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# Inorganic nanoparticles in biology: drug carriers and auxiliary tools in bioimaging and bioanalytics

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***Abstract*:**

**Matijević, M., Popović, I., Stepić, M., Nešić, M., Radoičić, M., Stanković, M., Šaponjić, Z., Petković, M.: *Inorganic nanoparticles in biology: drug carriers and auxiliary tools in bioimaging and bioanalytics. Biologica Nyssana, 9 (1). September, 2018: 1-19.***

Among various nano-scaled materials composed from a spectrum of chemical compounds, inorganic nanoparticles are very attractive due to their physico-chemical properties, as well as their availability, simplicity, possibility of modifications, stability and biocompatibility. They are, on the one hand, an useful tool in advanced analytical chemistry, in particular for studying of biologically-relevant processes, but also important as functional parts of the systems designed for controlled and targeted delivery of medicaments for treatment of a variety of diseases and for imaging. So far, thousands of compounds and systems have been developed for the above-mentioned purposes, but there are only a few reviews dealing with these topics. The aim of this review is, thus, to summarize recent applications of nano-structured inorganic materials in the field of drug delivery, bioimaging and bioanalytics, and to give a prospective from the standpoint of biology-related applications.

**Key words**: inorganic nanoparticles, photodynamic therapy, imaging

***Apstrakt*:**

**Matijević, M., Popović, I., Stepić, M., Nešić, M., Radoičić, M., Stanković, M., Šaponjić, Z., Petković, M.:: *Neorganske nanočestice u biologiji: nosači lekova i pomoćni alat u bioimidžingu i bioanalitici. Biologica Nyssana, 9 (1). Septembar, 2018: 1-19.***

Među različitim nanomaterijalima, neorganske nanočestice privlače posebnu pažnju zbog svojih fizičko-hemijskih osobina, kao i dostupnosti, jednostavnosti, mogućnosti modifikacije, stabilnosti i biokompatibilnosti. Neorganske nanočestice su korisna pomoćna sredstva u analitičkoj hemiji, posebno za ispitivanje biološki-relevantnih procesa, ali su i značajan funkcionalni deo sistema za kontrolisanu i ciljanu dostavu medikamenata za terapiju raznih oboljenja, kao i za medicinsku imidžing dijagnostiku. Do sada je razvijen veliki broj jedinjenja i sistema za gore-navedenu svrhu, ali se može naći samo nekoliko preglednih članaka na ovu temu. Cilj ovog revijalnog rada je da dâ zbirni pregled primene nano-strukturnih neorganskih

materijala u oblasti dostave medikamenata, bioimidžinga i bioanalitike, kao i da pruži buduće smernice sa stanovišta primene u oblasti biologije.

**Ključne reči**: neorganske nanočestice, fotodinamička terapija, imidžing

## Introduction

Nanomaterials are attracting more and more attention for use in biological systems. The number of their potential applications in biology causes an expansion of new scientific discipline, so called nanobiology. This term refers not only to the application of nanomaterials for investigations of important biological processes in health and in pathological states but also to the utilization of various nanomaterials as auxiliary tools in different analytical methods for investigations of biological systems and their components.

In this work, we are focusing on the application of inorganic nanoparticles for drug delivery, imaging and analytical chemistry, to cover the units which are interconnected and can be merged in practical work. Apart from those, there are also other numerous applications of nanoparticles, which are important from the standpoint of advances in technology, medicine and science in general. For instance, nanoparticles are widely used in diagnostics (imaging diagnostics, laboratory diagnostics, genetic diseases` and tumor diagnostics), radiosensitization, tissue engineering, drug delivery, therapeutic drugs, to the specific medical and other instrumentations such are nanoprobes, nanosensors and nanorobots (Su H. et all., 2017). Other application areas that are not covered in this review, but should be mentioned are the areas of the molecular biology as a bio-labels (Kumar & Sophia, 2018), surface chemistry, protein corona and intracellular nanoparticles pathways.

The literature data suggest that term “nano” in biology mostly refers to the particles smaller than 5

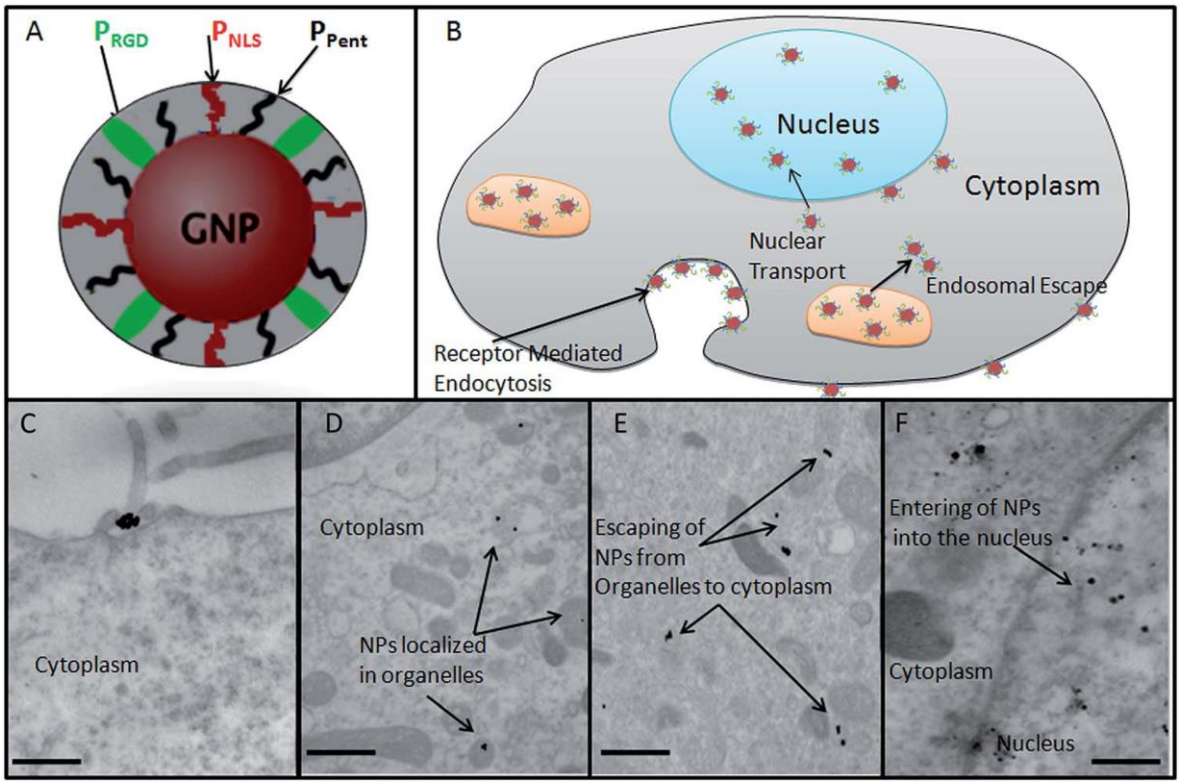


**Fig. 1.** Trajectory of peptide-conjugated gold NPs (GNPs) through the cell. A, Schematic of a functionalized GNP used in the study B. Trajectory of peptide-conjugated GNPs through the cell. C-F, Path of the NPs was captured using TEM images and is as follows: C, GNP-Peptide complex bound to the plasma membrane for entry into the cell via the endocytosis process, D, Internalized NPs were localized in vesicles, such as, endosomes and lysosomes, E, Escaping of NPs from vesicles into the cytoplasm, F, Entering the nucleus through nuclear pore complex (NPC) (scale bars = 100nm). Reproduced with permission from Yang et al. (2014).

μm (Singh & Lillard, 2009), which can be, with minimum risk, administered into the blood circulation. Comparing with the smallest human cells, i.e. erythrocytes, the dimension of a typical nanoparticle is about 5 times smaller, whereas in comparison to oocytes, the largest nanoparticle could be more than 120 times smaller. That indicates that nanoparticles (NPs), speaking in physical terms, can be ingested by a cell, reach cellular interior and become available for the interaction with intracellular organelles or to target specific biomolecules. NPs can be ingested by a cell through utilizing the existing cellular pathways for ingestion, and/or diffusion through the membrane in the case of smaller NPs. Another way, i.e. endocytosis, or a receptor-mediated pathway is illustrated in **Fig. 1**, on the example of a peptide-bound to the NP (Yang et al., 2014). Based on that, NPs can be designed for intracellular imaging, to target particular biomolecule or an organelle and to interfere with the intracellular processes/signaling, either for the diagnostic or the therapeutic processes.

In terms of a therapy, NPs as carriers for targeted and controlled drug delivery have attracted much attention. They have functions to preserve a drug until it reaches target tissue/organ and to secure targeted delivery and control a drug concentration (Pandey, 2017). After activation by various mechanisms, the drug is released and can act on desired site, thus minimizing side effects on healthy tissues. Although numerous medicaments have been designed to use intrinsic properties of diseased tissues, such as low intrinsic pH, due to a low oxygen concentration in tumor cells (Casciari et al., 1992), nanoparticle-based carriers are still attractive and promising approach for targeted therapy.

In analytical (bio)chemistry, NPs are used as auxiliary tools in various techniques. Thanks to their properties, they enable better precision of the method (Frigerio et al., 2012; Will et al., 2006; Lucena et al., 2011), and its increased selectivity and sensitivity (Ling et al., 1991; Arakawa & Kawasaki, 2010; Thompson et al., 2008). A waste amount of biologically important molecules are qualitatively and quantitatively analyzed with the assistance of NPs (Kawasaki et al., 2007; Chiang et al., 2010a; Popović et al., 2016; Popović et al., 2016a; Popović et al., 2016b). Some examples of methods which exploit the advantageous properties of NPs are mass spectrometry, chromatography, but also mass spectrometry imaging, and their application will be discussed in more details in this review.

## Physical and chemical properties of nanoparticles

NPs can be fabricated from various materials, and coarse classification involves organic and inorganic, and commonly used types are shown at the **Fig. 2**. Based on their size and composition, there are several groups of nano-structured materials: NPs (1-100 nm), nanocapsules (nanoscale shells made of a polymer),

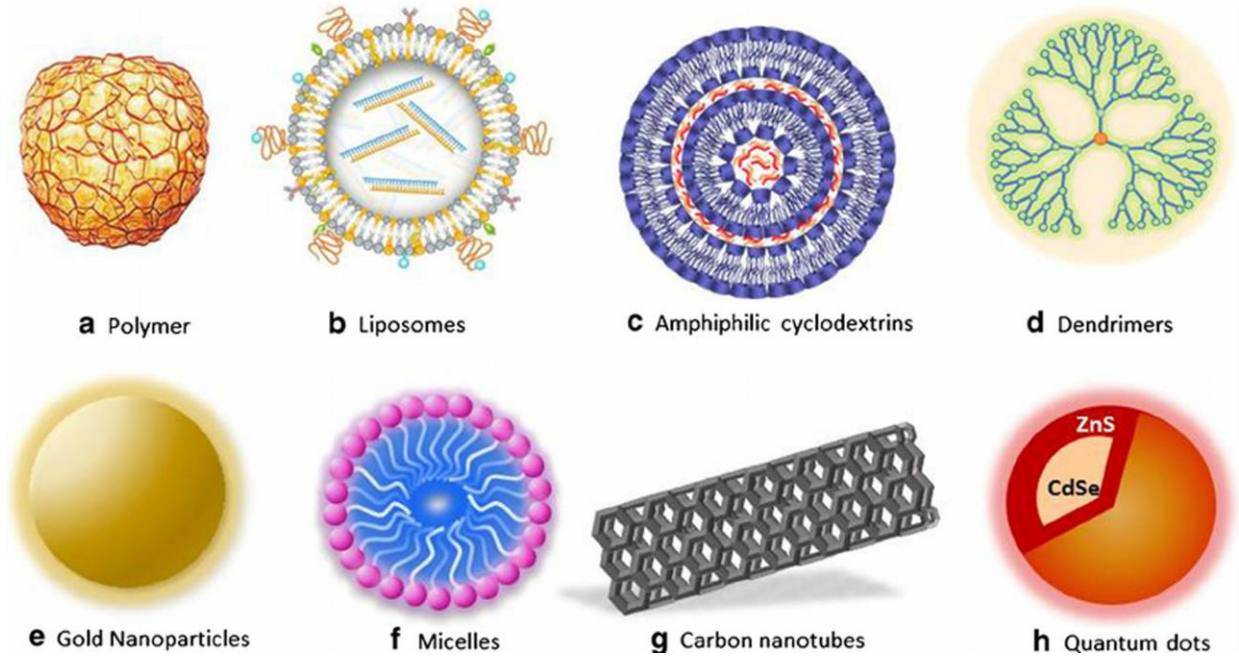


**Fig. 2**. Types of NPs commonly used for biomedical applications: (a) polymer, (b) liposomes, (c) amphiphilic cyclodextrines, (d) dendrimers, (e) gold NPs, (f) micelles, (g) carbon nanotubes and (h) Quantum dots (QDs), modified form (McCarthy et al., 2014).

fullerenes (made of a carbon and with various shapes), dendrimers (repetitively branched molecule), quantum dots (QDs), (a semiconductor nanostructures), nanostructures (size between intermediate and microscopic particles) and nanopores (with tiny hole in a thin membrane) (Akeson et al., 1999). In line with the topic of this review, the following part will summarize some biologically-relevant properties of organic vs. inorganic NPs.

Each of them, organic and inorganic, has its own advantages and disadvantages. Organic materials are made mostly from biodegradable materials, and they can be metabolized in the organism, finally resulting with $CO_2$ and water. As disadvantage, there is always a risk of premature degradation, which leaves the medicament exposed to enzymes and immunological system, causing too early activation of a medicament, which leads to the expressed side effects. This disadvantage could be avoided, or minimized, through the encapsulation of a medicament in the NPs (Dobrovolskaia & McNeil, 2007; Singh & Lillard, 2009).

Monitoring of the destiny/biodistribution of organic NPs in organism is sometimes difficult, due to limited possibilities to distinguish them in the surrounding organic milieu. The labeling techniques, for instance by some voluminous fluorescence dyes, might prevent the interaction with target molecules/tissue leading to the misinterpretation of the data. The application of inorganic materials for fabrication of NPs gives much more possibilities for surface functionalization, and much broader spectrum of methods which can be used for the monitoring of NPs` biodistribution. Modification of NPs allows controlled changes of the interface properties, which affects the dissolution and degradation rates, catalytic activity and possibility of stabilization through the adsorption of macromolecules (Stark, 2011). On the other hand, precaution is needed because inorganic material must be selected by making a compromise between biological inertness, availability and potential of surface modification. For biological applications, selection of inorganic materials for fabrication of NPs should be based on the information of their potential biological role. For instance, selected material should not contain a metal which might be a co-factor for any enzyme in the cells. In other case, the final concentration of metal should be under the enzyme-activating level (Chen et al., 2012; Lee & Yeo, 2015). The presence of higher concentrations of the enzyme cofactors, might lead to the enzyme activation and the interference with the intracellular signaling processes.

Inorganic materials made of non-biological metals enable also easier detection by instrumental methods, which utilize either properties of their atoms (magnetic or paramagnetic properties, for instance) or intrinsic fluorescence, i.e. optical properties. For example, titanium is not biologically abundant, and it can be detected with methods which differentiate inorganic from organic materials, i.e. NMR (Padro et al., 2000), or other approaches. Some of most frequently used NPs in medicine are those made of gold, which could be visualized by microscopy, or fluorescence labeling, or other method (Gonciar, 2014). Having in mind that the inorganic NPs are the focus of this review, the summarized list of the different types of inorganic NPs that are relevant for this review, is shown in the **Tab. 1**.

## Metal oxide semiconductor-based nanoparticles

A number of metals can form oxides that can conduct an electrical current, and NPs made of them are used as drug carriers, for imaging purposes and in analytical chemistry. The most commonly used are ZnO, CuO, $TiO_2$, $ZrO_2$ or MgO. Besides electro-conductivity, properties which are advantageous for the variety of applications are photo-responsivity, magnetism, possibility of surface modification, etc. Metal NPs have large surface-to-volume ratio and due to their high density and limited size of corner or edge on the surface site, metal oxide NPs exhibit unique chemical and physical properties. For instance, for the application in anticancer drug delivery systems, the size of metal NPs should be larger than 10 nm in order not to be cleared by the kidney excretion and captured by macrophages (Lee & Yeo, 2008), and on the other hand, to be smaller than 100 nm to reach the tumor tissue and enter the cell (Cho et al., 2008). Even within the range of 10-100 nm, small alteration in size of NPs makes a big difference regarding their properties, i.e., as the size decreases, the number of surface and interface atoms generates strain or stress and concomitant structural perturbations (Gleiter, 1995; Trudeau & Ying, 1996; Valden et al., 1998; Rodriguez et al., 2002; Song et al., 2003; Schoiswohl et al., 2004). In terms of the NPs uptake by mammalian cells, oxides of zinc, iron, manganese, and cobalt exhibit nonclassical interaction – the Trojan-horse-type, which enables diffusion of the toxins by packing it in the small particles (Stark, 2011).

Surface of inorganic NPs can be easily modified, and thanks to that property, they are often considered for drug discovery and therapy development. They can be modified for targeted drug

**Table 1.** Overview of different types of inorganic NPs from cited literature in this review

| System | Structure | Characteristics | References |
|---|---|---|---|
| AuNPs | Colloidal | Effective phototermal destruction of cancer cells and tissues | Sperling & Parak, 2010 |
| Semiconductor NPs: CdSe or CdTe | | Photoluminiscence in the form of fluorescence | |
| Doped oxide materials, $Y_2O_3$ | | Phosphorescence | |
| $Fe_2O_3$, CoNPs | | Magnetic moment | |
| Feridex | Colloid with low molecular weight dextran coating, with a particle size of 120-180 nm | Magnetic moment<br>Diagnostic agent in use | Cherukuri et al., 2010 |
| Cobalt ferrite, $CoFe_2O_4$ | | Magnetic moment<br>Binding to serum albumin proteins | Amiri et al., 2017 |
| $Fe_3O_4$ NPs | Naked, 80±5 nm | Magnetic moment<br>Higher accumulation in the lungs due to their *in vivo* agglomeration | Radović et al., 2015 |
| $Fe_3O_4$-PEG NPs | Functionalization with polyethylene glycol 600 diacid, 46±0,6 nm | Magnetic moment<br>Potential in Hyperthermia based cancer treatmens | |
| Platinum-tethered gold NPs-PEG | Au NPs functionalized with thiolated poly(ethylene glycol) (PEG monolayer capped with a carboxylate group of [Pt(R,R-dach)] | NPs functionalized with PEG do not make aggregate<br>Higher uptake than Pt(R,R-dach)<br>NPs are capable of delivering [Pt(R,R-dach)] to the cell and then releasing it | Brown et al., 2010 |
| Scg8-AuAg nanoroads | Gold-silver-(AuAg-) nanoroads labeled with molecular aptamers | Higher hyperthermia efficiency and selectivity to CEM cells than aptamer alone | Conde et al., 2012 |
| Carbon nanotubes | Carbon cylinders composed of benzene ring linked to the methotrexate attached to medicament-methotrexate | Water-soluble and biocompatible through chemical modification | Pastorin et al., 2006 |
| S1MPs, S2MPs | Mesoporous $SiO_2$ NPs, S1MPs which large pores are loaded with S2MPs | High biocompatibility<br>High surface areas and pore volumes<br>Controlled release dynamic of medicament | Tasciotti et al., 2008 |
| $TiO_2$ NPs | Colloidal $TiO_2$ NPs attached to potentional medicament – Ru bis-bipyrydil complex | Minimal dark cytotoxicity<br>High surface to volumes relation<br>The surface of $TiO_2$ can be modified<br>Controlled release dynamic of medicament | Nešić et al., 2016, 2017 |

delivery for various significant biomolecules (nucleic acids, proteins or peptides) or for specific tissues. Such targeted nanocarriers decrease overal drug toxicity and offer more effective biodistribution, as discussed above. The conjugate of a drug and nanocarrier can pass some natural body barriers, such as blood or brain barriers (Rawat et al., 2006) and deliver drug to the target tissue. There are several external activators, which employ inner properties of inorganic nanoparticle as a carrier, eventually leading to cytotoxic effects at the target tissue, which will be discussed more in the next chapter. Stimulus or activators can be high magnetic field or ultrasound applied locally, which increase the temperature of diseased tissue, due to the accumulated NPs in the tissue (Arruebo et al., 2007; Singh & Lillard, 2009; Lee and Yeo, 2015). Light as activator attracted much attention in later decades, because it can be easily

controlled and focused to minimize influence on the healthy tissue. Light can be used in a combination of photo-responsive drugs or nanoparticle/drug system, which is then called a photosensitizer.

Among inorganic NPs, we have selected for our investigations, those made of $TiO_2$, due to their availability, stability, non-toxicity, potential to modify particles surface, but also photo-responsivity, and its properties will be discussed in the next paragraph, with the focus on the photodynamic therapy.

The inorganic NPs, which are photo-responsive, can serve as a source of photogenerated charges that interact with the electronic properties of the biomolecules. The linking of inorganic NPs with (bio)molecules facilitate hole transfer across the interface, establishing efficient crosstalk between the (bio)molecule and metal oxide NPs. These photoactive bioinorganic conjugates have properties that make them good for light induced manipulation of biomolecules and their switching functions (Rajh et al., 2004).

$TiO_2$, which will be presented also later in this review, is typical n-type semiconductor material, with many good properties, such as cost-effectiveness, chemical and photo-stability, and excellent biocompatibility in the dark. Besides photo catalysis, energy storage system development and energy conversion, sun screening and sensor research, $TiO_2$ has a wide application in medical fields, too. It can be applied as anti-cancer agent, implant and a substrate for stem cell expansion (Hamidi et al., 2017; Oliveira et al., 2017; Sims et al., 2017).

## Quantum dots

QDs are semiconductors nanocrystals with size between 1-10 nm, which have unique and tunable absorption and emission properties, depending on their size and shape. For instance, they have large transition dipole moment, so can be precisely tuned from the UV to the infrared region (Lucky et al., 2015). Some of them exhibit photoluminescence or fluorescence (semiconductor quantum dots, e.g., CdSe, CdTe, CdTeSe/ZnS) (Gozuacik et al., 2014).

Structurally, QDs consist of a metalloid crystalline core and a “cap” or “shell” that shields the core, and further assignation of coatings or functional groups to the QD core–shell can give QDs a desired bioactivity. QDs` core consists of the metal complex which defines the structure group that particular QD presents. For example, the group III–V series QDs are composed of indium phosphate (InP), indium arsenate (InAs), gallium arsenate (GaAs) and gallium nitride (GaN) metalloid cores, and group II–IV series QDs, of zinc sulfide (ZnS), zinc–selenium (ZnSe), cadmium–selenium (CdSe), cadmium–tellurium (CdTe) cores and heavier structures such are CdTe/CdSe, CdSe/ZnTe) and hybrids composed of lead–selenium (PbSe). Regarding QD toxicity, it depends on multiple factors: QD size, charge, concentration, outer coating bioactivity (capping material, functional groups), and oxidative, photolytic, and mechanical stability have each been shown to be determining factors in QD toxicity (Hardman, 2006).

In biological systems, QDs have been investigated for the application mostly in cancer treatment, theranostics, cancer drug delivery, photothermal and photodynamic therapy. The ability of fluorescence emission of QDs, make some of them good imaging agents. Furthermore, photoluminescent properties of QDs have been exploited in the other fields of application, such as in analytical chemistry in environmental monitoring, pharmaceutical and clinical analysis and food quality control (Frigerio et al., 2012).

## Magnetic nanoparticles

The advances in the synthesis of biocompatible magnetic NPs in a reproducible way, allowed extensive research and further development of drug delivery systems based on magnetic field as an external driving and control force. Applications of magnetic NPs in biomedical areas, on the other hand, require the use of magnetic colloids, which consist of a suspension of magnetic particles of nano sizes in a carrier liquid like water, with usual particle concentrations in the range of $10^{21}$-$10^{23}$ particles/$m^3$ (Goya et al., 2008).

Magnetic iron oxide NPs are the most widely used NPs with magnetic properties, and there are various trade names for super oxide and ultra-small super oxide variations in structure (Shadab et al., 2015). Usually, inorganic nanoparticle core is coated by a suitable coating material, which increases the stability and solubility of the nano-drug conjugate, leading to higher rates of biocompatibility and aqueous stability in the saline environment of biological tissues. Feridex is an example of this commercially available iron NPs, which are coated with sugars (e.g. dextran) (Cherukuri et al., 2010). The enrichment of magnetic NP surface, for instance with $SiO_2$, can allow direct functionalization making it more suitable for biomedical application (Radović et al., 2015).

The other group of compounds with magnetic properties, facile synthesis and chemical stability, are ferrites of the general formula $MFe_2O_4$ where M = Fe, Mn and Co. Some ferrites exhibit additional

properties making them even more suitable for application in the biological systems, for instance, cobalt ferrite, $CoFe_2O_4$ binds strongly to serum albumin proteins (Amiri et al., 2017).

## Inorganic nanoparticles controlled drug delivery systems: Applications for anti-cancer therapy

In recent years, a combined nanotechnology – drug delivery systems have been developed by two components within the general formulation, nanocarrier/drug complex. The purpose of the nano-drug conjugation is to allow modification of the pharmacokinetics and metabolism of the drugs, particularly regarding reducing the side effects, such as non-selective toxicity to tumor cells and inactivity against drug-resistant cell lines (Llevot & Astruc, 2012). The drug delivery system with nanocarrier has even more advantageous properties, such as better encapsulation, bioavailability, lower toxic effects to the healthy tissues and possibility for controlled release (Pandey, 2017). In such manner, some of these features are related to each other. As instance, the encapsulation of the drug in the nanocarrier prevents quick elimination by the reticuloendothelial system, which consequently leads to higher levels of blood circulation and to increased rates of the transport through biological barriers. The final outcomes of these processes are better availability of drug at the targeted tissue and lower toxic effects to the healthy tissues. Moreover, in the focus of the researches is to develop the drug delivery system which is capable of maintaining constant concentration gradients by continuous and controlled release of therapeutic drugs.

These unique chemical and biological properties of the nanocarriers are linked to the NPs large surface area-to-volume ratio, as discussed above. This property allows them to combine, absorb and hold other compounds like drugs molecules, DNA, RNA, proteins (Shadab et al., 2015). Additionally, surface modification can enable the increase of the circulation time in the body, cell specific targeting and membrane permeability. By interacting with biomolecules placed on the cells surface and inside the cells, penetration into the tissues is promoted with the higher levels of specificity. Furthermore, it is possible to develop the advanced NPs drug delivery systems for the spatially and temporally controlled release of drugs in response to specific stimuli within the tumor microenvironment (Yin et al., 2013).

A stimuli-responsive delivery system improves the efficacy of the drug, and can be designed to react to the disease specific property (pH level, redox property or enzyme levels). Drug accumulation and release at the tumor site can be additionally intensified by external forces like magnetic field (Arruebo et al., 2007; Shadab et al., 2015), light (Mari et al., 2014; El-Hussein et al., 2015; Nešić et al., 2017) and/or heat (Cherukuri et al., 2010).

To date, there are only a few clinically approved nanocarriers that incorporate molecules to selectively bind and target cancer cells, and these drug delivery systems are mostly based on organic nanocarriers, such as liposomes and polymers, free or attached to proteins (López-Dávila et al., 2012). Inorganic nanocarriers, on the other hand, are much smaller, and the active form is usually simple metal based structure with gold (Brown et al., 2010), silver (Conde et al., 2012), carbon (Pastorin et al., 2006; Cho et al., 2008), oxides (mesoporous $SiO_2$, $TiO_2$, $Fe_2O_3$, graphene oxide) (Goya et al., 2008; Tasciotti

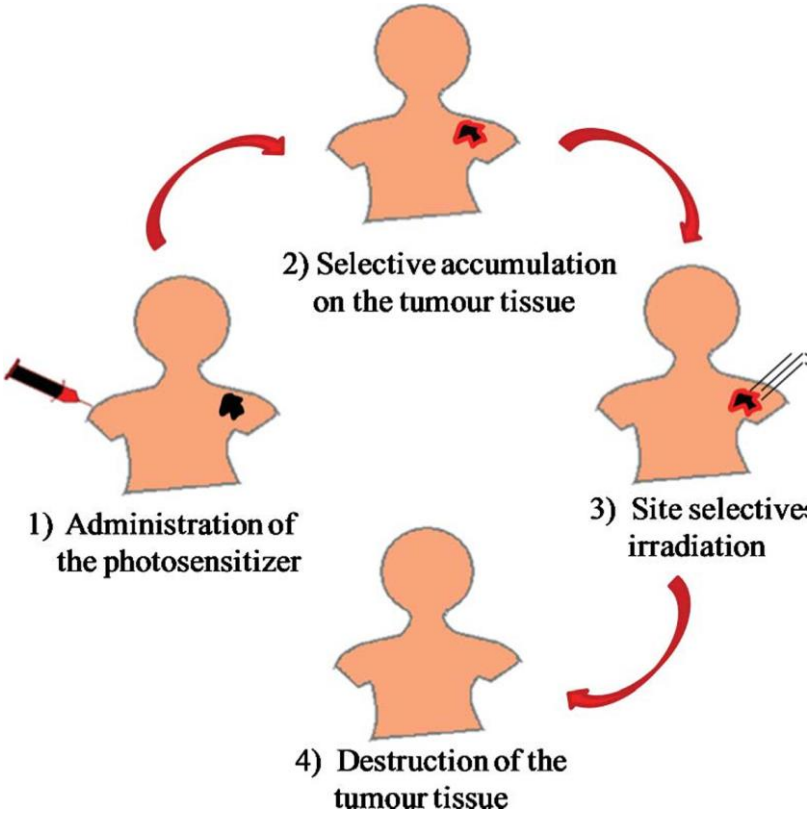


**Fig. 3.** Schematic representation of various stages involved in PDT. Reproduced with permission from the authors Avirah et al. (2012)

et al., 2008; Nešić et al., 2016; Nešić et al., 2017), or in the form of QDs (selenides, sulfides or tellurides of metals like cadmium, lead or zinc) (Sperling & Parak, 2010; Chen et al., 2014). Different designs varying in size, shape, and porosity allow easy conjugation with drugs for cancer therapy (Bhattacharyya et al., 2011) and they are more stable over large ranges of pH and temperature (Shadab et al., 2015).

## Photo-sensitive systems for drug delivery

Optical energy can trigger a variety of photochemical processes useful for therapies. It is the raising field in the development of new therapeutic approaches in the last decades. Photodynamic therapy (PDT) involves the administration of a tumor-localizing photosensitizer (PS), usually NP, which undergoes reversible changes upon light exposure of a specific wavelength. The induced changes in such manner, can lead to the release of therapeutic drugs, thereby providing spatio-temporal control of drug release (Shadab et al., 2015), or the excited PS can transfer its energy to molecular oxygen, thus generating cytotoxic reactive oxygen species (ROS) and singlet oxygen, which can modify cellular macromolecules leading to tumor cell ablation (Lucky et al., 2015). Simplified schematic representation of the stages involved in PDT, is shown in **Fig. 3**.

Inorganic, metallic, or composite NPs have been investigated as multifunctional carriers for PDT due to their unique characteristics such as optical properties and tunability in its shape, size, porosity, and that they may not degrade readily in the biological systems. It is also reported that the degree of drug resistance is far less than those encountered in chemotherapy, and that there is no cross-resistance between PDT and chemotherapy (Kim et al., 2015)

The most promising PSs are nanosized oxides, which exhibit distinctive optical absorption properties, transparency of the matrix to light absorption and chemical inertness. They can be easily attached to therapeutic medicament in the form of nanocomposite system, which can exhibit greater cytotoxicity (Nešić et al., 2017) and higher therapeutic effectiveness for cancer than the corresponding free drugs (Chen et al., 2011; Wang, Y. et al., 2015).

The most investigated NPs/metal oxides are mesoporous silica (Teng et al., 2013), titanium dioxide (Nešić et al., 2016) and zinc oxide (Zhang et al., 2014).

$TiO_2$ NPs are specially interesting as, upon ultraviolet (UV) light excitation, they absorb the energy higher than its own band gap energy (3.2 eV), which leads to excitation of the electrons from the valence to the conduction band, creating the electron/hole pairs and further generating active free radicals, thus allowing oxidation/reduction of species in surrounded medium. $TiO_2$ itself was reported to have a good anticancer effect in response to the light, owing to the production of active free radicals under UV irradiation (Wang, T. et al., 2015). In addition, the incomplete coordination sphere of the surface metal atoms exhibits the high affinity of $TiO_2$ NPs for linking with biomolecules and oxygen-containing ligands (Rajh et al., 2004).

While $TiO_2$ NPs with the anatase crystalline phase absorb UV light and consequently generate ROS, great chemical stability and minimal cytotoxicity of $TiO_2$ NPs are detected in the dark. In comparison with traditional organic photosensitizers, $TiO_2$ NPs can be maintained for a longer time in the body. Even $TiO_2$ NPs possess high photosensitization activity toward various cancer cell lines, for the suppression of *in vivo* tumors there are characteristics that need to be improved, as low penetration into tissue and the damage to normal tissue (Hou et al., 2015).

In the study of nanocomposite system based on $TiO_2$ NPs and daunorubicin, MTT assay have confirmed significant cytotoxicity when leukemia cell line, K562, was treated with the nanocomposite system, while low cytotoxicity was shown when K562 cells were treated solely with $TiO_2$ NPs, and thus $TiO_2$ NPs demonstrated important properties of a drug carrier and showed good potential for the applications in cancer therapy (Zhang et al., 2012).

In a similar study, it was demonstrated that the nanocomposite system made of $Pt(NH_3)_4Cl_2$ transitional metal complex and $TiO_2$ NPs, as well as individual components, lead to a significant decrease in C6 glioma cell proliferation; the reduction in the tumor volume was also confirmed (López et al., 2008).

In our previous work we studied *in vitro* light stimuli-responsive properties of nanocomposite system based on the colloidal $TiO_2$ NPs and transitional metal complex, cis-dichlorobis(2,2′-bipyridyl-4,4′-dicarboxylic acid)ruthenium(II). The system had the light controlled release properties, as the release of the complex was facilitated upon illumination with UV light, and sustained upon illumination with visible light. Results obtained by the investigation of the nanocomposite system cellular cytotoxicity towards melanoma cancer cells line A375 were in agreement with in vitro drug release test: while the nanocomposite system and its components exhibited the significant decrease of the cell viability upon UV irradiation, red light irradiation showed an extremely low anti-cancer effect (Nešić et al., 2017).

## Inorganic nanoparticles and tissue imaging

Inorganic NPs including semiconductor QDs, iron oxide NPs, and gold NPs have been developed as contrast agents for diagnostics by molecular imaging (Huang et al., 2011; Yu & Zheng, 2015). Compared to traditional contrast agents, NPs offer several advantages: their optical and magnetic properties can be tailored by engineering the composition, structure, size, and shape; their surfaces can be modified with ligands to target specific biomarkers of disease, as mentioned in the Introduction section. The contrast enhancement provided can be equivalent to millions of molecular counterparts; and they can be integrated with a combination of different functions for multi-modal imaging (Cho et al., 2010).

Broadly, the field of biomedical imaging can be divided into categories based upon the electromagnetic spectrum as shown in **Fig. 4**. Molecular imaging is a new frontier of biomedical research for visualizing, characterizing, and monitoring biological processes in cells, tissues, and organisms using sensitive instrumentation and contrast mechanisms. Molecular imaging differs from traditional imaging in that way in which the contrast agents are typically utilized to help identify particular biomarkers or pathways with high sensitivity and selectivity (Cho et al., 2010), and for that purposes, inorganic NPs is an actively explored technology for the development of contrast agents. This imaging function based on interrogation of biological processes to report on and reveal the molecular abnormalities that might point to a disease, being thus a powerful tool for the diagnosis of cancer, cardiovascular syndrome, or neurological disorders.

Imaging based on ionizing radiation generally refers to the detection of high frequency emissions from radioactive elements such as the gamma ray emitters $^{111}$In or $^{99m}$Tc (metastable nuclear isomer of technetium-99) or the passage of X-rays through the body. The main technologies involved are positron emission tomography (PET), single-photon emission computed tomography (SPECT), and X-ray computed tomography (CT). Magnetic resonance imaging (MRI) tends to operate on the other end of the spectrum in the MHz frequency range, relying upon contrast agents such as gadolinium or superparamagnetic iron oxide to modify the relaxivity of water molecules to provide soft tissue contrast (Pansare et al., 2012).

Compared with other imaging approaches, optical imaging is a versatile, economic and efficient modality for bio-imaging with high sensitivity, great choice for probe selection and it does not require precaution, like in the case of application of X-rays or other ionizing radiation. Various fluorescent molecules or nanomaterials, such as conventional organic fluorescein, semiconductor QDs, rare-earth co-doped up-conversion nanophosphors, etc., have been explored to label and image cancer cells both *in vitro* and *in vivo*. Integrating mesoporous silica with fluorescent materials towards multifunctionalization could endow them with simultaneous optical bio-imaging and drug transport capabilities (Chen et al., 2013).

There are numerous efforts to combine the unique advantages which nanoprobes have in cancer imaging, and to create a "universal" nanoprobe. Such nanoprobe should be multimodal, have a strong EPR (Electron Paramagnetic Resonance) effect, able to circulate in a body for a long time (Bouccara et al., 2015), be stable in physiological conditions, specific for target tissue, and not to interfere with physiological processes. Most inorganic NPs can meet some criteria, but one of the most challenging is the avoidance of renal clearance, which enables the prolonged blood circulation, and afterwards, accumulation in target, or tumor tissues. Some examples of inorganic NPs for various molecular imaging purposes are given below in the text, classified according to their purpose, i.e. imaging technique (Yu & Zheng, 2015).

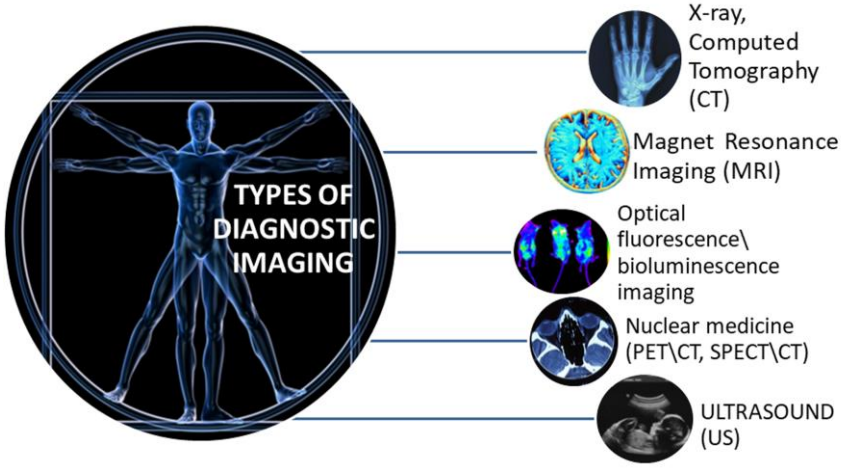


**Fig. 4.** Types of medical imaging: ionizing radiation (X-ray and CT), magnetic resonance imaging (MRI), ultrasound and optical imaging

## Major inorganic nanoparticles for molecular imaging

Contrast agents for various imaging purposes should be easy to design but it is required for them to have particular electrical, magnetic and optical properties. Their properties can be fine-tuned by tailoring NPs` composition, geometry and structure. Therefore, particles can be composed of metals, metal oxides, semiconductors, they can vary in size and shape, and be solid, or hollow. Some of NPs used in imaging techniques are iron oxide NPs, QDs, gold NPs, and others, which can be used in different imaging approaches (Cho et al., 2010; Huang et al., 2011; Chen et al., 2013; Bouccara et al., 2015; Yoon et al., 2017), and most inorganic NPs possess great potential for noninvasive and real-time *in vivo* diagnosis of disease (Chen et al., 2013).

In terms of magnetic resonance imaging (MRI), both, magnetic or superparamagnetic NPs can be used as contrast agents. Among them, iron/based NPs are routinely applied because they were approved by FDA for human use (Yoon et al., 2017). However, a caution is needed regarding the size of NPs for MRI. In general, reducing a size of ferro- or ferrimagnetic particles below critical, could lead to randomization of the magnetic dipoles in a short period of time, as a thermal energy becomes comparable to what is needed for spins to flip. Those NPs are superparamagnetic, because they do not have permanent magnetic moments in the absence of an external field, but they can quickly respond to it when applied (Cho et al., 2010).

QDs are currently replacing fluorescence dyes, because they have high absorption coefficients and broad emission range in visible and near infrared region (Cho et al., 2010). Gold NPs are also utilized in optical imaging, thanks to their optical properties, i.e. presence of strong extinction peaks in visible and near IR region (Pansare et al., 2012). Those extinction peaks are caused by the collective oscillations of conduction electrons in the presence of an incident light. This phenomenon is known as localized surface plasmon resonance. In addition, gold NPs can be used as contrast agents for CT imaging, due to their absorption coefficient for the X-rays, but also, they are capable of photoluminescence. Finally, gold NPs can enhance the intensity of Raman-active molecules and be used for the surface-enhanced Raman spectroscopy (Cho et al., 2010; Huang et al., 2011).

A particular class of NPs are rare-earth doped NPs, which exhibit sharp emission peaks, long fluorescence lifetimes, high quantum yields, and excellent photostability (Cho et al., 2010; Bouccara et al., 2015).

## Applications of inorganic nanomaterials in analytical (bio)chemistry

NPs have been used as an auxiliary tool to increase sensitivity and specificity of standard analytical methods. One of earlier applications of inorganic particles, was the use of magnetic particles (beads) in the affinity chromatography, in which the antigen was bound to the surface of a particle, and after specific and selective interaction with a component from a complex solution magnetic NPs could be easily collected and separated from the mixture (Chen & Chen, 2005). Also, NPs are used as the stationary phase in several chromatographic techniques, where they increase the active surface available for the interaction with analytes. In this chapter, the overview of inorganic NPs and their application in chromatography and mass spectrometry will be given and discussed.

### Chromatography

The application of NPs and nanomaterials in chromatography has been of great interest in recent years due to the unique physical properties of these substances, their large surface area-to-volume ratios, and their ability to be employed with a variety of surface chemistries (Guihen, 2013; Tang et al., 2014; Zhang & Qiu, 2015; Castillo-García et al., 2016). A number of carbon-based nanomaterials and inorganic nanomaterials have been considered for use in LC, some examples are: carbon nanotubes, fullerenes and nanodiamonds (Valcárcel et al., 2007; Scida et al., 2011; Guihen, 2013; Pyrzynska, 2013; Speltini et al., 2013; Zhang et al., 2013), metal NPs and nanostructures based on silica, because of their relatively high surface area, availability in various particle sizes and pore diameters, and the ease with which surface can be modified to contain a wide range of functional groups to increase specificity and sensitivity of detection and separation (Zhang et al., 2006). These properties have led to the use of silica NPs and related materials (e.g., silica nanofibers) in making stationary phases or supports for such methods as reversed-phase chromatography, HILIC, and UTLC (Ge et al., 2006; Jim et al., 2011; Newsome & Olesik, 2014; Aydoğan & El Rassi, 2016), alumina, zirconia and titanium dioxide (Zhang et al., 2006; Nesterenko et al., 2013).

Application of these nanomaterials have included the reversed-phase, normal-phase, ion-exchange, and affinity modes of LC, as well as related methods such as chiral separations, ion-pair chromatography and hydrophilic interaction liquid chromatography.

**Mass spectrometry**

Small molecules – metabolites (molecular mass less than 1000 Da) are significant for understanding of cellular processes and metabolism, and their importance is reflected in the development of relatively new discipline, called metabolomics. The metabolome represents the large scale qualitative and quantitative changes of all metabolites in a biological cell, tissue, organ or organism, which are the end products of cellular processes. This is of high importance for the understanding of biological processes. Metabolomics combine strategies for identification and quantification of metabolites with different analytical approaches and statistical methods, and the great efforts are made for their development. Metabolites are involved in different cell processes e.g. cell signaling which controls cell division, growth and differentiation.

Another very important and diverse group of small molecules are drugs. Qualitative and quantitative analysis of drugs (especially their biodistribution) is essential for the drug discovery, monitoring and understanding of their mechanism of action and pharmacological and toxicological effects (Monro, 1994; Mizojiri et al., 1996). Method that is routinely applied for detection and analysis of drugs is autoradiography, which for qualitatively and quantitatively investigation of the drugs in the tissues requires radioactive materials, and the procedure is rather time consuming.

Other methods that are in use for the detection of small molecules are: High-Performance Liquid Chromatography, HPLC (Araki & Sako, 1987; Rafii et al., 2007), capillary electrophoresis, CE (Caussé et al., 2000; Bayle et al., 2002), gas chromatography/mass spectrometry, GC/MS (Larsson & Lindgren, 2005), SERS (Pietzsch et al., 1997) and fluorescence spectroscopy (Ling et al., 1991). These techniques are time consuming, and additional methods for the sample preparation and additional derivatization are needed. Some of these methods have additional disadvantages such as low selectivity and low sensitivity for the detection of small molecules in biological samples.

Matrix assisted laser desorption and ionization time of flight mass spectrometry (MALDI TOF MS) is powerful technique that is traditionally used for the analysis of large, non-volatile, and termolabile biomolecules and biopolymers (proteins, DNA, saccharides). In this method, organic matrices are traditionally in use, like 2,5-dihydroxybenzoic acid (DHB), 9-aminoacridine (9-AA), 2′,4′,6′-trihydroxyacetophenone (THAP), α-cyano-4-hydroxycinnamic acid (CHCA), sinapic acid (SA). In theory, MALDI TOF can be used for the semi-quantitative mass analysis of all kind of molecules, but in practice that is not a case because of numerous disadvantages which are consequence of the use of organic matrices. Firstly, inhomogeneous distribution of samples molecules between matrix molecules (*hot spots*, *cold spots*) (Tholey et al., 2006; Jaskolla et al., 2009; Kuzema, 2011) lead to the mass spectra with poor quality, and eventually the reproducibility and the repeatability of a method is low. Second drawback refers to the analysis of small molecules; organic matrices have low molecular masses and the high number of signals in the low mass range (usually less than 500 Da) which interfere with sample signals. Matrices are usually organic acids and they have intensive signals in negative ion mode, so it is very difficult to detect the negative ions of samples (Petković et al., 2001a; Petković et al., 2001b). Another disadvantage is that the organic matrices do not tolerate high concentrations of salts. Biological samples have high concentrations of inorganic salts, and because of that the great number of matrix signals are present in spectra and the signals arising from the analytes are with underestimated intensity if not completely suppressed.

To overcome listed disadvantages of organic matrices, the inorganic matrices/substrates are much more in use. Wei et al. (1999), were synthesized porous nanostructures based on silicon (Desorption and ionization on silicon, DIOS). The term SALDI the first was used by Sunner et al. (1995), when replaced organic matrices with graphite, and refers to the techniques that use nanostructured substrates instead of organic matrices. Different inorganic materials which absorb ultraviolet light were used as substrates for SALDI: carbon (Chen & Chen, 2006; Kawasaki et al., 2009; Tang et al., 2009; Dong et al., 2010), silicon (Hu et al., 2007; Northen et al., 2007; Teruyuki et al., 2007; Guénin et al., 2009; Walker et al., 2010; Cheng et al., 2012), nanomaterials based on metals and metal oxide (Chen & Chen, 2004; Chen & Chen, 2005; McLean et al., 2005; Okuno et al., 2005; Chen & Chen, 2006; Huang & Chang, 2006; Wu et al., 2007; Kailasa et al., 2008; Kawasaki et al., 2008; Sherrod et al., 2008; Chen et al., 2009; Chiang et al., 2010b).

Substrates based on metals and metal oxides have additional advantages compared to substrates based on silicon and carbon. These substrates are more chemically stable in the air and have high conductivity (Chen & Chen, 2004; Arakawa & Kawasaki, 2010), the samples are NPs based on Au, Pt, Ag, ZnO, Fe and $MnO_2$/$MnO_3$. Different inorganic NPs are in use in analytics of different biological molecules and samples: Sherrod et al. (2008) describe selective ionization of olefin compounds (cholesterol and carotenoids) direct from

the mixture with silver NPs. Wu et al. (2007) were analyzed and quantified small, neutral carbohydrates from urine with gold NPs. Lee at al. (2007) found that $TiO_2$ NPs with diameter less than 20 nm interact with enediol compounds, which have an impact on increase of absorptivity in UV-Vis spectra of light. Chiu et al. (2008) analyzed urine samples for the detection of estrogen hormones – estrone, estradiol and estriol with silver NPs of a diameter (34 ± 3) nm. Watanabe et al. (2008) were used ZnO NPs that have anisotropic shapes, such as cubic or rectangular parallelepiped, for the detection of verapamil hydrochloride, testosterone, phospholipids, oligosaccharides and synthetic polymers. Semiconductor ZnS NPs with surface modification with different functional groups were used for the analysis of cyclodextrin and small proteins (Kailasa et al., 2008). Arakawa & Kawasaki, (2010) used oxidized graphitized carbon black (GCB) particles for the analysis of pharmaceutically active compounds. A common pharmaceutical compound, propranolol, was successfully extracted from Baltic Sea blue mussels and quantified using oxidized GCB.

$TiO_2$ is a good candidate for SALDI mass spectrometry, because it is readily available, non-toxic and efficiently absorb UV light of $N_2$ laser in MALDI instrument. It is first shown applicability of sol-gel $TiO_2$ films (Chen & Chen, 2004), and then applicability of $TiO_2$ NPs (Radisavljević et al., 2012), nanotubes (Lo et al., 2008) and nanowires (Kim et al., 2014) in SALDI analysis of biomolecules. The example of positive ion spectra obtained by SALDI method in which $TiO_2$ served as a substrate is shown in **Fig. 5**.

Scarce data were found in literature about tolerance of substrate on high concentration of salts in samples solutions. Popović et al. (2015) have shown that the quality of mass spectra of transition metal complexes obtained with $TiO_2$ NPs was idependent of the high concentration of sodium and potassium ions.

Size and shape of nanocrystals have impact on analytical performances and ionization efficiency in SALDI mass spectrometry (Popović et al., 2016; Popović et al., 2016a; Popović et al., 2016b). $TiO_2$ nanocrystals with various shapes and sizes, such colloidal $TiO_2$ NPs (NPs, average diameter ~ 5 nm), prolate nanospheroids (PNSs, length: 40–50 nm, the lateral dimension: 14–16 nm) and nanotubes (NTs, length: 100-150 nm, average diameter 11 nm), were investigated substrates for SALDI-TOF MS for quantitative analysis of small biomolecules such as various sex hormones (testosterone and progesterone), vitamins (vitamin A and E), carbohydrates and others (Popović et al., 2016; Popović et al., 2016a). In general, the best reproducibility was obtained with the larger nanocrystals, PNSs and NTs, making them good candidates for the quantitative determination of small molecules. However, for analysis of citric acid, dexasone, vitamins E and A, PNSs provided the highest sensitivity and reproducibility (Popović et al., 2016b).

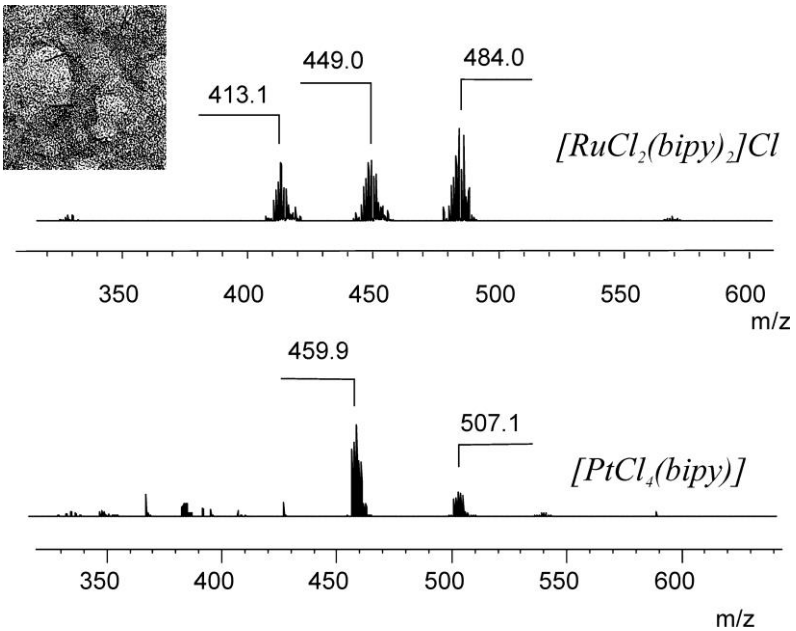


**Fig. 5.** Positive ion SALDI TOF mass spectra of inorganic complexes: the upper spectrum represents the spectrum of Ru-complex, whereas the bottom is the spectrum of Pt-complex. The spectra are acquired with the assistance of $TiO_2$ NPs with diameter of 5 nm. Transmission electron micrograph of $TiO_2$ NPs is given in the upper left corner of the figure. Reproduced with permission (Popović et al., 2016).

## Future use of nanomaterials in analytics of (bio)molecules – a summary

Inorganic particles often exhibit improved and some novel properties as their size approaches nanometer scale dimensions. The unique electronic and optical properties of nanocrystals may lead to future advances of analytical (bio)chemistry, biology, for investigation of biological processes and in medicine. Their additional and important application is the development of novel therapeutical approaches. In terms of therapy, novel NPs and activators are expected to be exploited. The challenge is to further minimize the side effects and involve

light (and potentially other stimuli) in therapy of deep tumors.

In terms of imaging, the future challenge is to target specifically a single molecule by a NP. One of advanced imaging approaches is mass spectrometry imagining which is a rapidly growing field, which uses nanotechnology (either for production of targets or for the interaction with molecules within the cell/tissue) for the visualization of molecules in tissues, based on the identification of molecules on ions generated. One of the problems with which is this approach facing is lateral resolution in cells and still, despite of the creativity of scientists, is not easy to visualize the intracellular content by this method. However, the potential of new materials and nanocomposites in those fields is yet expected to be exploited in the future.

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