect toxic metals in the environment. As a suggestion, free metal ion content can also be assessed by the use of potentiometric and amperometric electrodes and siderophore. This method is based on the release of proton (H^+) when the metal ion detached from the samples by the siderophore. The release of protons results in a measurable change of pH (potential).

Siderophore-based sensors for metal ions detection have great advantages; modified platforms commonly suffer from some limitations. The experimental parameters such as variety and concentration of buffer solution, pH and incubation time affect the platform outcomes. Various

detection limits for siderophore-based biosensors were observed in HEPES and PBS buffer solutions (Yin et al. 2016). Neubauer et al. (2000) showed that the specificity of desferrioxamine B to Co(III) is better than Fe(III) at high pH conditions. Previous research discovered that the fluorescence of pyoverdine could also be quenched by dissociative ferric ion under acidic condition (Barrero et al. 1995; Yoder and Kisaalita 2011). Moreover, some differences have been observed between different types of systems arising from a difference in the initial ligand concentration. In order to achieve reliable results and precise evaluations, experimental and concentration parameters should be adjusted.

The quenching efficiency of target ion can be influenced by the coexisting ions in samples. It should be noted that when siderophore-based sensors are used for the detection of targets in complex samples, the interaction of other metal ions should be considered addressed. The improvement of the specific binding of the siderophores to a particular metal ion can address this issue. For example, specific chelators with high binding constant to iron ions such as enterobactin (binding constant (K_a) of 10^{32} M^{-1}), desferrioxamine (K_a of 10^{32} M^{-1}) and rhodotorulic acid (K_a of 10^{31} M^{-1}) are considered to detect iron in multiplex samples.

Table 1: Comparison of analytical performance (linearity range and limit of detection) of siderophore-based metal ions detection systems.

Detection Strategy	**Type of metal ion**	**Type of siderophore**	**LOD**	**Linear range**	**References**
Immobilization of pyoverdine (PVD) on controlled pore glass (CPG) and packing into a flow cell	Fe (III)	Pyoverdine	10 ng mL^{-1} in solution 3 ng mL^{-1} in immobilized form	10–200 ng mL^{-1}	(Barrero et al. 1993)
Entrapping PVD in sol–gel glass , continuous flow and flow injection (FI) methods	Fe (III)	Pyoverdine	LODs 3 ng ml^{-1} and 20 ng ml^{-1} for the continuous flow and FI system	Not reported	(Barrero et al. 1995)
Immobilization of PVD on CPG	Fe (III)	Pyoverdine	Not reported	3–200 g l^{-1}	(Pulido-Tofiño et al. 2000)
An optical fluorescence quenching biosensor based on PVD–CPG composites	Fe (III)	Pyoverdine	Not reported	0-100 μg mL^{-1}	(Kadam et al. 2012)
Whole culture broth assay of *P. fluorescens* for online detection of ionic forms of iron	Fe (III)	Pyoverdine	≥10 μM in solutions	Not reported	(Gupta et al. 2008)
Immobilization of PVD in sol-gel glass and measuring the fluorescence quenching	Fe (II and III)	Pyoverdine	Not reported	0.28 - 0.56 mM	(Yoder and Kisaalita 2011)
The encapsulation of Az in sol-gel matrix	Fe (III)	Azotobactin (Az)	Not reported	0.1 to 2.0 mmol/L	(Sharma and Gohil 2010)
A fluorescence method employing azotobactin as an Fe(III) reporter for quantifying nontransferrin-bound iron in the serum	Fe (III)	Azotobactin	Not reported	0.07 to 3.24 μM	(Sharma et al. 2009)
A chemical sensors based on fluorescent siderophores for detection of trace levels of iron (III)	Fe (III)	- Azotobactin δ - Synthetic desferrioxamine B - Desferrichrome analogue	- 0.5 ng ml^{-1} for azotobactin δ - 0.6 ng mL^{-1} for desferrichrome analogue	0-95 ng mL^{-1} for azotobactin δ 0-180 ng mL^{-1} for desferrichrome analogue	(Palanché et al. 1999)
FRET-based optical chemosensor based on an indicator displacement assay	Fe (III)	*N*-Methyanthranyl desferrioxamine	as low as 5 nM	Not reported	(Orcutt et al. 2010)
A nano-scale liposome-based chemical sensors	Fe (III)	Desferrioxamine B	Not reported	0.1–1.0 nM	(Orcutt and Wells 2007)
A nanobiosensor based on photoinduced electron transfer (PET) phenomenon between fluorescein-desferrioxamine	Fe (III)	Desferrioxamine	2.16×10^{-2} μM	Not reported	(Su et al. 2010)
Encapsulation of siderophore within a spin-coated sol-gel thin film onto a quartz substrate, and incorporation in a flow cell system	Fe (III)	Parabactin	40 pM	Not reported	(Chung Chun Lam et al. 2006)
A dipodal sensor based on the quenching of the fluorescent intensity of receptor upon addition of Fe ions.	Fe(III)	A synthetic fluorescent siderophore named as probe 3	Not reported	Not reported	(Singh et al. 2009)
A siderophore-inspired nanoparticle-based colorimetric nano-biosensors	Fe (II and III)	Phenyl or catechol moiety	Not reported	8–25 mM	(Phillips et al. 2015)

A siderophore-based luminescent sensor	Molybdate	A synthetic derivate aminochelin	Not reported	Not reported	(Jedner et al. 2003)
A optical biosensor based on quenching of fluorescent PVD by copper ions	Cu^{2+}	Pyoverdine	50 nM 1 μM by naked eyes under UV light	0.2–10 μM	(Yin et al. 2016)
A nanobiosensor relied on siderophore coated magnetic iron nanoparticles	Al^{3+}	2,3-dihydroxybenzoylglycine (H_3L)	20 nM	Not reported	(Raju et al. 2017b)
A nanobiosensor based on siderophore coated Fe_3O_4-NPs	Al^{3+}	Natural intermediate fluorimetric siderophore, aeruginic acid (H_2L)	49 nM	Not reported	(Raju et al. 2017a)
Integrating Rhodamine 6G hydrazide (Rg_6NHNH_2) with H_2L	Cu^{2+} and Zn^{2+}	Aeruginic acid (H_2L)	37 nM for Cu^{2+} 120 μM and 100 μM for Cu^{2+} and Zn^{2+} in mixture, respectively	Not reported	(Raju et al. 2018a)
A new model for online biosensing monitoring of metal toxicity in environment based on PVD	Fe^{3+}, Cu^{2+} and Zn^{2+}	Pyoverdine	Not reported	Not reported	(Chiadò et al. 2013)

3. Approaches for pathogen detection

Siderophore is a potential biomarker for pathogen diagnosis. Recently, several strategies have been reported for the detection of microbial pathogens using siderophores. These approaches rely on both siderophore immobilization and high-affinity characteristics of siderophores to bacterial cell-surface receptors, which recognize the siderophores and facilitate the uptake of Fe. The prominent siderophore receptors which are characterized structurally and biochemically include FepA (enterobactin receptor) (Majumdar et al. 2016) and FhuA (ferrichrome receptor) of *E. coli* (Brandel et al. 2012), and FpvA (pyoverdine receptor) of *P. aeruginosa* [107, 108]. These receptors exhibit specificity for one or several siderophores and bind siderophore molecules with a dissociation constant in the nanomolar range. Specificity and high-affinity binding capacity of the siderophore receptors have become increasingly worthwhile for developing species-specific bacterial identification and capture equipments. Moreover, targeting of siderophore receptors is important for pathogen detection, because the proliferation and virulence of the host in the iron-limited environment associated with expression of functional siderophore uptake pumps. The mutations in these receptors in pathogens prevent siderophore binding.

A proof-of-concept example of siderophore-based pathogen detection introduced by Doorneweerd et al. based on polydimethylsiloxane (PDMS) stamping and immobilization of pyoverdine onto gold-plated glass chips for the capture of the human pathogen *P. aeruginosa* (Fig. 4A) (Doorneweerd et al. 2010). FpvA is an outer membrane protein of *P. aeruginosa* that binds its iron-bounding ligand (pyoverdine) (Cornelis 2010; Voulhoux et al. 2006). In this study, the reaction mixture of pyoverdine-gallium chelate was conjugated to bovine serum albumin (BSA) using carbodiimide chemistry. Subsequently, pyoverdine-BSA was applied onto a PDMS stamp with a pattern of repeating parallel ridges and the pattern of pyoverdine-BSA was pressed onto a gold-plated glass chips. In the first set of experiments, the chips were treated with solutions of DiO-labeled *P. aeruginosa* and the resulting emission pattern was visualized using fluorescence microscopy. DiO, 3,30-dioctadecyloxacarbocyanine perchlorate, is a commercially-available fluorescent dye that binds to cell membranes (Koichi et al. 2009). These experiments revealed a parallel pattern of DiO emission corresponding to the pyoverdine-functionalized regions of the chip. This pattern indicated that *P. aeruginosa* bind to the chip only where pyoverdine was attached. Because pre-loading of bacterial sample with a fluorophore is impractical for achieving rapid pathogen detection in real-world samples, the DiO-labeling step was ultimately circumvented by using light scattering, followed by Fourier transform analysis, to visualize the siderophore captured bacteria. Using this technique, 10^4 cells mL^{-1} were routinely detected. In some instances, *P. aeruginosa* from cultures at 10^2 cells mL^{-1}

was observed. Because only 15 minutes is required for maximum *P. aeruginosa* binding, make this method significantly more quick compared to traditional techniques such as polymerase chain reaction (PCR) for pathogen detection.

Following this report, the siderophore-modified chip methodology was extended to the detection of *Yersinia enterocolitica* (Kim et al. 2012). *Y. enterocolitica* is a Gram-negative pathogen causing gastroenteritis in human. It employs its xenosiderophore DFO for getting hold of iron. Ferrioxamine uptake is mediated by the receptor FoxA (Johnstone and Nolan 2015). A treated PDMS stamp with ferrioxamine-BSA conjugate was used as pattern for gold-plated glass surface. Subsequently, the chips were incubated with 10^8 CFU/mL of *Y. enterocolitica*, which were cultured under iron-deficient conditions, and analysis of the chips revealed a light-scattering pattern attributed to pathogen capture. This pattern was not observed for chips treated with unmodified BSA or when the cultures of *Y. enterocolitica* were pretreated with desferrioxamine to saturate FoxA. LIVE/DEAD staining indicated that 49.5% of chip-bound bacteria were alive, and incubation of the chips with dead *Y. enterocolitica* led to no patterning. As observed for the pyoverdine-modified chips, signal saturation was observed following a *ca.* 15-minute incubation (10^8 cells mL^{-1}). Optimized chips, bearing a 20–30% weight ratio of siderophore/BSA, afforded a detection limit of 10^3 CFU mL^{-1} observable by the naked eyes. The capture capacity of chips for *Yersinia* retained after one year of storage. Moreover, selectivity assays of the chips for other ferrioxamine-utilizing microbes, such as *Staphylococcus aureus*, *Mycobacterium smegmatis*, *P. aeruginosa*, and *Vibrio cholerae* revealed that only *V. cholera* was bound to the chips. Until now, a multiplex testing of chip performance with diverse sample species was not reported. Nevertheless, these results point to a need for multiplexing and incorporating orthogonal siderophores on a given chip for rapid species-specific identification in mixed bacterial samples.

The facilitated adjustment in biocompatibility, sizes, charges, stability, surface coating and core/shell structure of quantum dots (QDs) make them suitable NPs for biosensing methods (Jin et al. 2011). In a study, siderophore-modified CdSe/ZnS QDs were employed to capture *P. fluorescens* (Wu et al. 2009). *P. fluorescens* is typically soil- and water-borne microorganism, and rarely causes disease in humans with compromised immune systems (Madi et al. 2010). *P. fluorescens* expresses specific receptors FpvA, FptA and FhuA for siderophores PVD and pyochelin (Pch) and ferrichrome, respectively (Brandel et al. 2012). In this study, QDs were coated with polyethylene glycol-phosphoethanolamine (PEG-PE-QD), and then coupled with ferrichrome *via* carbodiimide coupling chemistry (reaction between amine groups of PEG-PE and a carboxyl group of ferrichrome). Incubation of the ferrichrome-QDs with cultures of *P. fluorescens* resulted in interactions between ferrichrome-ferric complex and its receptors on the bacterial outer membrane that make the bacterial cluster (Fig. 4B). The formation of clusters caused absorbance changes which were then detected by fluorescence microscopy and UV-visible spectroscopy. The clustering phenomenon was not observed when the ferrichrome-QDs were incubated with *B. subtilis* or with *P. fluorescens* cultures that were pre-incubated with ferrichrome. Toxicity, intrinsic blinking and chemical instability and low fluorescence are some restriction of QDs applications (Jin et al. 2011).

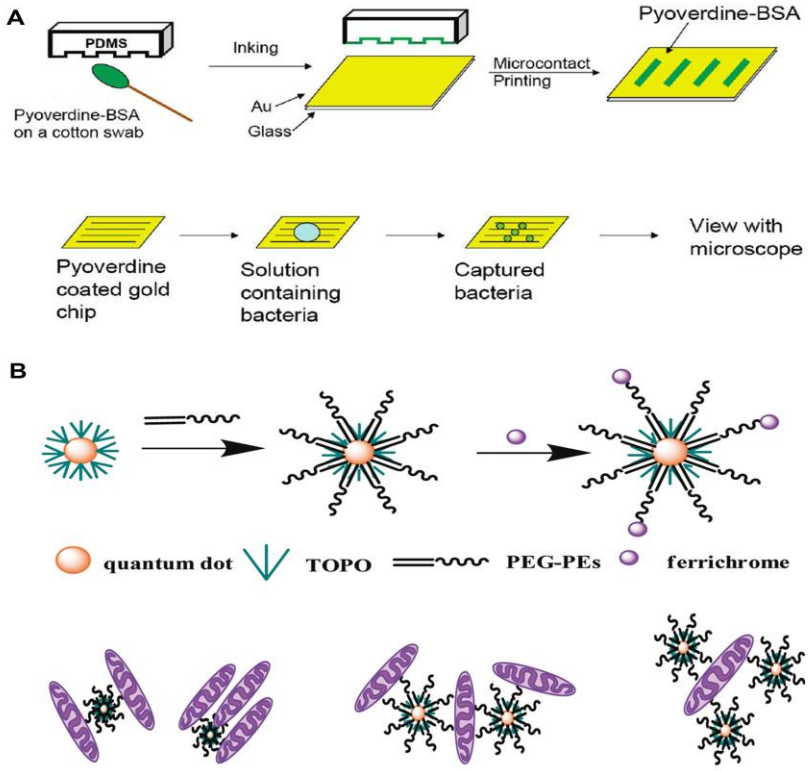

Fig. 4 (A) Detection of *P. aeruginosa* using pyoverdine-immobilization on gold-plated glass chips based on PDMS stamping; (B) Recognition of *P. fluorescens* with QD-ferrichrome bioprobes. Reprinted with permission from (Doorneweerd et al. 2010); Copyright (2010) American Chemical Society, and (Wu et al. 2009); Copyright (2009) American Chemical Society.

Approaches employed for the discovery of siderophore-binding proteins in cell extracts of pathogens can be considered as a basis for designing of biosensors for the pathogens detection. Petrobactin is a bis-catecholate, α-hydroxy acid siderophore that most notably is produced by the human pathogens, *B. subtilis*, *B. cereus* and *Bacillus anthracis* (Bachman et al. 2011) and also was isolated from marine bacteria (Himpsl et al. 2010). In this respect, a biotinylated derivative of petrobactin-Fe(III) complex was incubated with streptavidin-agarose beads, which were used to prepare a petrobactin-affinity column (Fig. 5A) (Bugdahn et al. 2010). First, the column was pre-treated with BSA to reduce non-specific binding, afterward *B. subtilis* cell lysates were loaded into the column and eluted with guanidinium chloride solution. SDS-PAGE analysis of eluted fractions revealed that only one protein was repeatedly retained on the column which identified as YclQ, an ABC transporter binding protein, by trypsin digest and mass spectrometry methods. YclQ is a petrobactin-binding protein in *B. subtilis* and binds selectively to both apo and ferric petrobactin (Zawadzka et al. 2009). This assay indicated that YclQ is the only petrobactin receptor expressed on the *B. subtilis* cell surface and can be applied for the detection of *B. subtilis* (Bugdahn et al. 2010).

According to this approach, incubation of bacterial samples with biotinylated siderophores and resin or magnetic streptavidin-bearing beads affords as a vehicle to separate the bound and unbound cells. Moreover, the biotin/streptavidin interaction may be employed in other immobilization strategies. Synthetic routes for other biotinylated siderophores, and biotin attachment strategies that do not compromise iron coordination or interaction with the target receptor, are required for this approach to become broadly applicable.

Inomata research group designed a set of siderophore-based piezoelectric biosensors for the detection of several microorganisms using AuNPs (Inomata et al. 2007; Inomata et al. 2014; Inomata et al. 2013). Piezoelectric biosensors are considered as mass measurement devices which rely on detecting the change of resonance frequency on a quartz crystal microbalance (QCM). The change in the oscillation frequency of the QCM device is proportional to any changes induced by mass binding to the electrode. The use of QCM allows for the detection of pathogens using probes modified with immobilized antibodies (Krewski et al. 2007). However, Inomata et al. introduced siderophores as new probes in QCM for the detection of different pathogens. In comparison with antibodies, they are less sensitive to temperature and denaturing conditions. Moreover, it is possible to synthesize them chemically in some cases.

In 2007, the hydroxamate-type artificial siderophore (TAPPA)-Fe(III) complex was immobilized on a deposited Au substrate by a stepwise self-assembling method. Fe(III)-TAPPA exhibits biological activity for the hydroxamate-type siderophore auxotrophic microorganism, *Microbacterium flavescens*, suggesting that Fe(III)-TAPPA can permeate the cell membrane of the microorganism. Modification of Fe(III)-TAPPA on the surface was confirmed from the cyclic voltammogram (CV) of the resultant Au electrode, Fe(III)-TAPPA/Au. The adsorption ability of *M. flavescens* on Fe(III)-TAPPA/Au was indicated by optical, scanning electron, and atomic force microscopy and QCM methods. This adsorption characteristic is due to the interaction between Fe(III)-TAPPA on an Au electrode and a receptor/binding protein within the cell membrane of *M. flavescens* (Inomata et al. 2007). In this study, the quantity measurement of *M. flavescens* adsorbed onto the FeIII-TAPPA/Au surface by means of the QCM measurement remained unclear. So, further experiments are needed to clarify the relationship between the frequency change of QCM and the total quantity of microorganism.

In another study with a similar manner, they demonstrated the detection of *E. coli* using an Au substrate modified with a catecholate-type artificial siderophore-Fe^{3+} complex (Inomata et al. 2013). Their hypothesis was based on the fact that *E. coli* secreted a catecholate-type siderophore known as enterobactin. Thus it is expected that the artificial catecholate siderophore-modified substrates would be adsorbed onto *E. coli* and provide a means for its detection. The detection limit of siderophore-Fe^{3+} complex/Au was $\sim 10^4$ CFU mL^{-1}. Lastly, the method set up relies on the combination of catecholate-type and hydroxamate-type artificial siderophore-modified AuNPs as a very powerful tool for multiplex microbes detection. These nanoparticles were found to selectively adsorb onto microbes and initiate selective aggregation. The aggregation of microbes *via* siderophore complex-modified AuNPs, led to large frequency changes when measured using siderophore complex-modified QCM sensors (Inomata et al. 2014). This modification caused a co-detection of *M. flavescens* and *E. coli*.

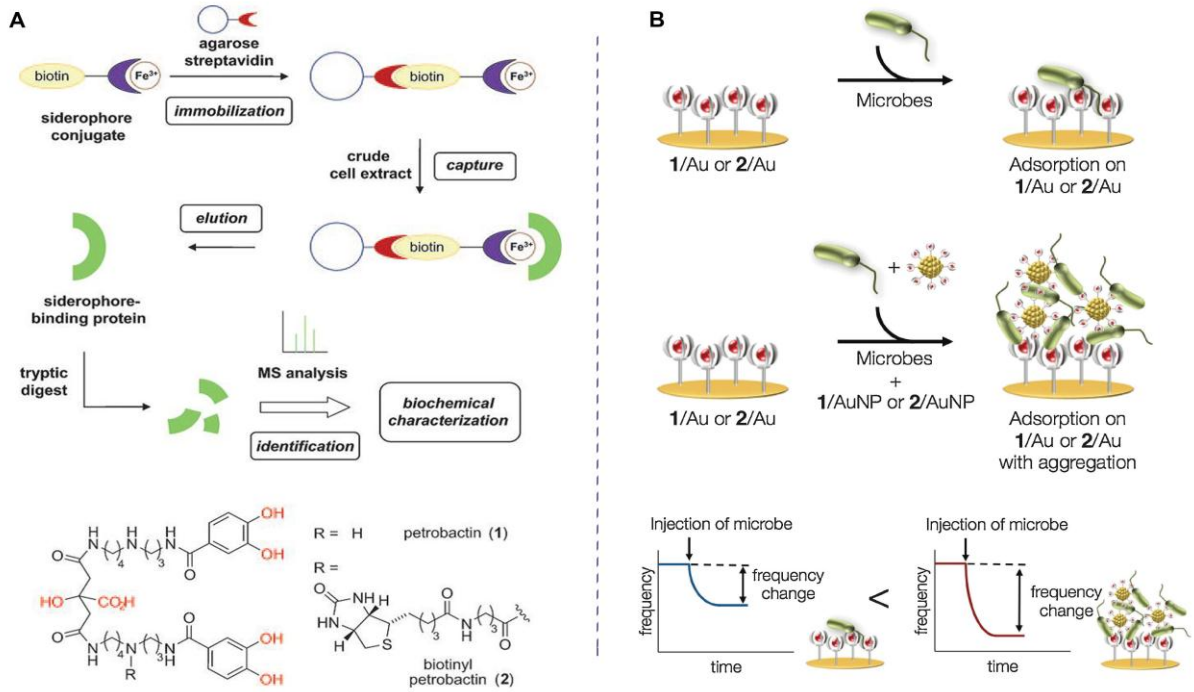

Fig. 5 (A) Isolation of siderophore-binding proteins YclQ in *B. subtilis* using biotin-siderophore conjugates as a basis for designing of biosensors for *B. subtilis* detection; reprinted with permission from (Bugdahn et al. 2010) (B) Artificial siderophore-based piezoelectric biosensors for the detection of microorganisms using Au substrate and AuNPs (1: hydroxamate type; 2: catecholate type) (Inomata et al. 2014).

Differentiation between viable and dead bacteria is a significant challenge in bacterial detection. The most common detection methods such as culture-colony counting, bacterial staining and PCR often cannot distinguish live from dead cells. This is important especially after decontamination and antibiotic therapy. However, the number of live bacteria are critically dependent upon iron uptake by siderophore. This is a highly conserved process that occurs only in intact bacteria. Wolfenden *et al.* designed a facile method based on desferrioxamine B siderophore to selectively and rapidly identify only viable bacteria in complex environments (Fig. 6A). DFB was bound to a glass slide and used to specifically capture viable bacteria from a mixture of viable and dead *E. coli*, as demonstrated by fluorescence microscopy (Wolfenden et al. 2012). The most important pitfall of this approach was the use of DFB which is a nonspecific siderophore of *E. coli* while by using of enterobactin, the major catecholate-type siderophore of *E. coli*, more accurate results would be obtainable.

The affinity of siderophores to specific receptor was exploited for developing efficient isolation and enrichment strategies for members of the *Pseudomonas* spp. (Fig. 6B). *via* Raman spectroscopy combined with pyoverdine as capture probe. In this platform, pyoverdine was immobilized covalently on planar aluminum chip substrates modified by (3-glycidyloxypropyl) trimethoxysilane (GOPS). After capturing, single cell Raman spectra of the isolated species were acquired. Due to the specific spectroscopic fingerprint of each species, the bacteria can be identified. This approach was a very rapid detection of *P. aeruginosa* and *P. fluorescens* from tap water samples, since it avoids the time-consuming culturing steps. By means of this system, concentrations as low as 5×10^3 CFU ml^{-1} can be readily detected within two hours. This pyoverdine-based Raman approach can be applied for the co-detection of opportunistic *Pseudomonas* (Pahlow et al. 2016).

Lastly, an assay was developed based on vibrioferrin siderophore-fluorophore conjugate (VF-FL) (Fig. 6C). Vibrioferrin is a unique member of the carboxylate siderophores commonly isolated from

marine *Vibrio* spp. which are closely associated with seafood-borne gastroenteritis (Amin et al. 2009). In this study, the probe selectively labeled *V. parahaemolyticus*, *V. cholerae*, and *V. vulnificus*, even in the presence of other species such as *S. aureus* and *E. coli*. These studies demonstrated that the siderophore-based platform provides a method to selectively target microbes expressing cognate receptors under iron-limited conditions (Chen et al. 2017).

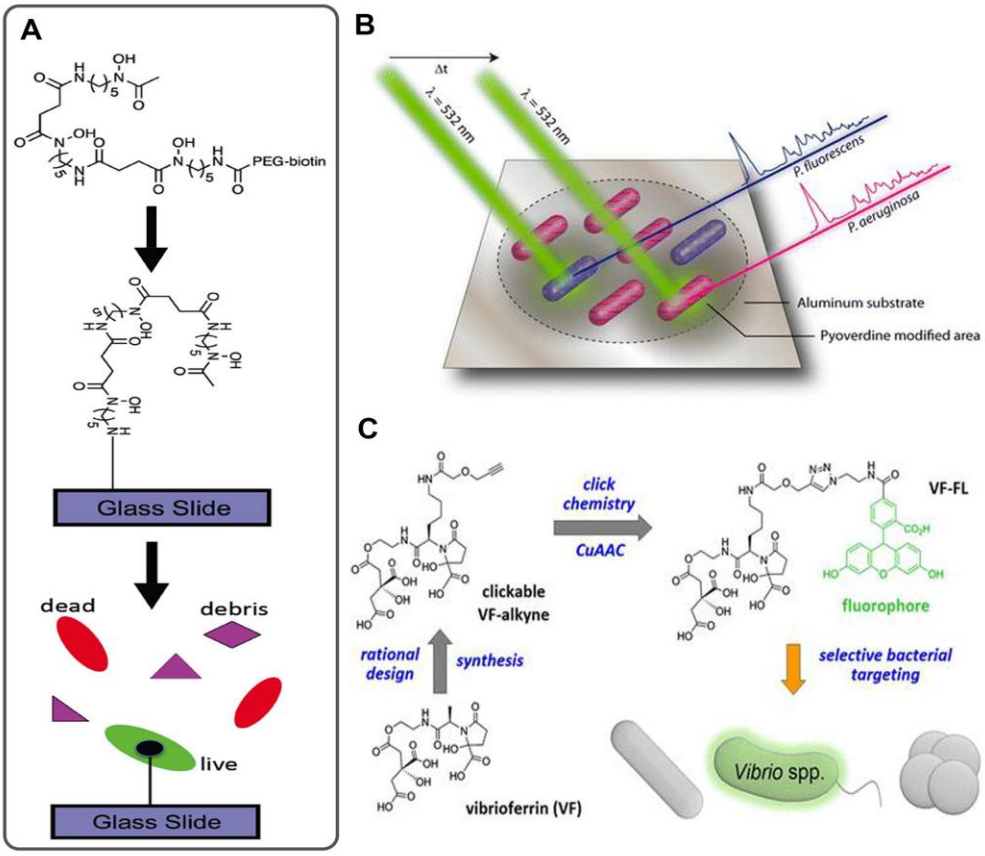

Fig. 6 (A) Determination of viable bacteria (*E. coli)* based on desferrioxamine B siderophore immobilized on glass slides (Wolfenden et al. 2012); (B) efficient isolation strategy for *Pseudomonas* spp using Raman spectroscopy combined with pyoverdine, reprinted with permission from (Pahlow et al. 2016); Copyright (2016) American Chemical Society (C) Siderophore-based platform for the detection of *Vibrio* spp. based on vibrioferrin siderophore-fluorophore conjugate (VF-FL), reprinted with permission from (Chen et al. 2017); Copyright (2017) American Chemical Society.

As mentioned above, the siderophores are considered as very promising capture probes for various microorganisms. Compared to antibody-based system, siderophores can be considered as "immutable ligands", since the probability for mutations within the siderophore uptake systems of bacteria is very low. In addition, it is possible to synthesize them chemically in some cases and they are less sensitive than proteins to different temperatures and denaturizing situations. Furthermore, a more interesting feature of siderophores is the possibility to selectively enrich viable bacterial cells.

Although each specimen of bacteria usually produces structurally unique siderophore, which can be utilized only by the producer strain, cross reactivity in biosensing assays occurs and poses a challenge especially in synthetic siderophores. For example, even though the structure of the pyoverdines slightly varies from strain to strain, but it can be detected by closely related species of *Pseudomonas* spp. by different affinities. Therefore, when the aim is to identify the actual species, the precise design of biosensors is essential. As another example, the diverse varieties of enterobactins with slight modifications are secreted by different genus of *Enterobacteriaceae* such as *E. coli* (Inomata et al.

2013), *Klebsiella pneumoniae* (Bachman et al. 2011), *Salmonella typhimurium* (Bister et al. 2004), *Proteus mirabilis* (Himpsl et al. 2010). In this line, interference of designed biosensors with different species remains a challenge to be solved, because more than one species of *Enterobacteriaceae* is involved in most of human diseases such as urinary tract infections (UTI). The fabrication of multiple detection platforms integrated with nanomaterials are considered for both *in vivo* and complex clinical samples analyses.

Table 2: Comparison of analytical performance of reported siderophore-based biosensors for diagnosis of microorganisms.

Detection Strategy	Microorganism	Type of siderophore	Type of receptor	LOD	References
Polydimethylsiloxane (PDMS) stamping and immobilization of pyoverdine onto gold-plated glass chips	*Pseudomonas aeruginosa*	Pyoverdine	FpvA	10^4 cells mL^{-1}	(Doorneweerd et al. 2010)
A siderophore-modified chip methodology	*Yersinia enterocolitica*	desferrioxamine	FoxA	10^3 CFU/mL	(Kim et al. 2012)
Siderophore-modified CdSe/ZnS quantum dots (QDs) coated with PEG-PE assay	*Pseudomonas fluorescens*	Ferrichrome	FhuA	Not reported	(Jin et al. 2011)
Detection of siderophore-binding proteins in cell extracts of pathogens with streptavidin-agarose beads	*Bacillus subtilis*	Petrobactin	YclQ	Not reported	(Bachman et al. 2011)
A siderophore-based piezoelectric biosensors for using AuNPs	*Microbacterium flavescens*	A hydroxamate-type artificial siderophore (TAPPA)	Not reported	Not reported	(Inomata et al. 2007)
A siderophore-based piezoelectric biosensors for using AuNPs	*Escherichia coli*	A catecholate-type artificial siderophore	Not reported	~10^4 CFU mL^{-1}	(Inomata et al. 2013)
A siderophore-based piezoelectric biosensors for using AuNPs	*Microbacterium flavescens* and *Escherichia coli*	the combination of catecholate-type and hydroxamate-type artificial siderophore	Not reported	Not reported	(Inomata et al. 2014)
A facile method in which siderophore selectively identify only viable bacteria	*Escherichia coli*	desferrioxamine B	Not reported	Not reported	(Wolfenden et al. 2012)
Siderophore -based Raman spectroscopy	*P. aeruginosa* and *P. fluorescens*	pyoverdine	Not reported	as low as 5×10^3 CFU ml^{-1}	(Pahlow et al. 2016)
An optical method based on siderophore-fluorophore conjugate VF-FL	*V. parahaemolyticus*, *V. cholerae*, and *V. vulnificus*	vibrioferrin (VF)	Not reported	Not reported	(Chen et al. 2017)

4. Approaches for other samples detection

In recent years, several studies reported the ability of siderophores for the selective recognition of various samples. A siderophore impedance sensor was constructed based on the formation of a siderophore-hemin complex prepared by modification of hemin on an interdigitated array microelectrode. Siderophore reacted with hemin and formed a complex on the electrode surface. As the conductivity of hemin was higher than that of siderophore, the formation of the complex led to decrease of conductivity on electrode surface which was measured by electrochemical impedance spectroscopy. The impedance change of constructed sensor was linear with the concentration of siderophore between 1 nM and 100 nM, with a LOD of 0.86 nM. The detection time was less than 15 min. Compared with conventional methods for siderophore, this approach is faster, more sensitive, and has potential application for the determination of pathogens (He and Yan 2015).

In another research, pyoverdine secreted by *P. aeruginosa* strain PA1 was employed as a biological recognition probe for the detection of furazolidone based on the rapid fluorescence quenching of pyoverdine by furazolidone. Furazolidone is a pesticide used for the treatment of infections of animals and humans and its detection is urgently recommended due to its large residual in the environment, and strong carcinogenicity and genotoxicity. The specific quenching of fluorescence of pyoverdine by furazolidone probably happens due to the electron transfer from siderophore to this pesticide. The total detection process could be completed within a few seconds in the optimal pH=7.2 in 50 mM 3-(N-morpholino) propanesulfonic acid solution. The linear range of the detection was 2–160 μM and

the LOD was 0.5 μM. This study introduced a novel fluorescent method for furazolidone detection in the aquatic samples (Yin et al. 2014). This study also opened a new approach based on the rapid and specific fluorescent siderophore-based biosensor for the detection of other pesticides with existing quenching phenomenon.

A selective fluorescent optical sensing method was designed for ciprofloxacin antibiotic detection in phosphate buffer (pH=7.0) with fluorescent PVD isolated from a non-clinical soil-borne *Pseudomonas monteilii* strain MKP 213. In the presence of ciprofloxacin, PVD showed new UV–vis absorption bands at 252 and 321 nm due to an internal charge transfer mechanism. Also, upon addition of ciprofloxacin, selective enhancement in the fluorescence profile of PVD with a 13 nm blue shift from 458 to 445 nm was observed. The combination of a long peptide chain along with the chromophore unit of PVD generated a converging cleft for ciprofloxacin recognition with LOD and LOQ of 7.13 μM and 21.6 μM, respectively without interference from other studied antibiotics. In this study, the addition of vancomycin and ceftazidime did not significantly change the fluorescence intensity of PVD (Pawar et al. 2016).

In another investigation, deferoxamine-gallium (III) cation capture agents were employed for the isolation and detection of target molecules including phosphopeptides, phospholipids, nitrotyrosine-containing peptides and sulfated polypeptides from a sample. The ability of deferoxamine-Ga(III) cation capture agents to bind target molecules was confirmed using AlphaScreen™ assays. Then, the target molecule-capture agent complexes were separated from the sample (Bossé et al. 2014). Eason demonstrated that tri-nuclear osmium or ruthenium complexes reacted with siderophores are suitable for use in nucleic acid amplification and sequencing techniques (Eason 2013).

The natural and artificial siderophores also have the potential to be employed as cancer therapeutics because cancer cells require high concentrations of iron for proliferation (Górska et al. 2014). Removal of iron using siderophore-based compounds from cancer cells would be an interesting approach for cancer therapy. In this regard, specifically labeled superparamagnetic iron oxide NPs (SPIONs) with siderophores which are conjugated to aptamers specific for cancer cell can provide a suitable non-invasive strategy for tumor imaging by magnetic resonance imaging (MRI) method.

5. Conclusions and future perspectives

This review presented an overview on recent advances in the development of siderophore-based biosensors (we recommend that this term is abbreviated as “siderosensor”) and nanosensors for a variety of detection areas. Siderophore is recognized as iron uptake component for microorganisms under iron-limited conditions. The superb specificity and high affinity of siderophores for numerous metal ions, or their receptors on microorganisms provide a basis for using these molecules as sensors or probes. To this end, many siderophores with desirable characteristics have been developed as rapid and point-of-care diagnostics for infectious pathogens. Rapid diagnosis and treatment of infection in its early stages play a major role in inhibiting the spread of infection. Combination of potential siderophore molecules with nanomaterial-based biosensing has opened new venues for diagnosis of either bacteria or metal ions. The major challenge in designing detection methods/tools mainly involves identifying siderophores that are suitable for detection purposes. Although some siderophores have potentially been used as biosensors, most of them have not yet been characterized. Thus, it could be hypothesized that some of the uncharacterized siderophores may turn out to be novel and potential biosensors. Furthermore, it is expected that siderophore-based biosensors be used as emerging diagnostic/therapeutic methods for cancer.

For further development in this field, the siderophores-based detection should be coupled with different analytical techniques in order to obtain more accurate measurements. Aptamers are considered as favorite candidates for designing siderophore-based biosensors due to their capability in conducting rapid, easy, and sensitive detection of targeted molecules (Danesh et al. 2018; Mokhtarzadeh et al. 2016). Furthermore, in the area of online monitoring, the existent trend is the miniaturization of the sensors and the incorporation of these compounds into nano/microfluidic platforms. Microfluidic-based biosensors can be designed for automated operation where all steps of an immunoassay are performed in a programmed manner to remove human errors and improve accuracy.

Acknowledgments

Funding for the laboratories of MR and KA has been received from Mashhad University of Medical Sciences, Mashhad, Iran.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AAS atomic absorption spectrometry
AuNPs gold nanoparticles
Az azotobactin
BSA bovine serum albumin
CMCP critical metal concentrations for pyoverdine
CV cyclic voltammetry
CPG controlled pore glass
DFB desferrioxamine B
FI flow injection
Fl-DFO fluorescein-desferrioxamine
FRET fluorescence resonance energy transfer
GO graphene oxide
GOPS (3-glycidyloxypropyl) trimethoxysilane
H_2L aeruginic acid
H_3L 2,3-dihydroxybenzoylglycine
ICP-MS inductively coupled plasma-mass spectrometry
ICPAES inductively coupled plasma atomic emission spectroscopy
ISEs ion-sensitive electrodes
LFA lateral flow assays
Ln lanthanide
LR linear range
LOC lab-on-a-chip
LOD limit of detection
MA-DFB N-methyanthranyl desferrioxamine
Mo Molybdate
MTS micelle-templated silica
MRI magnetic resonance imaging
NMs nanomaterials
NPs nanoparticles
NTBI or NTB-Fe nontransferrin-bound iron
PCR polymerase chain reaction
Pch pyochelin
PDMS polydimethylsiloxane
PET photoinduced electron transfer
POC point of-care
PVD pyoverdine
QCM quartz crystal microbalance
QDs quantum dots
Rg_6NHNH_2 rhodamine 6G hydrazide
SIMS secondary ion mass spectrometry
SPIONs superparamagnetic iron oxide NPs (SPION)
SXRF synchrotron X-ray fluorescence microscopy
UTI urinary tract infection
VF vibrioferrin
SNR signal-to-noise ratio
TRF time-resolved fluorescence
LRET lanthanide resonance energy transfer

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Highlights

- Siderophores are recognized as iron uptake component for microorganisms under iron-limited conditions.
- A variety of siderophores have been applied for the detection of metal ions, microorganisms, etc.
- This review mainly focuses on recent developed optical and electrochemical siderophore-based biosensors (siderosensor) and nanosensors.
- This review covers the prominent roles of nanomaterials in the development of siderophore-based biosensing devices.
- Future perspectives and challenges of siderophore-based nano-biosensors are discussed briefly.