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Review of measurement and analysis of biomarkers using inorganic complexes and metal-based nanomaterials

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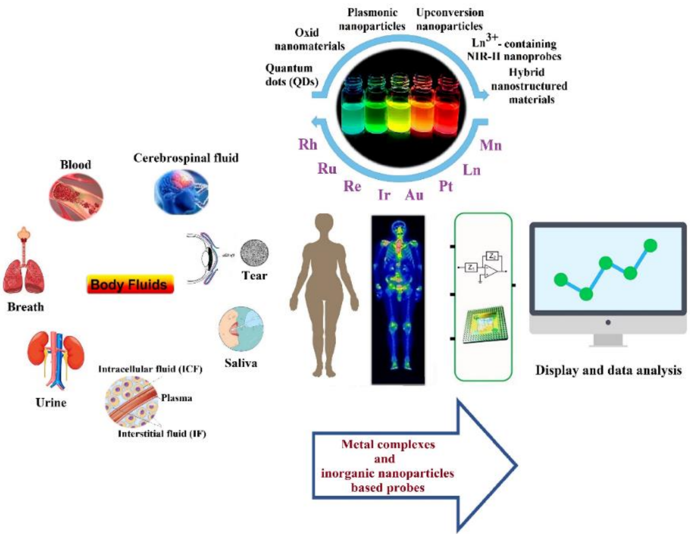
ABSTRACT

Biomarkers are biochemical/physiological changes in body tissues or fluids that can be accurately and reproducibly measured. They can indicate the entire spectrum of the disease and potentially the choice of the type and dosage of drugs can increase the effectiveness and minimize effective therapeutic interventions. Therefore, the identification of biomarkers is of particular importance in the development of pharmaceuticals and moving towards personalized medicine.

Nanotechnology as a new scientific field with novel combinations has taken the lead in the fields of medical diagnosis, imaging and therapeutic applications. Investigation of literatures determined that signal generation probes based on inorganic complexes and metal-based nanomaterials can generally be one of the suitable candidates for diagnosis. Therefore, in this study, the importance of using inorganic chemistry and nanotechnology in the field of identifying biomarkers has been discussed. In the first part of the review, the main definitions in this field have been explained. Then, a set of biomarkers associated with a specific disease and number of methods for measuring biomarkers are described. In the next section, the use of inorganic metal complexes and nanoparticles in probes for sensing and imaging is discussed and finally, current challenges and future prospects are presented.

Keywords

Biomarker, inorganic metal complexes, inorganic nanoparticles, imaging modalities, metal-based signal generation probes, nanotechnology.



Graphical abstract

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1. Introduction

The definition of biomarker dates back to the 1950s [1,2] In 1987, " Markers of signaling events in biological systems or samples" were introduced as biological markers [3]. In 1990, biomarkers were defined by McCarthy and Shugart "Measurements at the molecular, biochemical, or cellular level in wild populations from contaminated habitats or in organisms experimentally exposed to pollutants that indicate that the organism has been exposed to a toxic chemical and indicate the extent of the reaction of the organism." [4]. In 1994, a biomarker was pointed by Deplage as "a biochemical, cellular, physiological, or behavioral change that can be measured in tissues or body fluids or at the level of the whole organism that indicates exposure and/or effects of one or More contaminants." [5]. In 1996, biomarkers were stated by Gestel and Brummelen. According to this definition, a biomarker should by definition be used only to describe lethal biochemical changes caused by exposure to xenobiotics [6].

Given the increasing global importance of biomarkers in modern healthcare, in 1998 the Biomarker Definitions Working Group of the US National Institutes of Health (NIH) defined a biomarker as: "a feature (molecular, histological, radiographic, or physiological) that is measured and appraised as an representative of normal biological and pathogenic processes or pharmacological repercussion to a therapeutic intermediation" [7-11].

In 2000, the phrase biomarker appointed by De Lafontaine as: "primary responses to biochemical and/or physiological change(s) in organisms exposed to pollutants [12]. Therefore, accurate and reliable detection of biomarkers is very important for early diagnosis of the disease and thus the possibility of timely treatment [13,14].

William Osler (one of the founders of modern American medicine) has a theory in which pointed out the importance of diagnosis: "Diagnosis over medication is our priority." [15]. Biomarkers have a substantial role in the diagnosis and management of cardiovascular diseases, infections, immune and genetic disorders, and cancer [16].

1.2. Types of biomarkers

Many biomarkers have been reported in the literature and used in diagnostic products. They can be found in body fluids such as blood, serum, urine, saliva, tears or cerebral spinal fluid [17]. Biomarkers include changes in anatomy (bone density or tissue fluid balance), pharmacological actions, formation of metabolites (e.g. metabolomics, proteomics, glycomics, lipidomics), changes in enzyme rates, urinary and blood-related additional compounds, Blood glucose, amino acids, Nucleic acids [18]. disease-specific molecules such as pathogen-specific proteins, host response molecules (immunoglobulins) [17]. arachidonic acid cascade and especially factors derived from leukotriene B4) [18-20]. An increase in the amount of metal ions (copper, zinc, iron and aluminum) in the brain [21] and other cases [13,14].

1.3. Measurement of biomarkers

Measurement of biomarkers can help to explain the experimental results of clinical trials as well as the development and evaluation of new treatments. There are different methods to measure biomarkers [22] a range of techniques such as flow cytometry, polymerase chain reaction (PCR) Western blotting, (ELISA) enzyme-linked immunosorbent assay, atomic force microscopy (AFM) Fourier transform infrared spectroscopy (FT-IR), electron microscopy, gel electrophoresis, Nuclear magnetic resonance (NMR), Chromatography and mass spectrometry (MS) [13, 21,23,24] light scattering methods and X-ray absorption spectroscopy. [21] Molecular imaging is another measurement method that will be discussed further [25]

1.4. Biomarkers & imaging modalities

Molecular imaging is an incredibly diverse field and defined as the representation, identification, and quantification of biological processes and physiological status at the molecular and cellular levels in humans and other living systems and produces highly predictable clinical value. The emergence of molecular imaging as a scientific discipline is the result of advances in chemistry, biology, physics, and engineering and the application of imaging probes and technologies. The impact of molecular imaging on pharmaceutical sciences and clinical medicine has been extensive, because it helps in better diagnosis and as a result providing more effective treatment as well as monitoring its effectiveness, and on the other hand, it allows pharmaceutical companies to reduce the time required to introduce new therapeutic drugs to the market [18,25] Some of the methods are used for clinical applications include X-ray imaging, mammography, CT scan (computed tomography, axial computed tomography or CAT), PET (positron emission tomography), single photon emission computed tomography (SPECT), PET/CT and SPECT/CT scanner, magnetic resonance imaging (MRI), MR, MRS, ultrasound imaging, fluorescence-based imaging, photoacoustic imaging, each of which has its strengths and limitations [17,18], [20,21,23]. [26-30]

1.5. Leveraging Inorganic Chemistry for Detection

Inorganic metal complexes and nanoparticles have been widely used in biomedicine due to their particular optical, electrochemical, magnetic and catalytic properties. signaling methods (signal-producing probes) in diagnostics and have been used in contrast MRI, in vivo bioimaging, photoluminescence, electrochemical sensing platforms, and electrochemiluminescence (ECL) are among the biomedical applications. [15].

Inorganic complexes have unique chemical and photophysical properties that mainly depend on the identity of the metal center and the chemical structure of the ligands [31] long-lived phosphorescence [15, 32]. significant (large) Stokes shifts [14,33], high photostability, wide emission range, emission tuneability (tunable emissions) [15,34] Ability to withstand greater changes in pH and temperature, [35]. The possibility of regulating their chemical nature based on biological properties (membrane permeability, localization of organelles and/or interaction with specific biomolecules), [13] Ability to be conjugated with biological carriers in order to create cellular specificity and increase sensitivity [31] are among the advantages of inorganic Photoluminescent complexes that have caused photoluminescent mineral complexes to appear as attractive candidates for biological probes as signaling molecules for detection, [15,36]. Designing and leveraging coordination chemistry to prepare bright metal-based compounds is an exciting research proposal that is currently being explored by many [31,34,37] General reviews on the use of metal complexes for sensing have been published by various groups [38]. [31,39].
In this review, a summary of all the data collected from the literatures in Table 1 and provide insights into the future potential of these compounds for the investigation and treatment of human diseases.

Table 1. Typical Examples of detection platforms based on luminescent Inorganic metal complexes.

Luminescent probe	Application	References
Manganese (II) terpyridine complex	Suitable for use in two-photon fluorescence microscopy and MRI.	[40]
Rhenium(I) polypyridine isothiocyanate and maleimide complexes	Used in the development of various bioassays.	[31,41,42]
Rhenium(I)-dipyridophenazine complex	"Switch-on" probe for double-stranded duplex DNA.	[43,44]
Rhenium(I) complex conjugated with folic acid and PEG	Tumor cell marker	[42]
$[Ru(bpy)_3]^{2+}$ and $[Ru^{II}(bpy)_2L]^{n+}$ complexes	Detect anions, metal cations, highly sensitive applications in immunoassays and DNA assays	[42,45,46]
Ruthenium (II) complexes with 1,10-phenanthroline and bathophenanthroline derivatives	Environmental and biological HClO probing	[37,47]
Guanidinium group modified bipyridine-Ru(II) complex	Luminescent probe for the c-myc G-quadruplex	[35,45]
Ru(II) complexes conjugated with crown ether moieties	ECL sensors for metal ions.	[42,45,48]
cyclometalated Iridium (III) complexes	Suitable probes for LD visualisation in live cells and organisms, discrimination of Cys from other biothiols such as Hcy and glutathione (GSH)	[31,49]
Iridium(III) complexes with thiaaza and aza crown ether-substituted phenanthroline-based ligands	Multi-cation detection in single or multi-channel detection protocols.	[48]
Iridium (III) complexes functionalized with specific recognition elements	Detection of metal ions, small molecules, proteins, enzymes and cancer cells.	[50,51]

Table 1. continued

Luminescent probe	Application	References
Pt(II) based probes containing 4-amino-1,8-naphthalimide moiety	Bacteria imaging	[52]
Pt(II) complexes in the general form $[Pt^{II}(C^\wedge N)L]^{n+}$, $[Pt^{II}(C^\wedge N^\wedge N)L]^{n+}$	luminescent light switch for c-myc G-quadruplex DNA selectivity towards HSA	[52]
Pt(II) complexes with a central aromatic scaffold with pendant amine side chains	Luminescent probes for G-quadruplex DNA	[53]

Au(I)-phosphine complex containing a naphthalimide ligand	Promising candidates for imaging	[53]
Tetrakis(diisopropylguanidinio)zinc (II) phthalocyanine	Fluorescent probe for c-myc G-quadruplex	[54]
Lanthanide complexes using chromophores containing pyridine, carboxylate, ß-diketone group, salophene, etc.	Cell imaging	[31,55-59]

The vast majority of metal-based probes and nanoparticles produce optical signals such as absorption, fluorescence or phosphorescence. Consequently, a multiple assemble of precision tools has been developed for quantitative imaging and quantification purposes [15,60] These nanoparticles offer several important advantages including high quantum efficiency, size-dependent emission tunability, and enhanced photostability Conjugation with biomolecular targeting ligands (antibodies, aptamers, peptides or small molecules), high sensibility, good specificity, Cost-effective and easy assimilation, [17,60-62] cause Nanomaterial-based electrochemical biosensors as the most attractive type of biosensors which used in medical, environmental, food and other fields, [63-65], To date, several nanomaterials, Quantum Dots (Colloidal semiconductors), [15,17,18,29], [62,63] [66-70] metal oxide nanoparticles (CuO, ZnO, magnetice), [17,60,63,71] Up conversion nanoparticles (UCNPs), [17,72,73] plasmonic nanoparticles, including noble metal nanoparticles (Gold and Silver nanoparticles). [15,17]. [61,63,68,74] NIR-II nanoprobes containing Ln^{3+} [75] have been used for production and Amplified signals electrochemical biosensors.

1. 6. Hybrid Metallic Composite Nanostructures as Recognition Elements

Hybrid nanostructures offer distinct advantages compared to individual components and at the same time, it is possible to find new properties and functions for practical applications. Hybrid nanostructures have been used as immune probes to detect biomarkers. The components of a hybrid nanostructure can be chosen from a wide range of materials. [23] for instance, nanoparticles doped with lanthanide chelates, [15] nanoparticles consisting of latex particles, silica-based beads or inorganic lanthanide doped phosphors, [76] Metal nanoshells such as: (CdSe/CdS/ZnS), ZnS-CdS@MoS_2 /chitosan nanocomposite, Au@Ag core-shell colloids, Fe_3O_4/Au/Ag nanocomposites, Ag@SiO_2@SiO_2-RuBpy, (Fe_3O_4@nSiO_2@mSiO_2 @Aptamer) nanoparticles, Au/TiO_2 nanocomposite, TiO_2 nanosilk@MoS_2, [23,61,63, 68,77,78], The integration of inorganic complexes with nanomaterials such as metal- organic framework (MOF) is one of the approaches that can be used to develop the next generation of detection probes, [15,79-81]

2. Materials and methods - Search Strategy

In this study, the keywords i.e., Biomarker, inorganic nanoparticles, inorganic nanoparticles, metal-based signal generation probes were searched in various databases such as Scopus, Google Scholar, PubMed and ISI. The related articles written regardless of the time limit and based on the use of complexes and inorganic nanoparticles in diagnosis were evaluated and used to write this research.

3. Conclusions

As discussed, biomarkers are of great importance in biomedical research, including the drug development process and therapeutic evaluation strategies by understanding the relationship between measurable biological processes and clinical outcomes. The more understand about the nature of a disease process and the drug pharmacology that affects it, we will be able to make progress in diagnosing, staging, and monitoring disease and its response to treatment. At least since the 1980s, the need to use biomarkers in diseases such as cancer, cardiovascular diseases, infectious diseases, as well as diseases related to neurology and psychiatry has been widely discussed. The use of biomarkers in basic and clinical research, as well as research on potential new biomarkers for use as surrogates in future FDA trials, is a growing trend. In order to provide health care and quality of life in an optimal way, it is necessary to design innovative, Cost-effective, easy-to-use, and effective solutions. In this way, it becomes possible to check the health status and factors affecting the health by the patients themselves and their companions. Recent advances in medicine help in understanding various types of diseases, thereby making more accurately diagnose and choose treatment, as well as monitor the procedure of the disease.

In this review, the use of luminescent transition metal complexes as labels and probes for biomolecules has been highlighted. Examples have shown that the use ofmetal complexes in luminescence probes due to their rich photophysical properties is a promising field in the detection and identification of biomarkers and has a very bright future. In summary, with the targeted selection of metal centres and ligands, biologically-relevant substrates and reactive functional groups, transition metal complexes can contribute to a wide range of biological applications. Due to the amazing and fascinating properties of inorganic nanoparticles, they are usually used as powerful sensors and probes for the sensitive and selective detection and quantification of important biological analytes, and it is an attractive and fast-growing research field. Over the past few years, significant achievements have been made in the construction of biosensors. However, there are still opportunities for further development and acquisition of unique properties in nanomaterials in various fields, which are worth in-depth and systematic research. In this context, the use of new nanoparticle manufacturing techniques can lead to new optical properties that can be used for the development of theranostic nanomaterials. In the future, various developments can be envisioned using advanced nanomaterials and will likely accelerate healthcare diagnosis, treatment, and monitoring. In addition, it seems that biosensors based on nanomaterials will also attract more attention in other fields such as food safety and environmental analysis.

It is hoped that this review will help researchers to achieve new innovative compounds using luminescent metal complexes, functionalized metal nanoparticles, nanocomposite materials and other biomolecules to produce and develop robust, sensitive and reliable platforms for early detection of biomarkers as well as other critical target analytes. In this way, it has an effective role in the progress and development of inorganic medicinal chemistry.

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