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Application of Nanotechnology in Medicine. Smart Biomaterials and Biosensors

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ABSTRACT

Nanomaterials have found a wide field of application in medicine in terms of diagnosis, tracing, and treatment. This nanomedical technology involves drug delivery couriers, in vivo medical imaging, in vitro diagnostics, therapeutic techniques, biomaterials and tissue engineering products. In nanobiomedicine, tissue engineered scaffolds establish a tissue specific nanoenvironment to maintain and regulate cell behavior and function. Nanoscaffolds play a vital role in storing, releasing and activating a wide range of biological factors, along with aiding cell-to-cell communication and cell-soluble factor interaction. Certain fabrication methods such as self-assembly, phase separation, and electrospinning technology form 2D and 3D nanopatterns that play different roles in cell manipulation and functional tissue formation. Localized and controlled delivery of biological factors, response to certain stimuli, degradation rate of the nanomaterials and reproduction of the forming tissues, are issues with emerging research.

Recently, nanotechnology has revolutionized the development of biosensors. The transduction mechanisms have been significantly improved with the use of nanomaterials and nanostructures. Hybrid nanostructures, quantum dots, nanoparticles for enzyme immobilization, are widely used for the merging of chemical and biological sensors. The application of these nanomaterials for sensing several key pathways and regulatory events made the overall process fast, easy to execute, and better in terms of performance providing a friendly and result-oriented experimental support. Nanobiosensors are highly versatile and multifunctional so they can find application in broad biomedical and environmental fields.

KEYWORDS: Nanobiomedicine, smart biomaterials, nanomaterials, nanobiosensors.

1. Nanobiomedical technology

The engineering of human tissues to cure diseases is an interdisciplinary and a very attractive field of research both in academia and the biotechnology industrial sector. Three-dimensional (3D) biomaterial scaffolds can play a critical role in the development of new tissue morphogenesis via interacting with human cells.

Biomaterials after implantation experience a tremendously dynamic environment in physiological complexes that demand better techniques and meth-

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TABLE 1.

Nanobiomedicine applications

- Scintillation crystal materials for medical PET imaging devices
- Multimode imaging
- Intelligent nanoscale contrast agents for imaging and treatment
- Early cancer diagnosis
- Molecular diagnostics and disease pathology
- Drug storage, targeting and delivery
- Nanotech approaches to drug design
- Biologicals and targeted therapies
- Biological basis of compound activity
- Pharmacology and toxicology of nanoparticles
- Using biological building blocks to create novel materials and devices
- Mechanics of biological and bioinspired materials
- Using materials to probe, alter, and control biological responses
- Understanding biological responses to implanted or injected materials
- Gene delivery

Nanobiomedicine developing research fields

- Computational biology
- Developmental biology
- Cancer Research
- Stem Cells
- Biosurfaces and biointerfaces
- Cellular transport
- Protein-protein interactions
- Subcellular targeting
- Simulation of biological systems
- Systems approaches
- Genome analyses and techniques
- Cellular and molecular dynamics
- Medical diagnosis and treatment
- Placental Studies
- Drug kinetics
- Gene therapy
- Ethnics and legislation

All values are presented as mean±SD

odology to monitor (a) their molecular interactions with the host, (b) their biodegradation to structural integrity changes, and (c) their effect on functional tissue formation. Simple polymeric biomaterials act as scaffold and provide mechanical and physical properties required for tissue ingrowth. However, they provide insufficient biomimetic property and lack of interactions with human progenitor cells for the promotion of functional tissue formation. Therefore, the development of advanced functional biomaterials that respond to stimuli is the next choice to generate smart 3D biomimetic scaffolds, actively interacting with human stem cells and progenitors along with structural integrity to form functional tissue within a short period.

To date, the use of nanotechnology offer the design of smart biomaterials that interact with biological systems for a wide range of biomedical applications, from the delivery of bioactive molecules and cell adhesion mediators to cellular functioning for the engineering of functional tissues to treat diseases. (**Table 1**) Therefore the rational design of smart biomaterials and their creation in an economically viable route remain an interesting and upcoming field.

1.1 Nanomaterials and their applications in nanomedicine

Nanomaterials are defined as materials composed of natural or synthetic components with at least one dimension ranging between 1-100nm. The predominance of quantum mechanical phenomena at the nanoscale produces unique surface and bulk properties that do not manifest at larger scales. These have been used in a wide range of biomedical applications. This nanobiomedical technology includes: (1) drug delivery couriers, (2) in vivo medical imaging, (3) in vitro diagnostics, (4) therapeutic techniques, (5) biomaterials and (6) tissue engineering products. [1-3]

(1) Drug delivery. Nanoscale delivery vehicles can enhance the therapeutic efficacy and minimize adversities associated with available drugs, enable new classes of therapeutics, and encourage the re-investigation of pharmaceutically suboptimal but biologically active new molecular entities that were previously considered undevelopable

(2) In vitro diagnostics. Nanotechnology-based sensors (nanowires, nanotubes, nanoparticles, cantilevers, and micro-/nanoarrays) can enable fast and high throughput detection of disease biomarkers with higher sensitivity and lower sample consumption. It is also promising for the early detection of viruses, bacteria, and circulating tumor cells, as well as for single cell analysis.

(3) In vivo imaging. Nanoprobes (magnetic nanoparticles, quantum dots, and carbon nanotubes) pro-

TABLE 2.

Smart biomaterial for cellular/TE applications that respond to various types of stimuli (PEO= polyethylene oxide, PO=polypropylene oxide, DOX=doxorubicin, T=temperature)

Poly N-isopropylamide	T	Patterned cells seeding and co-culture
PEO-PO-PEO	T	Tissue engineering for cartilage formation
PNIPAm-Arg-Gly-Asp	T	Controlling osteoblasts adhesion and proliferation
Poly(2propylacrilic acid)	pH	Protein/DNA intercellular delivery
Chitosan/Polyethyleneimine (CS/PEI) blend	pH	Scaffold for cellular functioning and cartilage tissue engineering
Self-assembling peptide	T	Neural tissue engineering. Dermal fibroblasts growth and proliferation.
Azobenzen	Light	Human umbilical vein endothelial cells
Spiropyran	Light	Cell capture and release
Poly(2Acrylamido-2-methyl-propane-sulphonic acid-co-N-butylmethacrylate)	Electric Field	Controlled delivery of drug and cells
Poly(N-isopropylamide-acrylamide-chitosan) (PAC)-coated magnetic nanoparticles (MNPs)	Magnetic field, T, pH	Human dermal fibroblasts and normal prostate epithelial cells culture and cancer drug delivery
Poly(6-)-methacryloyl-D-galactopyranose)-SS-poly(γ-benzyl-S-glutamate) (PMAgala)-SS-PBLG)	Redox reaction	DOX delivery and human hepatoma cell receptor targeting
Poly(ethytlene-glycol)-Poly-acrylate	Light	Human mesenchymal stems cells (MSCs) growth, proliferation and chondrogenic differentiation
Gold (AU) membrane microchip	Electrochemical	Controlled release in implants
Antibacterial Ti-Ni-Cu shape memory alloys	T	Cellular compatibility (e.g. L929, MG63)

vide a faster, less invasive, and more accurate way to diagnose diseases, especially neoplasmatic pathologies, at their earliest stages and monitor disease progression. Other fields of future application are: (a) reporting in vivo efficacy of therapeutics, (b) tracking nanocarrier bio-distribution in the body, (c) helping surgeons to locate tumors and their margins, (d) identify important adjacent structures, and (e) mapping sentinel lymph nodes.

(4) Therapeutic techniques. Certain nanomaterials have unique therapeutic properties that differ from conventional drugs, and can, therefore, be directly used to treat diseases. It is proved that hafnium oxide- and gold-based nanoparticles can greatly enhance X-ray therapy, gold nanoshells/nanorods, carbon nanotubes and magnetic nanoparticles can induce hypothermia to kill cancer cells and finally, nanocrystalline silver is being used as an antimicrobial agent.

(5) Biomaterials. Biocompatible nanomaterials that have optimal mechanical properties can be used as dental restoratives and bone substitutes. Nanocoatings or nanostructured surfaces can also improve the biocompatibility and adhesion of biomaterials.

(6) Tissue engineering. Nanotechnology can enable the design and fabrication of biocompatible scaffolds at the nanoscale and control the spatiotemporal release of biological factors. These biocompatible scaffolds may resemble the native extracellular matrix to direct cell behaviors and eventually lead to the creation of implantable "ready for use" tissues or even organs.

1.2 Nanobiomedical technology for the formation of functional tissues

In normal tissues, cells are surrounded by extracellular matrix (ECM) which is characterized by a natural web of hierarchically organized nanofibers. Early artificial scaffolds were designed to provide cells sup-

TABLE 3.

Nanomaterials used for improving biosensor technology

Nanomaterial used	**Key benefits**
Carbon nanotubes	• Improve enzyme loading • Higher aspect ratios • Ability to be functionalized • Better electrical communication
Nanoparticles	• Aid in immobilization • Better loading of bioanalyte • Better catalytic properties
Quantum dots	• Excellent fluorescence • Quantum confinement of charge carriers • Size tunable band energy
Nanowires	• Highly versatile • Good electrical and sensing properties for bio-and chemical sensing • Better charge conduction
Nanorods	• Good plasmonic materials which can couple sensing phenomenon well • Size tunable energy regulation • Can be coupled with NEMS (NanoElectroMechanical Systems) • Induce specific field responses

All values are presented as mean SD

port and structural integrity on a macroscopic level. In nanotechnology, scaffolds also establish a tissue specific nanoenvironment to maintain and regulate cell behavior and function. Nanoscaffolds play a vital role in storing, releasing and activating a wide range of biological factors, along with aiding cell-to-cell communication and cell-soluble factor interaction. [4,5]

(1) By **emulating the complexity and functionality of ECM**, nano-topographic surfaces and nano-featured scaffolds encapsulate and control the spatiotemporal release of drugs and growth factors and eventually direct cellular behaviors that range from cell adhesion to gene expression. Living cells are highly sensitive to local nanoscale topographic patterns within ECM. The 2D cell-nano-topography interactions enable investigators to direct cell behavior whereas 3D artificial scaffolds exhibit a very similar physical structure to protein nanofibers in ECM. [6]

(2) The 2D and 3d morphology of the designed nanoconstructs plays **significant role in cell manipulation and eventually in functional tissue formation**. [7] (**Fig.1**) The creation of engineered substrates such as nanospheres, nanotubes, and nanofibers as well as various nanopatterns, such as gratings, pillars, and pits with different nanofeatures, have enabled the exploration of cell nanotopography interactions, and the manipulation of cell morphology, signaling, orientation, adhesion, migration, proliferation, and differentiation. (**Fig.2**) Aligned nanofibers and nanogratings can rule the alignment and elongation of many different cell types. Polymer nanogratings, disordered nanopits and vertically aligned TiO2 nanotubes help the differentiation of mesenchymal stem cells. In nanograting substrates the endothelial cells can be organized into multicellular band structures forming aligned capillary-like tubes. [8-12]

(3) The fabrication methods used for the final nanotechnology design is crucial for the role that the nanopattern will assume. *(a) Self-assembly technology*, emulates the process of ECM assembly and can thus produce very thin nanofibers. *(b) Phase separation technology,* allows for continuous fiber network fabrication with tunable pore structure, and the formation of sponge-like scaffolding. *(c) Electrospinning,* is a very simple and practical technique, suitable for the creation of aligned and complex 3D structures. Nanofibers with core-shell structures prepared by electrospinning can be internally loaded with growth factors.

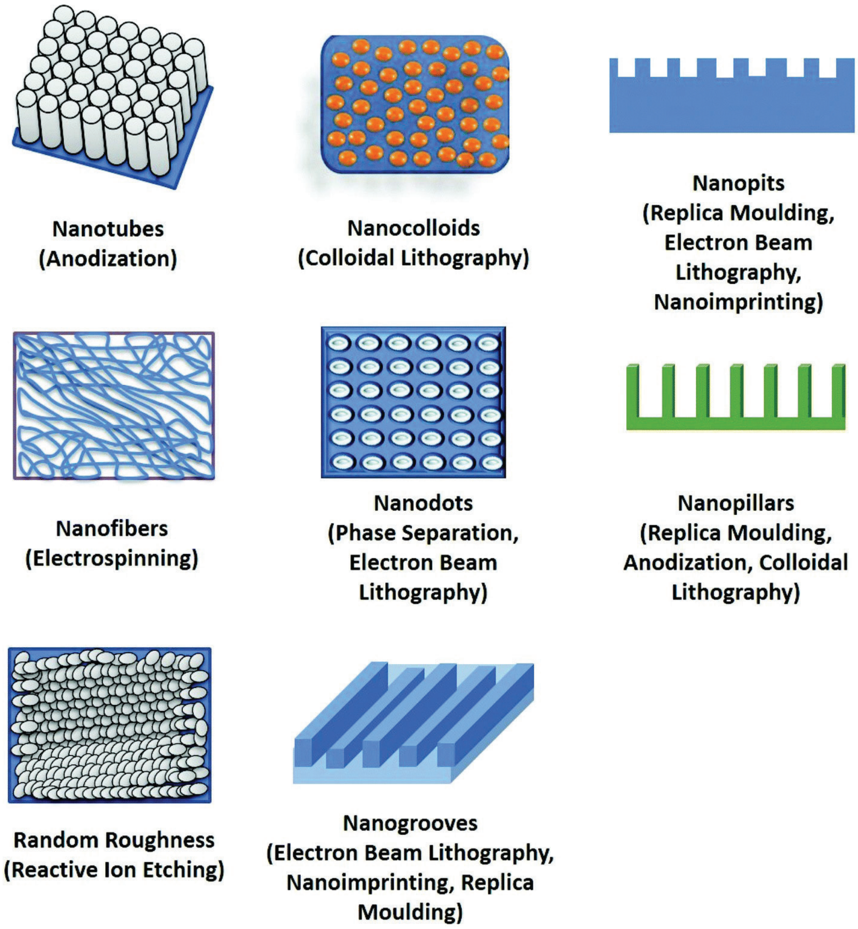

Figure 1. *Schematic of fabricated nanotopographic features used to guide cell behaviors via cell-nanotopography interactions. (Adapted from ref [7])*

Additional adjustments to control the thickness and porosity of the polymer shells will further enhance the release kinetics of growth factors from these particular scaffolds. [13-15]

(4) The key factor for tissue regeneration and growth is **the localized and controlled delivery of biological factors** in the 3D scaffolds. Controlled release of angiogenic factors, such as Vascular Endothelium Growth Factors (VEGFs) and beta-Fibroblasts Growth factors (bFGF) enhance vascularization essential for maintaining continuous blood supply to developing tissues. Controlled release of beta-transforming Growth factors (TGFb-1,2) and Insulin-like Growth Factor-2 (IGF-2) enhance cartilage regeneration. [16]

(5) The next step for the development of smart 3D biomimetic scaffolds is **the use of advanced functional biomaterials that respond to stimuli**. Externally applied stimuli could be changes in pH, temperature or light that will lead to chemical changes of the smart biomaterials. These chemical changes will provide local cells and progenitors with certain signaling, to form functional tissue within a short period. [17] **(Table 2)**

(6) The degradation rate of the smart biomaterials or the secretion rate of growth factors of the stimulated cells is very important for the perpetual function of tissue regenerating or tissue repairing cells. If the degradation rate is too high, the nanomaterial construct will mechanically fail and the cells will stop the protein synthesis and developing extracellular matrix will never be accomplished. If the rate is too low, the cells will never receive the proper amount of stimuli and will never produce the proper amount of extracellular components. The release of factors in a **spa-**

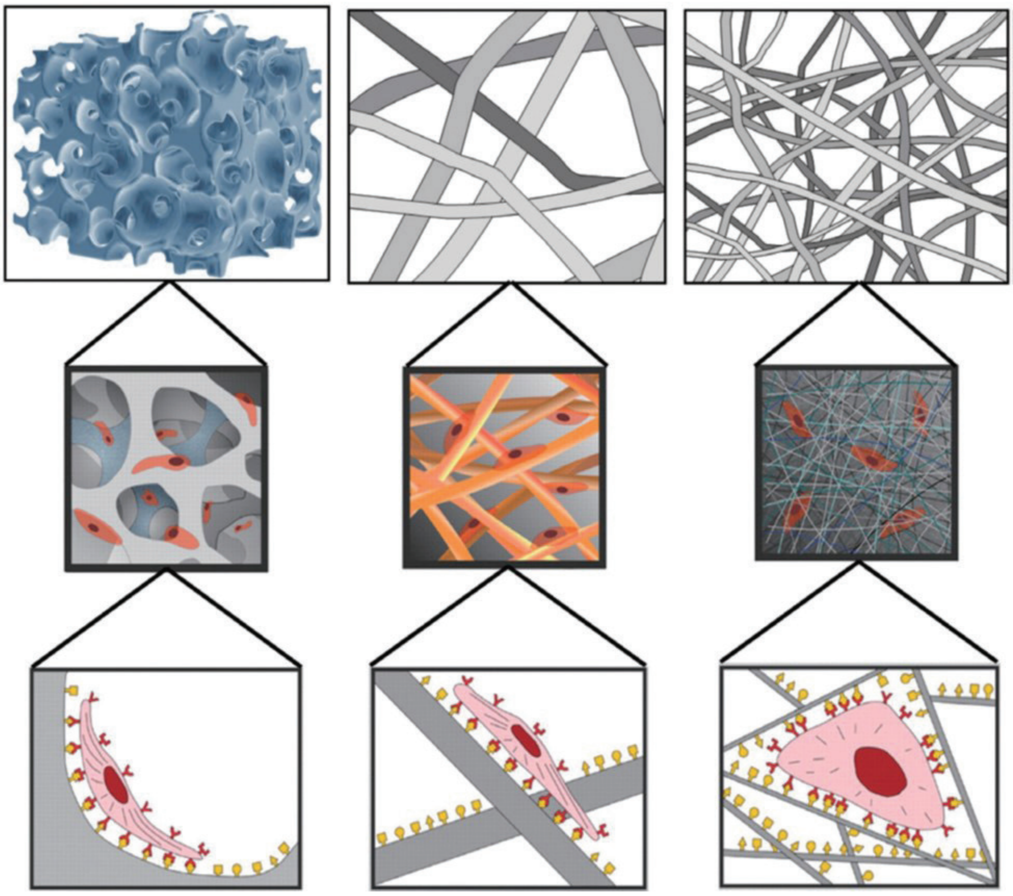

Figure 2. Illustration of how nanoscale fibrous scaffolds provide an environment for cells which better resemble the fibrous extracellular matrix of cartilage tissue. (Adopted from ref [4])

tiotemporally controlled manner is very important and it is related with tuning particle formulation and composition that could help drive tissue growth to completion. [18]

The idea of "organ-on-a-chip" in the foreseeable future will replace the expensive and life-costing animal testing used for drug development and for evaluation or optimization of nano-particulate systems for drug delivery. It will also replace many steps implantation or transplantation techniques for any tissue repair. [19] In orthopedics, as well in dental surgery, (a) nanofibers reproduce ECM architecture, (b) nanocomposites based scaffolds - such as nano-hydroxyapatite/collagen - play important role on the reconstruction of bone tissue, and finally, (c) carbon nanotubes affect mechanical strength and electrical conductivity as well as they cover implant surfaces to produce adjacent tissues. [20,21] In general, when we try to produce or regenerate complex tissues, cells seeded into biocompatible and nanostructured scaffolds reassemble into functional structures. These functional structures resemble native tissues and under the stimulation of growth factors spatiotemporally delivered by nanoparticles they may be developed into complex tissues or organs.

2. Biosensors

A **biosensor** is an analytical device, used for the detection of a bioanalyte. A **bioanalyte** is any substance, chemical or biological element, undergoing chemical analysis. A biosensor can be defined as a sensing device or a measurement system designed specifically for estimation of a material by using the biological interactions and then assessing these interactions into a readable form with the help of a transduction and electromechanical interpretation.

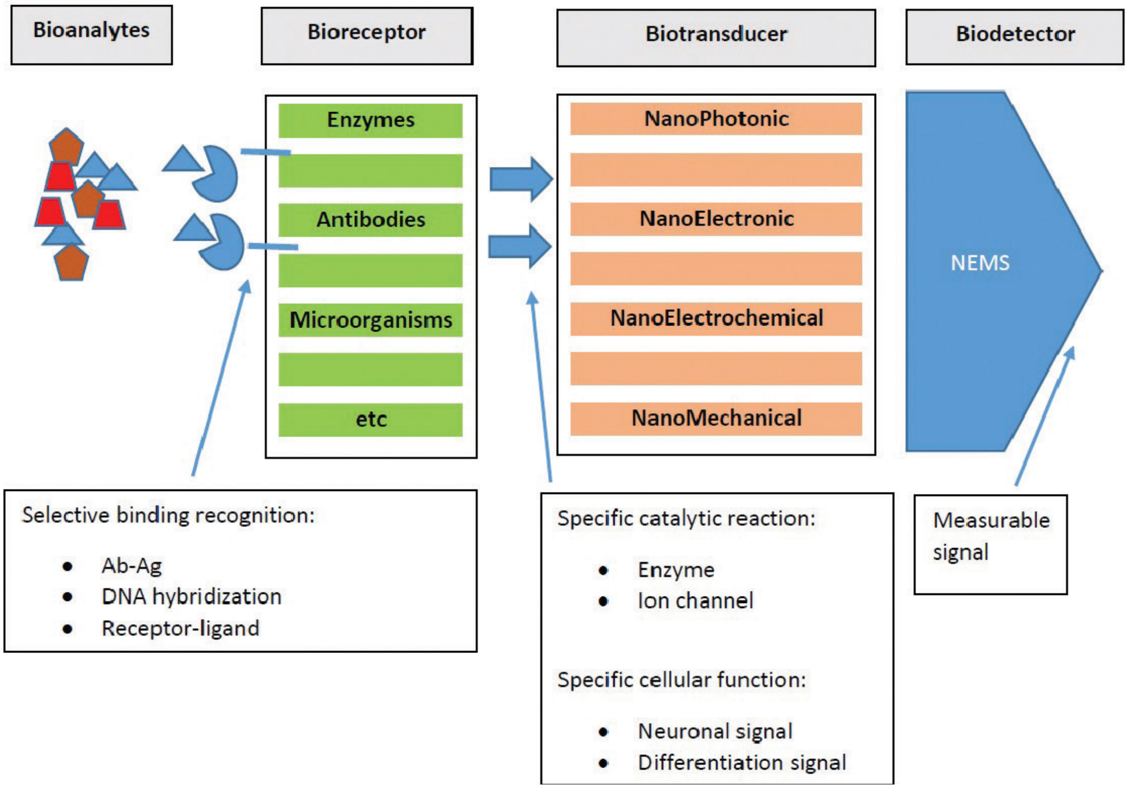

Figure 3. *Schematic of a nanobiosensor (Drawing by the author I.K.T.)*

A biosensor is comprised of three parts: (a) The **bioreceptor,** is that component of a biosensor which serves as a template for the material to be detected. (b) The **biotransducer**, the main function of this device is to convert the interaction of bioanalyte and its corresponding bioreceptor into an electrical form. The name itself defines the word as *trans* means change and *ducer* means energy. So, transducer basically converts one form of energy into another. The first form is biochemical in nature as it is generated by the specific interaction between the bioanalyte and bioreceptor while the second form is usually electrical in nature. (c) The **biodetector** that receives the electrical signal from the biotransducer component and amplifies it suitably so that the corresponding response can be read and studied properly. It is also called bioelectronic system (or bio-sensor reader device) and includes a signal amplifier, a processor and a display. **(Fig.3)**

2.1 Nanobiosensors

Nanobiosensors are the sensors which are made up of nanomaterials. The size constraints of these materials makes them very special as they have most of their constituent atoms located at or near their surface and have all vital physicochemical properties highly different from the same materials at the bulk scale. They can play very efficient roles in the sensing mechanism of the biosensor technology. Integrated devices of the nanomaterials with electrical systems give rise to **nanoelectromechanical systems (NEMS)**, which are very active in their electrical transduction mechanisms. Several nanomaterials have been explored on the basis of their electronic and mechanical properties for their use in improved biological signaling and transduction mechanisms. Some of such materials that are widely employed include nanotubes, nanowires, nanorods, nanoparticles, and thin films made up of nanocrystalline matter. [22] **(Table 3)**

2.2 Classification of nanobiosensors

Classic bio-sensors are classified according to (1) the type of their bio-receptors or (2) the type of the con-

TABLE 4.

Biosensors' classification

According to bioreceptor's type	According to biosensor's type
• Antibody/antigen interactions	• Electrochemical
• Artificial binding proteins	• Optical
• Enzymatic interactions	• Electronic
• Affinity binding receptors	• Piezoelectric
• Nucleic acid interactions	• Gravimetric
• Epigenetics	• Pyroelectric
• Organelles	
• Cells	

nected bio-transducers. **(Table 4)** However, nanobioreceptors follow a different classification based on the nature of nanomaterials incorporated in the biosensing operation and being involved for improving the sensing mechanism. *Nanoparticle-based biosensors* include all the sensors which employ metallic nanoparticles as the enhancers of the sensing biochemical signals. (**Fig.4**) *Nanotube-based sensors* are these involve carbon nanotubes as enhancers of the reaction specificity and efficiency. *Nanowire-based biosensors* are biosensors using nanowires as charge transport and carriers. *Quantum dots-based sensors* employ quantum dots as the contrast agents for improving optical responses. [23] **(Table 5)**

2.3 *Applications of nanobiosensors*

Nanobiosensors are highly versatile and multifunctional so they can find application in biomedical fields, environmental monitoring of pollutants, toxicants, and physical aspects like humidity, heavy metal toxicity, and even presence of carcinogens. [24] **(Table 6)**

(1) Biomedical Applications. Biosensors have been used for biological detection of serum antigens, carcinogens, and causative agents of many metabolic disorders. With the addition of nanoscale interventions, diagnosis has been more precise. The incorporation of nanomaterials has enabled the detecting enzyme systems to be immobilized, and this has allowed the recycling and reuse of costly enzymes. The implementation of nanoscale innovations like NEMS improved sensitivity and accuracy. Biochips and microarray based testing have enabled the testing of more than one disease in short time. Magnetic nanoparticles have been synthesized and used for isolating and heavy metals resembling in properties with iron from the blood serum. Magnetic nanoparticles are used to selectively evaluate biochemical responses. Thus, nanobiosensors are developed and used in different ways of their incorporation in sensing mechanisms. [25-33]

(2) Environmental Applications. This is a broad application area involving (a) the detection of pollutants, toxic intermediates, heavy metals from waste streams, directly relevant to public health, as well as (b) the monitoring of weather conditions like the estimation of humidity, directly relevant to public safety. The sensors based on nanomaterials can be very versatile in terms of their detection and monitoring. Carcinogens and harmful intermediates leading have been isolated through the use nanofabricated compounds, such as the endocrine-disrupting compounds. Techniques of bioremediation, when engineered with the use of nanomaterials, can be scaled up and used to optimize the environmental quality and decontaminate the

TABLE 5.

Nanoparticle based	
Acoustic wave	• Preferred particles: gold, platinum, cadmium sulphide, and titanium dioxide • Amplify the sensing responses • Improve overall preciseness of bio detection limits
Magnetic	• Preferred particles: iron or ferrite compounds • Screen of specific antigens from mixtures by using antibodies bound to magnetic nanoparticles
Electrochemical	• Preferred particle: gold (Au) • Facilitate or analyze biochemical reactions with the help of improved electrical means.
Nanotube based	• Preferred particle: carbon • Electronic conductivity, dynamic physicomechanical properties, high mechanical strength, high folding abilities
Nanowire based	• Preferred particles: carbon, silicon • Very good electron transport properties • Enhanced detection of biological and chemical species

TABLE 6.

Applications of Nanobiosensors	
Biomedical	
• DNA sensors	Genetic monitoring, Diseases
• Immunosensors	HIV, hepatitis, viral diseases, drug testing, cancer
• Point-of-care sensors	Blood, urine, electrolytes, gases, steroids, drugs, hormones, proteins
• Bacteria sensors	Food industry, medicine, environmental
• Enzyme sensors	Diabetics, drug testing
Environmental	
	Pollution and toxicity detection
	Ground water screening
	Agricultural monitoring
	Ocean monitoring
	Weather conditions
Miscellaneous	
	Metallurgy

hazardous contaminants. Specific biosensors have been developed for detection of nitrates, inorganic phosphates, and biological oxygen demand like parameters attributing to environmental restoration. In this manner, all these nanobiosensor applications are highly energy saving, economical and time saving in nature. [34-38]

(3)Miscellaneous Applications. In metallurgy, separation of impurities existing in a complexed form is required, and nanobiosensors can be used to separate the impurities selectively by trying out different configurations of the sensing enzymes. There is emerging need for developing microbiological and biochemical assays coupled with nanobioengineering based innovations to produce handy applications of sensing materials. This will have a direct effect on public health and safety. [22] Ⓐ

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