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# The translational paradigm of nanobiomaterials: Biological chemistry to modern applications

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ABSTRACT

Recently nanotechnology has evolved as one of the most revolutionary technologies in the world. It has now become a multi-trillion-dollar business that covers the production of physical, chemical, and biological systems at scales ranging from atomic and molecular levels to a wide range of industrial applications, such as electronics, medicine, and cosmetics. Nanobiomaterials synthesis are promising approaches produced from various biological elements be it plants, bacteria, peptides, nucleic acids, etc. Owing to the better biocompatibility and biological approach of synthesis, they have gained immense attention in the biomedical field. Moreover, due to their scaled-down sized property, nanobiomaterials exhibit remarkable features which make them the potential candidate for different domains of tissue engineering, materials science, pharmacology, biosensors, etc. Miscellaneous characterization techniques have been utilized for the characterization of nanobiomaterials. Currently, the commercial transition of nanotechnology from the research level to the industrial level in the form of nano-scaffolds, implants, and biosensors is stimulating the whole biomedical field starting from bio-mimetic nacres to 3D printing, multiple nanofibers like silk fibers functionalizing as drug delivery systems and in cancer therapy. The contribution of single quantum dot nanoparticles in biological tagging typically in the discipline of genomics and proteomics is noteworthy. This review focuses on the diverse emerging applications of Nanobiomaterials and their mechanistic advancements owing to their physiochemical properties leading to the growth of industries on different biomedical measures. Alongside the implementation of such nanobiomaterials in several drug and gene delivery approaches, optical coding, photodynamic cancer therapy, and vapor sensing have been elaborately discussed in this review. Different parameters based on current challenges and future perspectives are also discussed here.

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## 1. Introduction

Nanomaterials are abundantly found in natural habitats. Their complex behavior and properties are full of clues and instructions to a searching eye. Despite their existence, due to technological limitations and unavailability of investigative tools, they remained out of sight for a long time. The recent scientific period has proved to be a golden era for nanotechnology contributing to the worldwide growth and progress of the economy. Not only it has created an enormous impact on the medical and pharmaceutical industry, but also on other fields like electronics, and chemistry comprising of designing, developing, and application of materials at the nanometer (nm) scale [1]. With the advent of electron microscopes in the 1930s, a new horizon of material research was unveiled, and with full commercialization in the 1960s, there came an explosion of opportunities and potential for new forms of investigation in the nanoscale domain [2,3]. The interaction of the classical fields of biology and nanotechnology has evolved as the field of bio-nanotechnology, which serves as an interdisciplinary term for various related technologies including nanoparticles, nanotoxicology, nanoscience, nanobiology, and other intricate parts of material sciences [4–6] (Fig. 1). Increasing demands have occasioned large production and utilization of nanomaterials day by day. This bulk production and usage have raised concerns over the toxicity of nanomaterials on the ecosystems and human health [7–9]. Several concepts of the technology which are being used today have originated from nanobiology, encompassing nanodevices, nanoparticles, and nanoscale materials that fall within the same category [10]. The term particle refers to a substance of small dimension in all of its axes, for example, a fine powder. Therefore, nanoparticles are described as the particles sized between 1 and 100 nm. The distinction between nanoparticles and nanomaterials lies in the fact of dimensional characteristics of these materials. Nanomaterials, on the other hand, are not necessarily the same as they need to have at least one dimension on the nanoscale, for example, nanofibers. The overall effect is a function of the material surface area and the consequences that have on the material behavior [11]. To better illustrate the surface area perspective, the descriptions below show two cylindrical objects of identical volumes; however, due to their differences in internal structures, their overall surface area is very different [2].

With the evolution of technology, the potential to examine materials on smaller to microscopic scale levels have also developed which further demands newer techniques to manipulate their structure and composition of them. Noticeable innovations have been observed in the field of material sciences where it is desirable to understand every aspect of a physical structure, along with life sciences where we deal with the complexities of human systems. The human body efficiently arranges proteins and other molecules with nanoprecision hence material engineering deals with the fact that how accurately have those materials been produced to interact with the body. Moreover, the different aspects of material engineering also focuses on how nano-engineering has essentially benefitted the functionality of materials in the body [12,13]. Recent advancements in the field of nanotechnology have pushed the boundary of nanosciences so far that it has evolved the studies and application of the technology in almost every other field of science [14]. To fulfill the growing demand of nanomaterials, many new approaches for synthesis and industrial preparation of nanomaterials are being discovered each day. However, the logarithmic expansion of production of metal and metal oxide nanomaterials has slowly raised issues like toxicity and biocompatibility which could eventually become a threat to ecosystems and human health [15]. Hence, the detailed mechanisms of biological effects of nanomaterials concerning their antibacterial efficacy

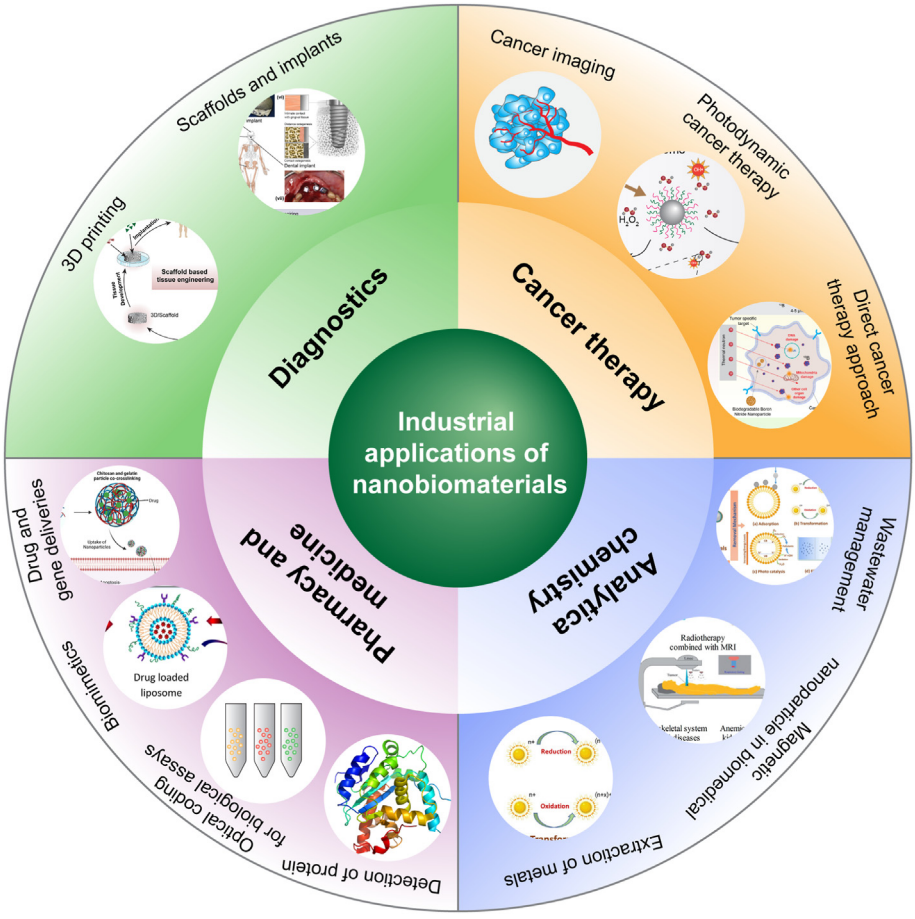



**Fig. 1.** Schematic diagram explaining the interdisciplinary industrial applications of nanobiomaterials.

and cytotoxicity need to be explored and discussed [16,17]. This unique approach derived from the biological concerns provides scientists to apply nanosciences for cutting-edge biological and medical research with better scopes for the future. Biologically inspired nanotechnology can enlighten us in certain ways to develop systems, resulting in several elegant profiles that could be applied in various spheres of life [18]. However, working with 1000 parts in a millimeter, also known as a micrometer (μm) is less familiar to most people and the thought of 1000, 000 parts of 1 mm or more appropriately, nanometer (nm) is beyond most people's scope of perception. Whereas the concept of measurement in the form of meter, centimeter, and a millimeter is well understood by all and consistently employed to meaningfully represent size. As a result, nanometer-scale materials are not only extremely small but also crucial for precise engineering and effective performance. To illuminate these concerns, this review provides a brief overview of nanobiomaterials, their applications, their future perspectives and their significant importance in terms of commercial industries.

## 2. Characterization of nanobiomaterials

The cells regarded as the basic unit of life, are the building blocks of living organisms with a typical size of 10 μm. This brings us to the conclusion that the cell organelles are even smaller and are in the sub-micron size domain. Further detailing states that, the proteins with a typical size of 5 nm approx. is comparable with the dimensions of man-made nanoparticles [19]. This simple comparison gives an idea of utilizing nanoparticles as very small probes that would allow to spy on the cellular machinery without too much interference.

The naked eye can see objects down to ~20 μm, however, an optical microscope pushes this boundary line of resolution to ~0.2 μm but not beyond that. All of these are limited to a certain wavelength of visible light. Thus, to view objects at nanoscales, electrons are used instead of light which provides a resolution as high as 0.001 μm or 1 nm scale. Specific specialized tools related to electron technology are available for the characterization of nanomaterials (Fig. 2). These include scanning electron microscope (SEM), transmission electron microscope (TEM), scanning tunneling microscope (STM), and atomic force microscope (AFM). Though all these techniques are principally different, their functions and applications are more or less the same, which is to produce high-resolution images of material surfaces and bulks [20]. Spectroscopic techniques like RAMAN could be used to study rotational, vibrational modes of a nanostructure. This method essentially relies on RAMAN scattering of monochromatic laser light. The shift or variation in energy level gives us information about the subject being examined [21]. Other characterization techniques include particle size analysis and x-ray diffraction by various methods like dynamic light scattering or DLS [22].

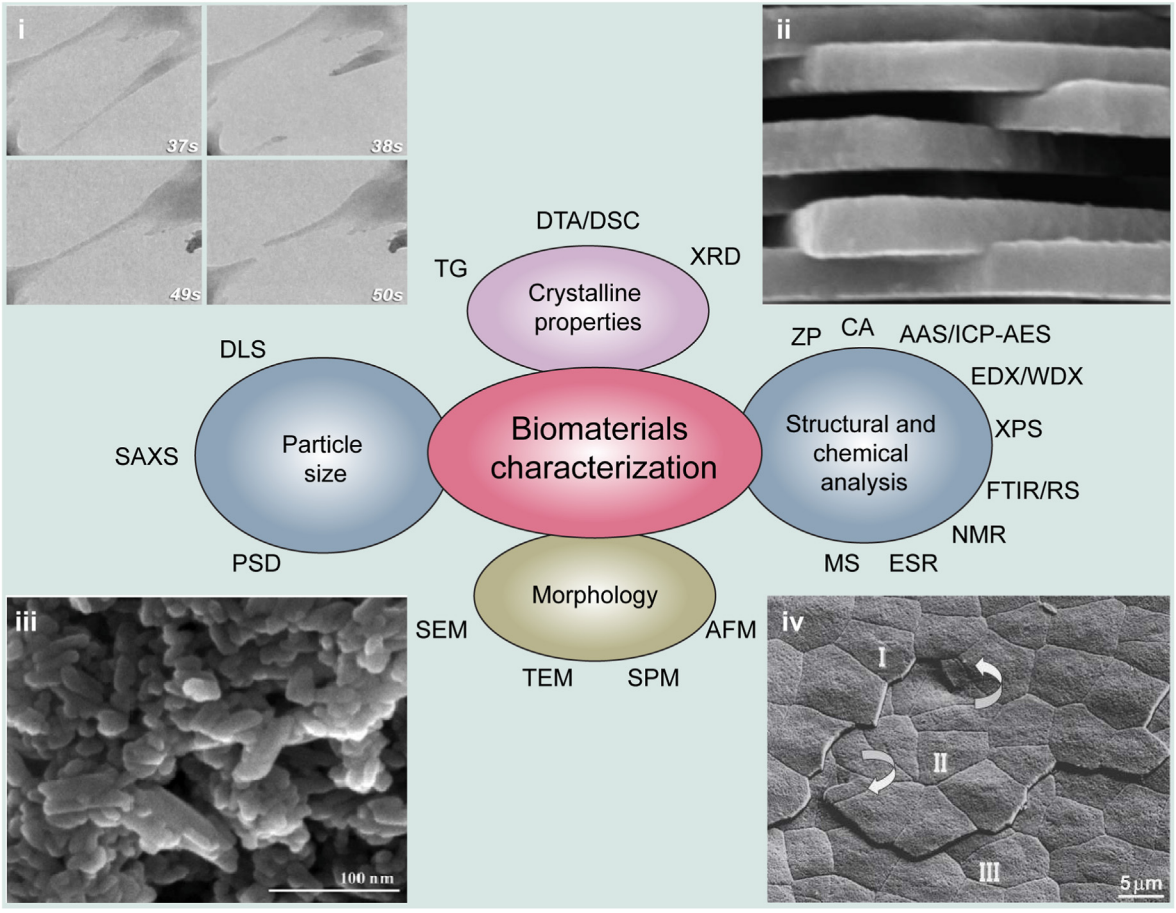



**Fig. 2.** Diagrammatic representation of various techniques for biomaterials characterization {Figure adapted from Ref. [23]}. **(i)** TEM still image sequence showing *in situ* deformation of organic matrix between plates with the time intervals shown in seconds. Adhesion at the wall is strong and failure will occur by deformation of the ligament. The recoiling broken strand shows densification at its base. {Figure adapted from Ref. [24]}. **(ii)** SEM image of a fractured nacre surface showing the presence of interlocking between platelets of nacre responsible for its mechanical response {Figure adapted from Ref. [25]}. **(iii)** FE-SEM image of a hydroxyapatite (HAp) {Figure adapted from Ref. [26]} **(iv)** SEM image showing two screw dislocations and spiral growth associated with three layers in nacre. The center core and corresponding spiral growth domain are oriented counterclockwise connecting layers I and II; the core and corresponding domain at the bottom left are clockwise relating to layers II and III. This shows how the layers are forming simultaneously on top of one another {Figure adapted from Ref. [27]}.

## 3. Biomedical and pharmaceutical applications

Biomaterials, that interact with biological systems use multidisciplinary ideas and technologies from various fields like medicine, pharmaceuticals, biology, tissue engineering, material science, and chemistry can be natural, synthetic, or biologically derived [28,29]. Although biomaterials have been widely used in the medicinal and pharmaceutical industries like dental bone implants, contact lenses, drug delivery, tissue regeneration, and stem cell engineering, the advent of new technology requires the development of novel biomaterials and integrated systems [30,30]. Healthcare facilities can be improved by examining and improving biological structures, processes, and functions at nano-scale levels. The expansion of high-quality biomaterials or implants could be accelerated by taking the benefits of nanotechnology such as scaffolds or nano-assemblies [31]. Nanotechnology plays an elemental role in the development of medical devices based on biomaterials. In this way, nanobiomaterials can serve as a bridge between nano and bio. A wide range of usage of these novel materials in drug delivery, regenerative medicine, and tissue engineering has been discussed in detail.

### 3.1. Drug and gene deliveries

Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for targeted drug delivery purposes and controlled release of therapeutic agents [30]. Essential features like a large surface area also have a large affinity for drugs and smaller molecules, like ligands or anti-bodies for targeting organs and controlled release of drugs. Nanomedicine and nano delivery systems are a relatively new but expeditiously developing science where materials in the nanoscale range are implemented to serve as diagnostic tools or deliver therapeutic agents to specifically targeted sites in a controlled manner [32]. Recently, several superlative applications of nanomedicine, such as chemotherapeutic, biological, and immunotherapeutic agents, have been mentioned significantly in the treatment of a wide range of diseases.

Novel techniques using nano tools might end up as surgical procedures or even eradicate cancer. These techniques are performed at the cellular level from organ to organ, the order in which cancer cells propagate. Nano-based delivery systems could also be used in other industrial sectors like food and pharma [33]. Nano-based delivery systems could also be used in other industrial sectors like [33,34], however, the toxicological aspects must be considered. The efficacy of the compound of interest varies in a dose-dependent manner. This review presents the recent advancements in the fields of nanomedicine and nano-based delivery systems by summarizing the overall applications of recent advancements in nanomedicine and nano-based drug delivery systems by thoroughly scrutinizing the principle and applications of different nanomaterials for both the development of new drugs and improvement of older ones.

Unlike the larger molecules, nanoparticles have the ability to reach far more sites in the body. Also, they have added several advantages like, circulation for a longer period, higher surface areas, efficient control drug release in target organs, and crossover capability of the blood-brain barrier. The amalgamation of drugs into nanoparticles allows them to be delivered directly to the specific desired tissue hence making the procedure more efficient, moreover, this reduces dosage. Nanoparticles have the capability to pass through Peyer's patches, which essentially regulate the environment of the small intestine and therefore can be operated intravenously [35]. Nevertheless, nanoparticles also face certain issues rather than challenges such as undesirable recognition as foreign body and consequently filtration by the liver or spleen before the release of drug. To avoid such circumstances, solutions need to be optimized for each drug-nanoparticle combination to obtain the intended size, release rate, and circulation time. Initially, the drug is incorporated into the particle to deliver the drug to its specified target. Larger amounts of the drug can be incorporated during the process of formation of the nanoparticle, whereas the drug could be theoretically attached to the nanoparticle after its formation through absorption [36]. A few methods routinely used for this purpose are solvent evaporation, spontaneous emulsification, salting out, coacervation, and polymerization. Additionally, to improve the quality of the product and prevent nanoparticle aggregation, surfactants, and stabilizers can be added.

Following the incorporation of drugs into them, the nanoparticles need to be optimized for desired characteristic functions. A few checkpoints that need to be considered during this optimization period include the final size of the particle, aggregation of the nanoparticle, and the surface properties. Encapsulation efficiency is measured to correlate the size of nanoparticles and drug volume, to achieve more sustainable dissolution of particles [37]. At the same time, the target site of the nanoparticles must also be considered. For instance, nanoparticles whose surfaces had been notified with chitosan were found to have an increased penetration tendency towards the mucosal surfaces. On entering a human body, nanoparticles must cope with the basal systems and mechanisms like plasma protein adsorption, phagocytosis, etc. [38]. Phagocytes attach to the nanoparticle surface when opsonins present in the bloodstream get adsorb onto the hydrophobic sites of the nanoparticle. This phenomenon can be prevented by grafting hydrophilic particles onto the surface such as polyethylene glycol [39]. Although the activity of the phagocytes might be helpful if the desired target is the liver itself, this uptake could be dangerous sometimes, if there are cytotoxic components in the particles. Initially, researchers were determined to solve this problem by suppressing the reticuloendothelial system; however, later it was found that this could lead to a new set of problems and therefore has not been an ongoing focus of research further. Instead, hydrophilic nanoparticles are favored for drug delivery purposes because they are filtered out at a considerably lower rate than their hydrophobic counterparts. To harvest the fact for further advantages, nanoparticles can either be treated with hydrophilic polymers after production or polymerized at the very initial stages [36]. Chitosan and gelatin are among the frequently used hydrophilic polymeric materials, utilized in the process of polymerization [14]. Both are capable of forming nanoparticles through an ionic gelation method (Fig. 2).

Organic, inorganic, and polymeric nanostructures, including dendrimers, micelles, and liposomes are regularly considered in designing the target-specific drug delivery systems [40]. Particularly those drugs with poor solubility having less absorption ability are labeled with these nanoparticles. However, the efficiency of these nanostructures as drug delivery vehicles varies according to their characteristic properties (biophysical/chemical). Newly developed drug delivery molecules could release therapeutic molecules at active sites in the body only after reaching the targeted diseased tissues.

Studies done by Ryu et al. [41], covers the therapeutic applications of bio-reducible polymers as gene delivery carriers. Bio-reducible polymers have distinctive advantages over common cationic gene delivery carriers for the release of genetic materials. Various gene therapy approaches for the treatment of several cardiovascular diseases, diabetes and cancer have been highlighted in this article. Lim et al., [42] discussed different carbon-based carriers for drug delivery applications.

Nanotechnology is intended to enhance the biodistribution, stability, targeting, and retention of the active medicinal component (or radionuclide) system and to introduce theranostic techniques [43]. Majority of nanoparticulate nanomedicines incorporate already approved drugs in clinical evolution, which are elicited from a variety of drug delivery principles, including polymeric micelles, dendrimers, liposomes, and some inorganic nanoparticles [44–46]. Every nanotechnology sub-type has associated issues that may delay clinical application. Liposomes are unquestionably dominant on the nanoparticulate medicine market and were the first nanoscale compartments to receive FDA approval (Table 1), despite the armaments of nanoparticulate targeted systems which are currently in preclinical development or in clinical studies [47,48]. The use of liposomes as medication delivery systems for both small compounds and macromolecules was suggested shortly after they were discovered in 1965 [49,50]. Liposomes actually possess all the necessary

**Table 1**
Nanomaterials in clinical trials.

| Nanomaterials | Drug/Gene | Formulation Name | Phase | Targeting Disease | Identifier |
|---|---|---|---|---|---|
| Lipid nanoparticles (10–1000 nm)/Liposomes (25 nm-2.5 μm) | Azithromycin | ALIS | Phase III (Recruiting) | Mycobacterium Infections, Nontuberculous | NCT04677569 |
| | Env-C Plasmid DNA | Plasmid DNA Vaccine | Phase I | HIV Infections | NCT04826094 |
| | Oxiconazole nitrate | solid lipid nanoparticles (SLNs) gel system | Phase I (Completed) | Tinea | NCT03823040 |
| | Cisplatin | LiPlaCis | Phase I/II | Advanced or Refractory Solid Tumors, Metastatic Breast Cancer, Prostate Cancer, and Skin Cancer | NCT01861496 |
| | | SPI-77 | Phase II | Ovarian cancer | NCT00004083 |
| | Doxorubicin | ThermoDox | Phase III | Non-resectable hepatocellular carcinoma | NCT02112656 |
| | | PanDox | Phase I (Recruiting) | Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer (Stage IV, Non-resectable, Metastatic) | NCT04852367 |
| | | 2B3-101 | Phase I/II (Completed) | Brain Metastases, Lung Cancer, Breast Cancer, Melanoma, Malignant Glioma | NCT01386580 |
| | 9-Nitro-20-(S)-Camptothecin | L9-NC | Phase I/II | Ewing's Sarcoma, solid tumors | NCT00492141 |
| | | DLPC-9NC | Phase II (Completed) | Lung diseases, Cancer | NCT00250068 |
| | Oxaliplatin | MBP-426 | Phase I (Completed) | Metastatic solid tumors | NCT00355888 |
| | Gemcitabine Hydrochloride, Paclitaxel | EndoTAG-1 | Phase III (Recruiting) | Triple-Negative Breast Cancer | NCT03002103 |
| | Liposomal Lurtotecan | OSI-211 | Phase II (Completed) | SCLC, Carcinoma, Small Cell | NCT00046787 |
| | Docetaxel | LE-DT | Phase II (Completed) | Solid Tumors, Pancreatic Cancer | NCT01186731 |
| | Paclitaxel | LEP-ETU | Phase II (Completed) | Neoplasm | NCT00100139 |
| | Ferumoxytol | MM-398 | Phase I (Completed) | Solid Tumors ER/PR Positive Breast Cancer Triple Negative Breast Cancer Metastatic Breast Cancer with Active Brain Metastasis | NCT01770353 |
| Polymeric Nanomaterials (1–1000 nm) | Paclitaxel | Paclical | Phase III (Completed) | Epithelial Ovarian Cancer, Primary Peritoneal Cancer, Fallopian Tube Cancer | NCT00989131 |
| | | NK105 | Phase III (Completed) | Breast Cancer Nos Metastatic Recurrent | NCT01644890 |
| | Camptothecin | CRLX101 | Phase II (Completed) | Pilot study on cancer (different types and stages) | NCT01612546 |
| | Docetaxel | BIND-014 | Phase II (Completed) | KRAS Positive Patients with Non-small Cell Lung Cancer Squamous Cell Non-small Cell Lung Cancer | NCT02283320 |
| Dendrimer (~20 nm) | Imaging agent | 18 F-OP-801 | Phase I (Recruiting) | Amyotrophic Lateral Sclerosis | NCT05395624 |
| | | OP-101 | Phase II | COVID-19 | NCT04458298 |
| PLGA (10–1000 nm) | Ciprofloxacin | CIP-CS-PLGA-NPs | Early Phase 1 | Antibiotic Resistant Infection | NCT05442736 |
| Magnetic nanoparticle (50–200 nm) | Iron nanoparticles | MAGNABLATE I | Early Phase 1 | Prostate Cancer | NCT02033447 |
| Silver nanoparticle (40–180 nm diameter, >1000 nm length) | Colloidal silver NP | SNITCH | Phase I | Chronic Rhinosinusitis (Diagnosis) | NCT03243201 |

characteristics to enable the formation of very toxic and/or poorly soluble medications, such as paclitaxel and amphotericin B [47,51]. Liposomes, for instance, are constrained by their low encapsulation effectiveness, propensity to aggregate, and *in vivo* drug leakage of water-soluble medicines (Fig. 3). Anomalies in liposome manufacturing include specifications as a result of process scaling, a lack of GMP processes, and problems with batch-to-batch consistency [52]. Several years of research resulted in the creation of the first FDA-approved nanoparticulate medicines (Doxil R/Caelyx R) and additional therapeutics [53]. With no evidence of improved efficacy, the most frequently seen therapeutic benefit so far have been a decrease in toxicity. However, lately approved liposomal nanoparticulate nanomedicines, Vyxeos R (daunorubicin/cytarabine liposomal formulation), demonstrated enhancement in survival and response rates, with reduced toxicity in phase III clinical trials in patients (above a certain age group) with therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes [54]. Nanoparticulate nanomedicines must undergo an expensive and drawn-out clinical translation process. Nanoparticulate nanomedicines technique is typically far more complicated than traditional formulation technology, which uses free medication dispersed in a base (e.g., tablets, capsules and injections) [55–57]. The biological hurdles, large-scale manufacturing, biocompatibility and safety, intellectual property (IP), governmental requirements, and overall cost-effectiveness in contrast to existing medicines are serious concerns related to clinical development [53,58–61]. Regardless of whether they are therapeutically effective or not, these issues can place considerable barriers in the way of nanoparticulate nanomedicines entering the market. Large-Scale manufacturing, size of nano-constructs, regulatory challenges and toxicity of nanoparticle systems are the major pitfalls for bench to bedside translation [43]. A more thorough examination of the regulatory issues relating to the use of nanoparticles in medicine is warranted. It is crucial to characterize the nanomaterial throughout all design stages and to make sure that any contact with biological systems, sample preparation, or extraction techniques does not change the system's characteristics or affect measurements [62]. As a result, controlling the production process and identifying crucial variables that affect the biological behavior and toxicity of these nanoparticles must be a major emphasis of nanoparticle pharmaceutical research [63]. Strong and proven quality control measures are essential. For the systemic evaluation and control of nanomedicines, it is also

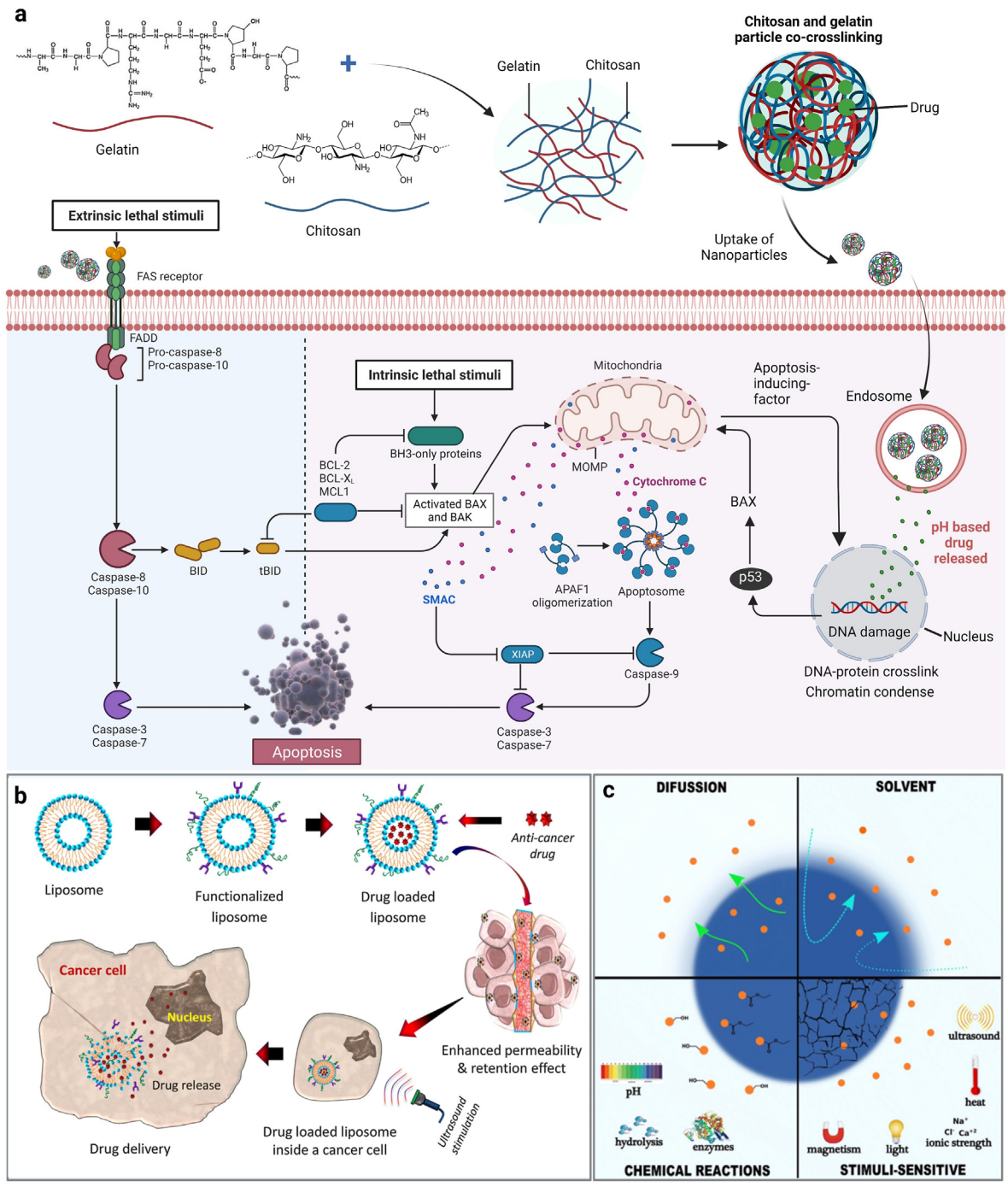



**Fig. 3.** **(a)** Chitosan and gelatin particle co-crosslinking with drugs and uptake of nanoparticles. Endosomal formation uptake the nanoparticle and then releases the drug based on specific pH into the cytoplasm where it performs DNA damage and apoptosis of the cancer cell by Caspase-3/7. **(b)** A step-by-step demonstration of liposome-based drug delivery used for cancer therapy. Image adapted from Ref. [66]. **(c)** Different types of nano-carriers are employed to perform controlled drug release mechanisms. {Adapted from Ref. [67]}. FADD: Fas-associated protein with death domain; BID:BH3-interacting domain death agonist; SMAC: Second mitochondria-derived activator of caspases; MOMP: Mitochondrial outer membrane permeabilization.

crucial that quality-by-design pharmaceutical procedures (such as those outlined by the FDA's cGMP guidelines) be followed [62,64].

Carbon allotropes such as graphene oxide, carbon nanotubes, and nanodiamonds are utilized for the delivery of the water-insoluble drug, antigens, antibodies, and nucleic acids to cancer cells. The study done by Jeong et al. [65], nanoparticle systems describes the gold nanoparticle (AuNP) based drug delivery and molecular imaging. Surface modifications of AuNPs and their applications in the delivery of small chemical drugs as well as gene materials such as pDNAs and siRNAs are discussed. Molecular probe design and imaging using AuNP are also presented with a detailed review of the optical and fluorescence quenching properties of AuNPs.

In this way, nanotechnology offers multiple benefits in the treatment of chronic human diseases through site-specific and target-oriented delivery of medicines. However, inadequate knowledge about the nanostructure toxicity serves as a major drawback and undoubtedly warrants further research to improve the efficacy with higher safety to enable safety measures related to the implementation of these medicines.

Henceforth, designing these nanoparticles must be done with care and caution, to make it helpful in tackling unsafe conditions arising. Considering the above facts, different nano-based drug delivery systems, significant applications of natural compound-based nanomedicines, targeting sites, controlled release of drugs, as well as other challenges associated with nanomaterials in medicine needs to be focused. To form an idea of the future perspective, seemingly nanotechnology is going to prosper through many stages of the industrial revolution and commercial implementation.

### 3.2. Nacre

Nacre, also known as the mother of pearl, is an organic-inorganic composite system, produced by some molluscs as an inner shell layer. The material is strong, resilient, and iridescent, and this is what the pearls are composed of. It is a shiny, glossy inner layer beneath the rough surface of the shell of an oyster. When the outer shell layer is dissolved in an acid, it reveals the pearly white or beautiful blue-green underlying nacre. Nacre usually is consisting of alternating layers of aragonite platelet and organic materials film.

One of the most studied natural materials in the field of biomimetic is the nacre, the mother of pearls. Essentially it consists of 95% calcium carbonate, in the form of aragonite, which is layered with 5% of polymeric organic matter. It has a fracture strength of about 3000 times pure calcium carbonate [27]. The unique microstructure of the nacre shows how mechanical strength can be utilized for improvement and yields suggestions on improvements of various man-made materials. The strength of a composite can be improved by thriving for the strength of its components, whereas nacre stands as an example of careful placement of weaker materials that could yield similar results. Nacre has been known to be characterized by some biomedically desirable properties. To point out those, nacre has a hierarchical organization, mild processing conditions, durable interfaces, good fatigue performances, viscoelastic properties, and some extent of self-healing [68]. Hence, incorporating these significant features in biomaterials, by studying nacre's structure and formation, would highly privilege the existing methodologies. The calcium carbonate, which is present as aragonite tablets in nacre, covers about 5 μm in length and is about 0.5 μm in thickness. These tablets can be further segmented into numerous nanograins of an approximate size of 10–50 nm in diameter held together by an organic matrix. The aragonite tablets grow individually in between the polymer sheets in the organic matrix via the assembly of nanoparticles that are nucleated from colloidal amorphous calcium carbonate [69,70]. These nanograins possess deformable properties just like it is observed to occur between the constituent tablets on the microscale, such as deformation and rotation. Based on their orientation, natural nacre is structured mainly in two forms: sheet and columnar. These are distinguished based on their orientation of the centers of successive platelets stacked on top of one another and are located in the shell for optimal performance [71]. Both these forms consist of layers of about 300 μm thickness composed of sublayers of aragonite platelets that are separated by organic layers of 20–50 nm [72]. These sublayers are again separated by mesolayers and multiple organic layers. These thick mesolayers are obtained as the results of seasonal effects since changes in the feeding patterns limit available ions for the formation of minerals. Within each aragonite layer, there are larger domains of platelets that have crystallographic orientation [27].

#### 3.2.1. Biomimetic nacre (layer by layer processing)

These days' biomedical devices are often the detailed combinations of processed methods designed in such a way that they produce the best result when interacting with the body. For instance, artificial nacre-like coatings have been fashioned in a layer-by-layer approach using a lamination process. Several different methods have emerged to produce thin layer structures to enhance the mechanical behavior of the individual components.

Tang et al., [73] mentioned the use of the layer-by-layer approach to produce artificial nanostructured nacre made of polyelectrolyte multilayers which contained the same properties of nacre, such as tensile strength and organic matrix of nacre. For experimentation, they layered montmorillonite clay tablets with polyelectrolytes in such a way that the tablets oriented themselves parallel to the surface to maximize the attractive energy. As a result, a composite of films was produced that measured about 50–200 nm where the individual clay layer was approx. 3 nm thick, and the polyelectrolyte essentially mimicked the functions of those found in nacre. Over 75% of the molecules remain tightly coiled such that all of them contain sacrificial loops which in turn help to dissipate energy, prevent deformation, and strongly adhere to the clay surfaces. Tang et al., [73] estimated a tensile strength of 100 MPa and Young's modulus of up to 11 GPa, and explained how surprisingly Young's modulus was found to be low by highlighting the fact that the montmorillonite platelets lacked the nano asperities that are present in nacre which Katti proved to provide additional friction in between layers.

Lin et al., [74] presented a study where montmorillonite was used as their chief component, but they used a combination of hydrothermal and electrophoretic assembly to intercalate the polymer into the montmorillonite. It was found that the driving force behind the laminate's structure resulted in increased entropy caused by the desorption of solvent molecules and henceforth the process was found to rely on self-assembly. Since the layers in their composite are much thinner than those found in natural nacre, there was less space for polymer folding and cross-linking that provides the organic layer of the nacre with many of these characteristic deformation properties.

On the other hand, Wei et al., [75] also showed a layer-by-layer approach to producing thin films of polymer that closely resemble the organic and inorganic properties of the nacre which is similar to the above-mentioned processes. They typically emphasize the importance of insoluble biomacromolecules which act as a framework for the soluble bio macromolecules which offer negatively charged surfaces for the nucleation of the aragonite platelets. To replicate these properties in the film, they replaced diazo-resins and acrylic acid to provide the framework and nucleation sites respectively and further treated the organic multilayer with $CO_2$ gas diffusion which was perfectly tuned to provide the desired $CaCO_3$ thickness. This resulted in a suitable film that closely resembled the structure of the nacre and the model for adjustable fabrication of layer-by-layer nanocomposites. This method succeeded in developing a thinner, more homogenous, and less ordered layer. However, it was limited to certain structures and was not allowed for coating complex geometries [76,77].

Silver is well-known for ages due to its antibacterial and anti-inflammatory properties [78]. Lok et al., [79] proved that the antibacterial activity is linked to size with the smaller particles having higher activity. Strong evidence supported the fact that by stabilizing the surface with albumin, they could prevent nanoparticles from forming aggregates. Aggregation otherwise resulted in decreased effective surface area, as well as limited the degree with which they could associate with the bacterial cells. However, there were also concerns regarding the release of large amounts of silver into the human body which could be detrimental. To resolve this issue, Podsiadlo et al., [80] produced layer-by-layer composites using the immobilization technique so that silver nanoparticles were prevented from entering or spreading in the human body. In this approach, they assembled poly(-diallylmethylammonium chloride), montmorillonite clay, and silver nanoparticles coated with starch to prevent the aggregation of nanoparticles. Consequently, due to this immobilization of silver nanoparticles within the film, it was possible to limit the amount of eluted silver to less than 3 μg/L which was not detrimental to mammalian tissue cells.

### 3.3. Detection of proteins

Protein detection evaluates the concentration and number of different

proteins in a particular specimen. In many species, protein may be identified using a variety of techniques and approaches. Important ramifications for clinical diagnosis, therapy, and biological research have been shown for protein detection. Proteins play an integral role in a cell's machinery, structure, and communications. Although understanding their functionalities is an extremely difficult task but is equally necessary for the progression of human wellbeing. Among various nanomaterials known, gold nanoparticles are widely used in immunohistochemistry studies to identify the protein-protein interaction. However, the multiple simultaneous detection capabilities of this technique are somewhat limited. Surface-enhanced Raman scattering spectroscopy technique is an established technique used for the detection and identification of single dye molecules. A combination of both these methods in a single probe system of a nanoparticle can immensely improve the multiplexing capabilities of protein probes. The group of Prof. Mirkin demonstrated a sophisticated multifunctional probe that is built around a 13 nm gold nanoparticle. These particles are coated with hydrophilic oligonucleotides which contain a Raman dye at one end terminally capped with a small molecule recognizing element e.g., Biotin. Using this molecule has several added advantages as this molecule is catalytically active and further coated with silver in the solution of silver and hydroquinone. After the attachment of the probe to a small molecule, or an antigen, the substrate is exposed to silver and hydroquinone solution. Along with the ability to recognize small molecules, this probe can also be modified to obtain antibodies on the surface for the easy recognition of proteins. When tested in the format of protein array against both small molecules and proteins, the probe has shown no cross-reactivity [81,82].

A sensor array containing a total of six non-covalent gold nanoparticle-fluorescent polymer conjugates has been created to detect, identify, and quantify protein targets. The mechanism further can be explained as the quenching of polymer fluorescence by the gold nanoparticles which is further disrupted by the affected nanoparticle-polymer interaction in presence of proteins. This produces distinct fluorescence response patterns that are highly repeatable and can be quantitatively differentiated by linear discriminant analysis (DLA). These patterns are characteristic of individual proteins at their nanomolar concentrations. Proves of further works have been noted, which demonstrate the construction of novel nanomaterial-based protein detector arrays with potential applications in the medical diagnostic field.

### 3.4. Optical coding for biological assays

The flourishing research in genomics and proteomics has generated several sequence data and can be developed more with high throughput screening technologies. Logically, a variety of array technologies that are recently being used in parallel research analysis, are likely to reach a saturation level where the number of array elements exceeds several million. A three-dimensional approach, based on optical “bar coding” of different polymeric particles in solution, is limited only by the number of unique tags that are reliably produced and detected by one. Single quantum dot nanoparticles were successfully used in place of organic dyes in various bio-tagging applications and hence were proved to be a good replacement [83]. Multicolor optical coding for biological assays can be achieved by embedding different-sized quantum dots (zinc sulfide-capped cadmium selenide nanocrystals) into polymer microbeads at effectively controlled ratios. Their novel optical properties provide these highly luminescent quantum dots with ideal fluorophores for wavelength and intensity multiplexing. The use of intensity level 10 and a total of 6 colors could code for one million nucleic acid or protein sequences. Imaging techniques and spectroscopic measurements indicate that the quantum dot tagged beads are highly uniform and reproducible, leading to almost 99.99% bead identification accuracy, under favorable conditions. Studies employing southern hybridization show that the target and coding signals can both be read at the single-bead level. This idea has been taken one step further by combining differently sized polymeric microbeads having different fluorescence colors and quantum dots [84]. This spectral coding technology has brought new opportunities in different fields like gene expression, high throughput screening, medical diagnostics, etc.; and is expected to open newer doors further.

## 4. Utility of nanobiomaterials in diagnostics

### 4.1. Nanostructured scaffolds and implants

Continuous research and substantial studies have demonstrated that nanostructured materials, compared with conventional materials, promote greater amounts of specific protein interactions, henceforth stimulating new bone formation more efficiently. Indications have also been found regarding the features of scaffolds, when the ingredients of the scaffolds are nanoscaled, a variety of interactions can be stimulated at the cellular level (Fig. 4). Some of those interactions induce favorable cellular functions while others may lead to toxicity. The mechanism of interactions between nanoscaled materials and the cells along with the current research status of the nanostructured scaffolds for tissue engineering purposes needs to be focused.

The layer-by-layer composites and hydrogels are very well suited for integration with the body. However, other nano components used in scaffolds are also effective. One of the finest approaches found by researchers to produce these scaffolds is freeze-casting (Fig. 4). To form its desired crystalline structure, water-based slurry ejects solutes into channels between the ice crystals. When the included solute is ceramic, setting the material and draining the water leaves a scaffold that makes a very dense composite [70]. Along with these procedures of making scaffolds, researchers have recently developed ways to do the same with hydroxyapatite. Before this method of freeze-casting was discovered, porous scaffolds made from hydroxyapatite were used which were too weak to bear loads. One of the commonest methods was the particulate leaching technique which used porogen, gelatin spheres, or salt crystals, to give the scaffold porosity and could later be leached out of the foam with water to leave the wanted empty spaces [27]. Those empty spaces or pores left of about 300 μm that is needed for osteoblast conduction, but the same method can be applied with nanoparticles to yield highly porous foams with high interconnectivity between pores. Moreover, from then on, freeze-casting has allowed for the production of hydroxyapatite scaffolds with usually higher compressive strength [85]. Deville et al., demonstrated a technique that is based on a ceramic slurry that is poured into a mold, freeze-dried, and finally sublimated under pressure [85]. They produced foams with lamellar, cellular, or dense microstructures depending on the processing conditions. The strength of the lamellar region was found to be similar to that of a compact bone, which has a compressive strength of 145 MPa for foams with 47% porosity and 65 MPa for a porosity of 56%. In this experiment, they used initial hydroxyapatite particles of size 2.4 μm. However, evidence stated that repelling small particles from the super cooled ice front is easier than repelling larger particles and even smaller particles have the potential to reach the lower porosity without sacrificing the interconnectivity of the pores. Fu et al., mentioned a different method, where they were able to produce dense scaffolds with a unidirectional pore structure by directional freezing of aqueous hydroxyapatite suspensions on a cold substrate [86]. These scaffolds could then be utilized to increase the material density without damaging the microstructure. Although this work did not extend to testing these scaffolds in the body, they might be better suited for bone engineering applications because the initial aqueous phase could be mixed with glycerol or dioxane to achieve a high degree of control over the final microstructures [86]. Another freeze-casting system was processed by Launey et al., [87] who created a ceramic suspension to serve as the matrix which was then filled with metal to form tablet-like structures. To successfully optimize the complexities of many length scales found in a natural system, they added sucrose to the final microscopic asperities and designed their system to mechanically align the lamellae [87]. While using sucrose for their system, they also speculated on other additives that could act as replacements for sucrose, to

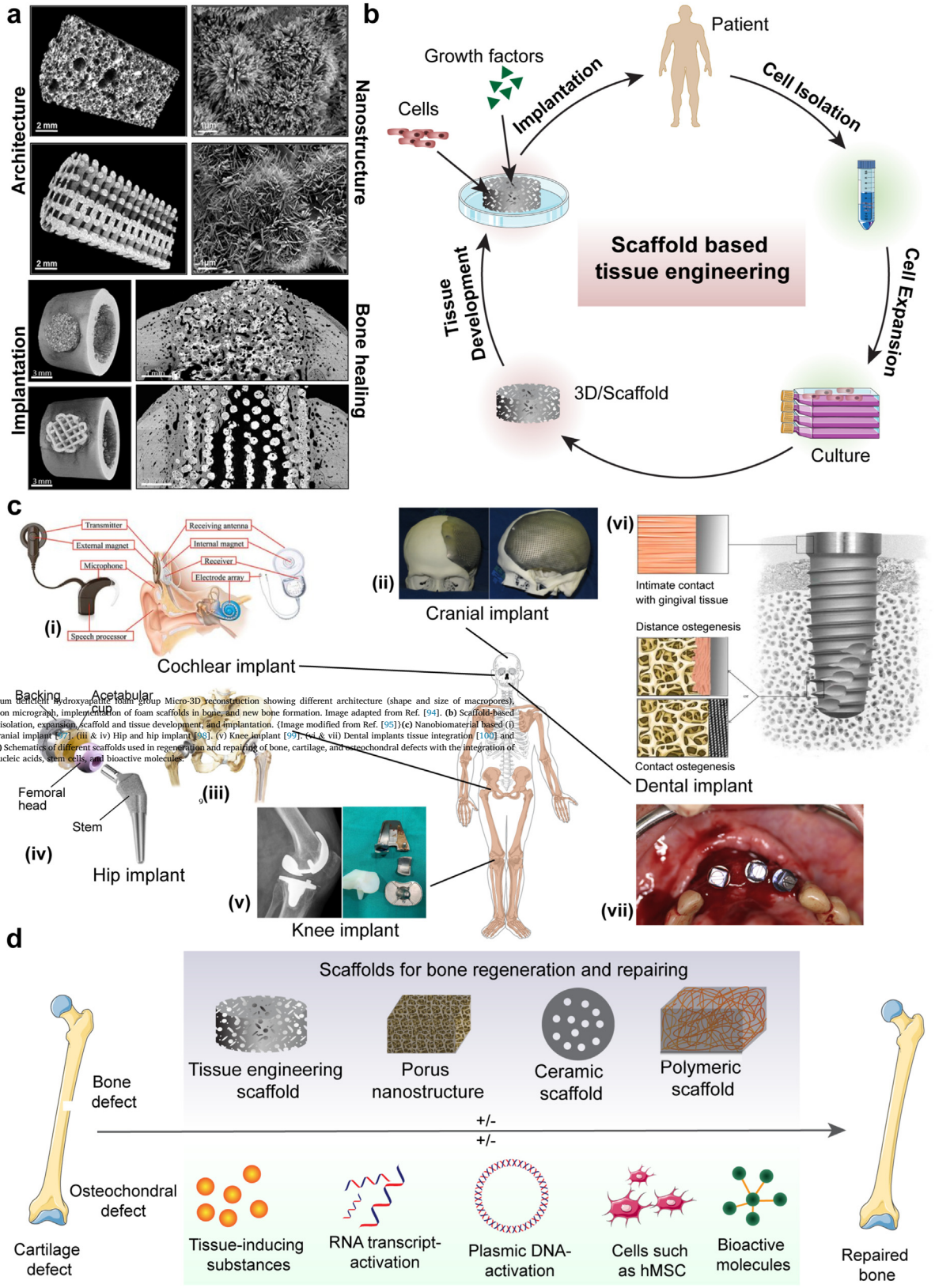



**Fig. 4.** **(a)** Biomimetic calcium deficient hydroxyapatite foam group Micro-3D reconstruction showing different architecture (shape and size of macropores), nanostructure scanning electron micrograph, implementation of foam scaffolds in bone, and new bone formation. Image adapted from Ref. [94]. **(b)** Scaffold-based Tissue engineering steps, cell isolation, expansion, scaffold and tissue development, and implantation. {Image modified from Ref. [95]}**(c)** Nanobiomaterial based (i) Cochlear implant [96], (ii) Cranial implant [97], (iii & iv) Hip and hip implant [98]. (v) Knee implant [99]. (vi & vii) Dental implants tissue integration [100] and insertion of implant [101]. **(d)** Schematics of different scaffolds used in regeneration and repairing of bone, cartilage, and osteochondral defects with the integration of tissue-inducing substances, nucleic acids, stem cells, and bioactive molecules.

maximize the interfacial tension, surface roughness, degree of supercooling, and viscosity [87]. To improvise this system as a whole, grafting a methacrylate group onto the ceramic before the metal infiltration to enhance the covalent bond formation between the two components is done [88]. As a result, a composite was obtained that did not demonstrate failure by delamination and showed crack-bridging ligaments, both of which testify to the beneficial mechanical properties of the matrix [87]. The material had a capacity to support tensile strains greater than 1%, toughened during crack propagation, and had a fracture toughness twice that of the bulk materials [88]. The surface-modified nanobiomaterials and their covalent interaction with exposed reactive groups is the primary factor that determines their physical and chemical properties [89–91]. One of the studies concluded that the chemical modification with the help of covalent bonding between several signaling molecules and scaffolds can be used as a therapeutic approach [92]. However, as a desirable alternative to a few hazardous and chemical techniques, enzymatic methods for nanobiomaterials functionalization have been investigated intensively. For instance, using tyrosinase enzyme for fabricating a biocompatible silk fibroin-chitosan copolymer for silk was obtained. Similarly, a polylactic acid–chitosan copolymer can be obtained using porcine pancreatic lipase for improvement of cell adhesion that can be used as a scaffold material in tissue engineering [93].

#### 4.1.1. Multifunctional nanofiber scaffolds as drug delivery systems

Nanofibrous biomaterials have proved to be very appealing for drug delivery applications, due to their promising structural and functional features which are alike the native extracellular matrix (ECM). An array of natural and polymeric materials can be engaged in the production of nanofibrous biomaterials [102]. These nanofibrous biomaterials can be formulated from a wide range of polymers for drug delivery applications [103,104]. Polymeric biomaterials can be categorized into natural and synthetic polymeric biomaterials. Natural polymeric biomaterials include chitosan, chitin, gelatin, cellulose, collagen, and lignin [105]. These natural polymers can be used to mimic ECM and are biocompatible [106]. However, they are burdensome to form into continuous nanofibers [107]. Thus, synthetic polymeric biomaterials with properties biodegradable in nature, have been amalgamated with natural polymeric biomaterials, due to their molecular weights being long enough to fabricate nanofibers after elongation [108]. Polymers such as polyethylene oxide (PEO), polycaprolactone (PCL), poly lactic-co-glycolic acid (PLGA), and poly N-vinylpyrrolidone (PVP), have been approved as biomaterials, and are usually employed to form composites with polymers for the fabrication of nanofibers, and for sustainable and controlled drug delivery or release [109]. Apart from this, some nanostructured materials can be spontaneously used for loading and releasing bioactive molecules or to bind endogenous growth factors, simultaneously. On the other hand, successful fabrication of 3D scaffolds was possible with these biomaterials. A major example is the use of peptide amphiphiles. Stupp and coworkers engineered a heparin-binding peptide (HBPA) nanogel that was able to bind and was capable of mimicking physiologic BMP-2 signaling [110]. A recent study showed, that in the extracellular environment, sulfated polysaccharides bind covalently to glycoproteins such as syndecan and non-covalently to fibronectin fibers, also bind BMP-2 through a heparin-binding domain and regulate its bioactivity [111]. Consequently, this BMP-2 binding PA promotion growth factors in bone regeneration in a rat critical-size femoral defect model with does ten times lower than usually required [112]. Reports have been produced that BMP-2-binding PA nanogels provide significant capacity for bone regeneration in a well-known pre-clinical posterolateral lumbar fusion model with eight to ten times lower dosage requirement of BMP-2 than are given generally. Another study depicted that, hydrogels that were designed with BMP-2 mimicking peptides, had the potential to induce osteogenic differentiation of rat MSCs in vitro. Later on, this osteogenic capacity was established *in vivo* using a rat cranial defect model [113]. In 2017, Lee et al., [112] stated that peptide amphiphiles were functionalized with supramolecular glycopeptides nanostructures containing sulfated monosaccharides, Lee et al., [114] given that the sulfate chains of heparin are expository motif, for the binding of many osteogenic growth factors under physiologic conditions [115].

#### 4.1.2. 3D printing

Over the past few decades, allografts and autografts are considered potential treatment options for several musculoskeletal disorders. Allografts can be used to replace damaged tissues in cases of bone malignancies, trauma, and other degenerative recessions. However, these therapeutic approaches come with a few drawbacks, including high costs, mismatches in tissue size and source, and immunological rejection. Tissue engineering, which uses biomaterials to regenerate or replace damaged tissues, is emerging as a viable therapy option [116,117].

Additive manufacturing, otherwise known as three-dimensional (3D) printing, is progressing in engineering, manufacturing, art, educational, and medical fields. With the advancement of science and technology, it is now feasible to develop implants with a variety of internal structures and forms. To overcome the issues of tissue mismatching, various nanoscale biomaterials with the help of 3D printing and bioprinting can be used to construct personalized bone implants. The implication of nanotechnology and nanomaterials have made noteworthy progress in highlighting 3D printing and bioprinting as possible platforms for engineering live bone tissues, which can be attributed to their nano-structural impact [118,119].

3D bioprinting can allow the replication of bone–muscle–tendon and musculoskeletal interfaces resembling real tissues with controlled microstructures and biological compositions [120,121]. The incorporation of several nanomaterials like nanofibers and nanocrystals can be used to strengthen the physical and mechanical behavior of 3D printed bone implants with electro-spun nanofibers being the most prevalent [122,123]. To maintain the cell functionality and withstand the shear force, soft hydrogel-based matrices as bioinks are favored for 3D printing. To overcome the constraints of mechanical qualities and equip the composites with the necessary regenerative capability, the 3D-(bio)printed hydrogel structures can be strengthened by combining with different nanomaterials like nanofibers [124–127].

The human adipose-derived stem cell (hADSC)-laden alginate hydrogel was bio-printed with a strengthening poly(lactic acid) (PLA) nanofiber to generate a tissue that can resemble the nanofibrous matrix of soft musculoskeletal tissue while maintaining its mechanical characteristics [128]. Similarly, 3D printing and nanofibrils can be utilized to improve the physical characteristics of a gelatin-based hydrogel that will be employed as reinforcement material and mimic the extracellular matrix (ECM) shape [122]. To aid bone regeneration, bioactive gold nanoparticles (GNPs) with tunable size and surface modification were used as a reinforcement material for a 3D printed PLA construct by fused deposition modeling (FDM) of a gelatinmethacryloyl (GelMA) hydrogel which showed a stiffness level equivalent to natural bones. Another 3D printed microstructure incorporated with the gold nanoparticles of cyclic arginine-glycine-aspartate peptide conjugate was shown to induce osteogenic differentiation by upregulating the osteogenesis-related factor gene expression [129].

Osteosarcoma, a malignant neoplasm in which tumor cells create osteoid, appears to be popular among young people. Surgical excision and chemotherapy are two current treatment options for osteosarcoma, which can induce bone abnormalities that can be overcome through bone tissue engineering. Natural polymers, synthetic polymers, and bio ceramics can be utilized to counteract the negative effects of chemotherapy. Unlike chemotherapy, the distinction between tumor cells and normal healthy cells may be accomplished with the use of nanocarriers and modern nanotechnology. Natural polymers like chitosan, alginate, collagen, gelatin, and silk fibroin and bio-ceramics like calcium phosphate, calcium silicate, and bioglass can be used to design 3D printed scaffolds with the help of nanotechnology. A few synthetic polymers, for

instance, polycaprolactone, polyurethane, poly(lactic)acid, and poly(vinyl) alcohol can also be incorporated to make scaffolds for bone regeneration. Understanding how various nanocarriers like nanoliposomes, polymeric nanoparticles, gold nanoparticles, silver nanoparticles, and mesoporous silica nanoparticles may be used to load anti-cancer drugs into 3D scaffolds could help solve the problem of remaining osteosarcoma cells in future [130].

A few common bioprinting techniques like ink-jet-based bioprinting, pressure-assisted bioprinting, laser-assisted bioprinting, solenoid valve-based printing, extrusion printing, and acoustic-jet printing are in use by scientists to print biomaterials such as cells and proteins into 3D structures. These 3D structures may be employed as tissue models for drug testing, disease models for cancer research, and constructs for implantation in animals or humans [131].

#### 4.1.3. Silk based proteins

Silk is classified as polymers that are twirled into fibers by Lepidoptera larvae including silkworms, spiders, scorpions, mites, and flies [132,133] Natural silk fibers are produced from arthropods such as silkworm that constructs cocoons from silk fibers. These cocoons are rich in different classes of a protein termed fibroins and sericin. These proteins consist of 18 different amino acids with glycine, alanine, and serine presence in greater concentrations [134]. Silk obtained from silkworms can be classified as mulberry and non-mulberry silk based on the food sources of the worm. Silk proteins are secreted from specialized glands after the biosynthesis in epithelial cells. Silk has been employed in various biomedical applications since ancient times. Silk protein has the desirable potential to design biomaterials that can be used for various biomedical applications including drug delivery, wound healing, tissue engineering, electronic devices, and others [132,135]. In absence of the silk protein sericin, the fibers display less inflammatory tissue responses enabling successful implantation and cell culture. Silk fibers exhibit high tensile strength, and flexibility and are resistant to compressive forces making them suitable for sutures or as load-bearing composites. Apart from exhibiting high tensile strength, these silk fibers are resistant to cumulative deformation. Silk fibers are comparatively more stable in the environment because of their extensive hydrogen bonding, hydrophobic nature of the protein, and their crystallinity [136]. Silk proteins have repetitive hydrophobic crystalline regions allowing them for protein self-assembly which eventually leads to strong physical interactions providing strength and toughness to the biomaterials. The presence of this hydrophobic domain within the silk fibers enhances the hydrophobic drug carrier interactions allowing the effective loading and release of the drug [137]. Silk-based drug delivery systems are vastly exploited for cancer treatment owing to the controllable processibility of the silk materials into different morphologies such as films, hydrogels, particles, and even scaffolds. Scaffold biomaterials could influence the quality of cartilage produced and thus used in the tissue engineering process [138,139]. Silk scaffolds are stable and possess a slow degrading structure, making them suitable for tissue engineering, inducing chondrogenesis, and can be employed in a wide range of clinical applications. Porous silk scaffold is believed to guide the process of attachment, proliferation, and migration of osteocytes and could also induce osteogenic differentiation of stem cells resulting in bone recovery [138]. The fibroin protein present in the silk biomaterial can promote tissue regeneration. Sericin possesses cytoprotective and mitogenic actions on fibroblasts and keratinocytes, making it an appealing candidate for skin and tissue repair materials development. The silk fibroin also acts as an excellent natural macromolecular material that is biocompatible and regulates tissue engineering, along with cartilage and osteochondral repair [139]. The silk protein fibroin and sericin provide structural and functional properties to the mechanically flexible and bioresorbable sensors. These silk proteins provide controllable biodegradability, and mild immune and inflammatory responses making these sensors ideal for clinical application [140].

### 4.2. Cancer therapy

#### 4.2.1. Nanoparticle mediated cancer imaging

Nanoparticles are well-known due to certain features like their high surface-area-to-volume ratio (relative to larger particles), the potential for numerous sites for chemical modification, and so on. All these characteristics make them highly suitable for imaging applications. Likewise, their ability for chemical modification may be used to amplify the imaging sensitivity [141]. Superparamagnetic iron oxide nanoparticles (IONPs) have been used for MR imaging of lymph nodes following the macrophage uptake, which may be beneficial in the detection of metastatic diseases [142,143]. Instances have been seen where IONPs have been conjugated to the amino-terminal fragments of urokinase plasminogen activator for specifically imaging breast cancer [144], at the same time, this is been observed that conjugation with an antibody to EFGR was used for imaging of brain tumors [145]. For developing surface-modified IONP for cancer imaging, generalized chemical methods are being improvised [146]. A new approach has been proposed recently, which is based on the *in vivo* assembly of nanoparticles with the imaging agents [147]. Different types of nanoparticles have been conjugated with chelates of paramagnetic Gd 3+ to enhance the contrast of MR including the dendrimers, micelles, and CNTs [148]. Principally, highly specific imaging of small numbers of malignant cells could be achieved by conjugating a targeting agent, such as a mAb, with the Gd 3+ -chelates to affect the MR relaxivity or conjugating with other imaging probes. Handling sensitivity issues hands-on is a problematic issue in imaging research. One of the potential approaches is to amplify the signal in the area of interest by delivering a suitable enzyme. Gold nanoparticles have shown great effect in enhancing the contrast in X-ray images providing advantages relative to triiodobenzene [149]. Along with the enhancement of contrast in X-ray imaging, gold nanoparticles have also been observed to affect X-ray scattering. Thus, they can further be utilized to localize the radiation and improve treatment [150,151]. According to principles, nanoparticles can be used for both imaging and treatment applications [152]. For example, Titanium Dioxide nanoparticles may be used to enhance CT scans image contrasting, as well as to sensitize for photodynamic therapy [153]. Magnetic nanoparticles have been utilized for several purposes like improved MR imaging, hyperthermia, and some other applications for advanced cancer treatment [154]. The αv β3 integrin-specific peptide motif RGD may be used to direct IONPs to malignant cells for both enhancing the contrast as well as hyperthermia-based therapy [155]. Many times, a conjugation of IONPs with methotrexate [156], paclitaxel (PTX) [157], or any other anticancer drugs [158] are used in diagnostic applications as well as for therapeutic purposes. Among other established nano materials quantum dots, gold nanoparticles, and carbon nanotubes have been modified and utilized for potential theranostic applications [159].

Types of Nanoparticle Systems currently being used in cancer immunotherapy.

In the present-day world, several nanoparticle systems are being studied for cancer immunotherapy (Fig. 5). Among a wide array of nanoparticles, polymer-based nanoparticles are the ones to gain the most popularity [160]. A variety of polymers have been approved by FDA, such as polyethylene glycol, poly (lactide-o-glycolic) acid, and chitosan, owing to their biodegradable, biocompatible, and nontoxic features for synthesizing improved nanoparticle systems for cancer immunotherapy [161]. Other frequently used nanoparticle systems include the inorganic (such as gold nanoparticles) and lipid-based nanoparticles (such as liposomes) [162], as mentioned in Fig. 5. Fig. 5 shows immunotherapeutic and different target moieties, along with the main stages of the cancer cycle. All these nanoparticle systems can be favorably used for targeting cancer cells and delivering antigens and supplements to the target site with good accuracy and precision for the activation of the immune system.

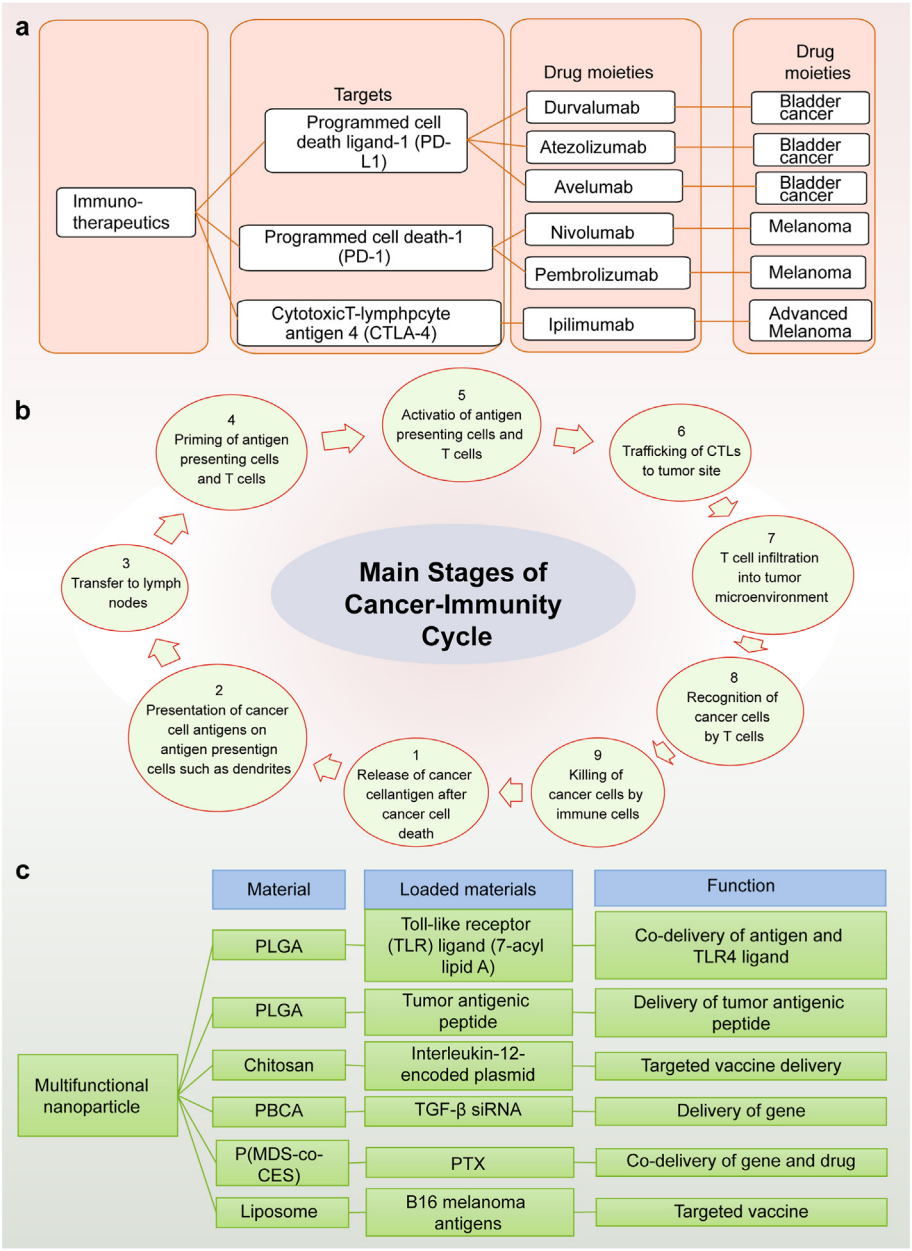



**Fig. 5. (a)** Food and Drug Administration (FDA) approved immunotherapeutic for cancer treatment. **(b)** Main stages of cancer immunity cycles. **(c)** Examples of multifunctional nanoparticulate systems for cancer immunotherapy that are being studied *in vivo*; PLGA: Poly (lactide-o-glycolic acid), PBCA: Polybutyl cyanoacrylate, and P(MDS-co-CES)-A triblock polymer. Images a-c are adapted from Ref. [163].

#### 4.2.2. *Multifunctional nanoparticle systems*

All cell types release membrane-enclosed nano- or micro-sized particles known as extracellular vesicles (EVs) [164]. Delivering, initiating, and creating activity in both proximal and distal recipient cells enables EVs to function as cell-to-cell communicators [165]. Additional EVs are released by tumor cells, and these EVs are essential for cellular communication in the tumor microenvironment, which promotes tumor growth and invasion [166,167]. The absence of reliable and repeatable techniques for the isolation of a pure vesicular population is one of the key issues facing EV use for clinical usage. There isn't a definite agreement on the best way to isolate a pure EV population that is free of contamination by similar-sized vesicles from various origins. This is a significant barrier to the use of EVs and their components for clinical usage, cancer screening, and early diagnosis [168]. Nanobodies have been utilized to target peptides specific the viruses, selected using variable fragments of the camelid single-domain antibodies phage display library. An enzyme linked immunosorbent assay (ELISA) detection system was established. This was accomplished by biotinylating the nanobody and using streptavidin-coated ELISA plates that could only exclusively catch the H5N1 virus to direct the nanobody's capture [169]. Appreciable development has been observed in the field of cancer immunotherapy which was introduced during the last decades. Although clinical trials of cancer vaccines have not yet gained substantial success, research is still going on for the former. In addition to several other factors, this unremarkable accomplishment could be a result of the traditional drug delivery methods used initially which were not very safe. However, with the advancement of nanotechnology, specially nanoparticle-based modalities, new opportunities and areas of research have been explored for the treatment of cancer [170]. To be precise, cancer vaccines have been essentially delivered using multifunctional nanoparticles, which exhibit several benefits, including targeted drug delivery of immunotherapeutic (such as immune checkpoint inhibitors)

using stimuli-responsive nanomaterials resulting in reduced off-target effects and an increase in the efficiency of the drugs. Other added advantages of these nanoparticle systems include the simultaneous delivery of multiple therapeutic moieties, where the agents being used for treatment and imaging can be integrated to the core and on the surface of the multifunctional nanoparticles for targeting affected tissues [171]. Some examples of multifunctional nanoparticle systems for cancer immunotherapy have been represented in Fig. 4. Current research has revealed that nanoparticles have multi-facilitated functions for (a) working as an effective substitute for the generation and transduction of chimeric-antigen receptor T cell, (b) inculcating tumor-suppressing activity to tumor-associated macrophages, and (c) knocking down Kras oncogene addition by using nanoCrisper-Cas9 delivery system [172]. Apart from these, nanomedicine platforms can be improvised for the improvement of the cancer therapy function by using multifunctional nanoparticles.

*4.2.2.1. Phage nanobiomaterials.* Bacteriophages are viruses having viron as biomaterials that can be modulated for their application in nanotechnology. The application of phage in different nanotechnology aspects has been possible due to emerged Phage display technology. Phage display technology has made great strides over the past two decades and has emerged as a potent tool in a wide range of scientific areas, including biotechnology, materials science, cell biology, pharmacology, and diagnostics. Molecular and imaging diagnosis [173] peptide drug discovery [174], targeted drug and gene delivery [175], vaccine development [176], identification of novel receptors and ligands, and [177] nanomaterials are some of the fields that presently profit from the system [178]. Excellent studies have been done on several phage-related topics, including phage biology [179] and the use of phage display in various contexts [180–182]. Phage display technology is a powerful, high-throughput technique for finding peptide ligands for a specific target. The method uses a library of phage particles that exhibit a wide range of peptides or proteins to determine the particular target for binding [183]. It is a promising method for locating apatite and cell-specific sequences that can be coupled to promote cell-specific adhesion for mineralization of biomaterials. Ramaraju et al. [184] have studies experimentally with different phage-derived single and dual-functioning peptides. They incubated control peptides on HA powder (Sigma Aldrich, St. Louis, MO) at 37C in Trizma buffer (pH 7.5) for 3 h in a 96-well Millipore filter plate to sieve the petides. Unbound peptide solution was filtered into a fresh plate and the amount was quantified using standards. Measured bulk peptide concentrations ranged from 0 to 2000 mg/ml. No affinity was demonstrated by the peptides towards the tissue culture polystyrene surfaces; hence no peptide was bound to the plate walls which could cause an overestimation of peptide binding to minerals [185]. Assessment of affinity to apatite was done by constructing Langmuir isotherms of bulk versus bound peptides to determine the binding affinity (K1).

Peptides produced from phage displays have also been used in T lymphocyte-mediated immune responses at later stages [186]. In a ground-breaking study, Kraft and colleagues tested a 12-mer library on recombinant v6 integrin produced as a transmembrane truncated soluble receptor, recovering the RGD motif in 51% of the clones and the DLxxLx motif in 27%—the latter of which turned out to be highly selective for v6 [187]. The peptide motif RTDLDSLRTYTL (Bpep), which was derived from the clones chosen for this study, was used in a later study as a Chimeric Antigen Receptor (CAR) targeting domain. The Bpep-CAR, which consists of the v6-binding peptide followed by a triple glycine linker, an IgG4 hinge region, the CD4 transmembrane domain, and the cytoplasmic signaling domain of $CD3^{-}$, was genetically engineered into primary human T cells. The human ovarian cancer cell line OVCAR-3 and two primary ovarian tumor lines (RSN001 and RSN002), both positive for v6 integrin, were both identified and eliminated by the Bpep-CAR-exposing lymphocytes in vitro. Bpep-CAR-expressing T cells were stimulated to release large amounts of IFN- after interacting with v6 integrin [188]. Phage display has found a large number of tumor-targeting peptides, therefore more CAR T cell applications are anticipated in the near future thus evolving cancer therapy. With advancement of these phage based technology, the derived peptides have been used for many nanotechnologies related application and biosensing.

*4.2.3. Photodynamic cancer therapy*

Photodynamic cancer therapy is based on the destruction of the cancer cells by laser-generated atomic oxygen, which might be cytotoxic. The special dye that is used to generate the atomic oxygen, is taken by the cancer cells in a greater quantity in comparison to a healthy cell. Henceforth, only the cancer cells should be destroyed when exposed to laser radiation. Unfortunately, the remaining amount of dye molecules migrate to the skin tissues and eyes, and causes irritation, sensitivity, and makes the patient vulnerable to daylight exposure which might remain in the body for up to six weeks or more. Here, the role of nanotechnology plays its part in cancer therapy. Thus, to avoid this side effect of the dye, a hydrophobic version of the dye molecule was enclosed inside a porous nanoparticle. Then it was found that the dye did not spread to other parts of the body but instead remained trapped inside the Ormosil nanoparticle [189]. The dye stayed trapped inside the Ormosil nanoparticle and did not spread to the other parts of the body. On the other hand, the oxygen generating ability also remains unaffected and oxygen is easily diffused out via the pores of sizes about 1 nm [19].

Through the courses of treatment, patients could drink fluids containing nanorobots which are programmed to attack cancer cells and viruses and reconstruct the molecular machinery and structural components of the cells. In one process, cancer cells could be identified, removed, and healthy cells could be surgically implanted to facilitate the processes. Furthermore, keeping the future perspectives in mind, there could be an entire field of nano surgery to support or cure practically everything from natural aging to diabetes to bone spurs. As a consequence, there would be almost nothing left to be repaired by nano surgery [190].

*4.2.4. Nanobiomaterials driven direct cancer therapy approach*

Surface activation, or the creation of functionalities on the surface of nanobiomaterials, is a process used in a variety of chemical surface modification procedures. Because of the relatively small size of nanomaterials, they can target specific target sites by binding with several ligands, nucleic acid, peptides, or antibodies. Due to various intrinsic properties of nanomaterials, for instance, their interaction with ROS, and heat along with their biocompatibility have proved the nanomaterials to be useful as a potential therapeutic option in the case of cancer [91,191,192].

Few nanomaterials-driven direct cancer therapy approaches like using metalloid boron as an enzyme inhibitor, oxygen capturing, and using hydroxyl radicals for inducing cancer cell death are in use [192]. Because of boron's biological function in the control of gene expression, proliferation, and growth, boron neutron-capturing treatment (BNCT) employs metalloid boron as an inhibitor [193]. Boric acid and boron nitride function as abundant boron sources for the growth inhibition of cancer cells and other therapeutic approaches. Boron nanosheets, nanotubes, nanoparticles, and rare earth boride nanostructures are examples of boron-based nanomaterials created for therapeutic application [194].

To satisfy the octet rule trivalent boron reagents can adapt an $SP^3$ tetrahedral configuration. The change from $SP^2$ to $SP^3$ configuration of carbonyl carbon leads to inhibition of enzymatic activity. Therefore, to inhibit the hydrolytic enzyme activity boron reagents can be used as an alternative to carbon. Additionally, the inhibition of enzymes is influenced by boron's affinity for the oxygen that forms borates [195]. The biocompatibility of boron-made nanomaterials, based on their structure, size, shape, and surface chemical characteristics, might be employed as an alternative to carbon, according to a literature study by Adeel et al. [192], that combined various findings of prior studies on cancer therapy.

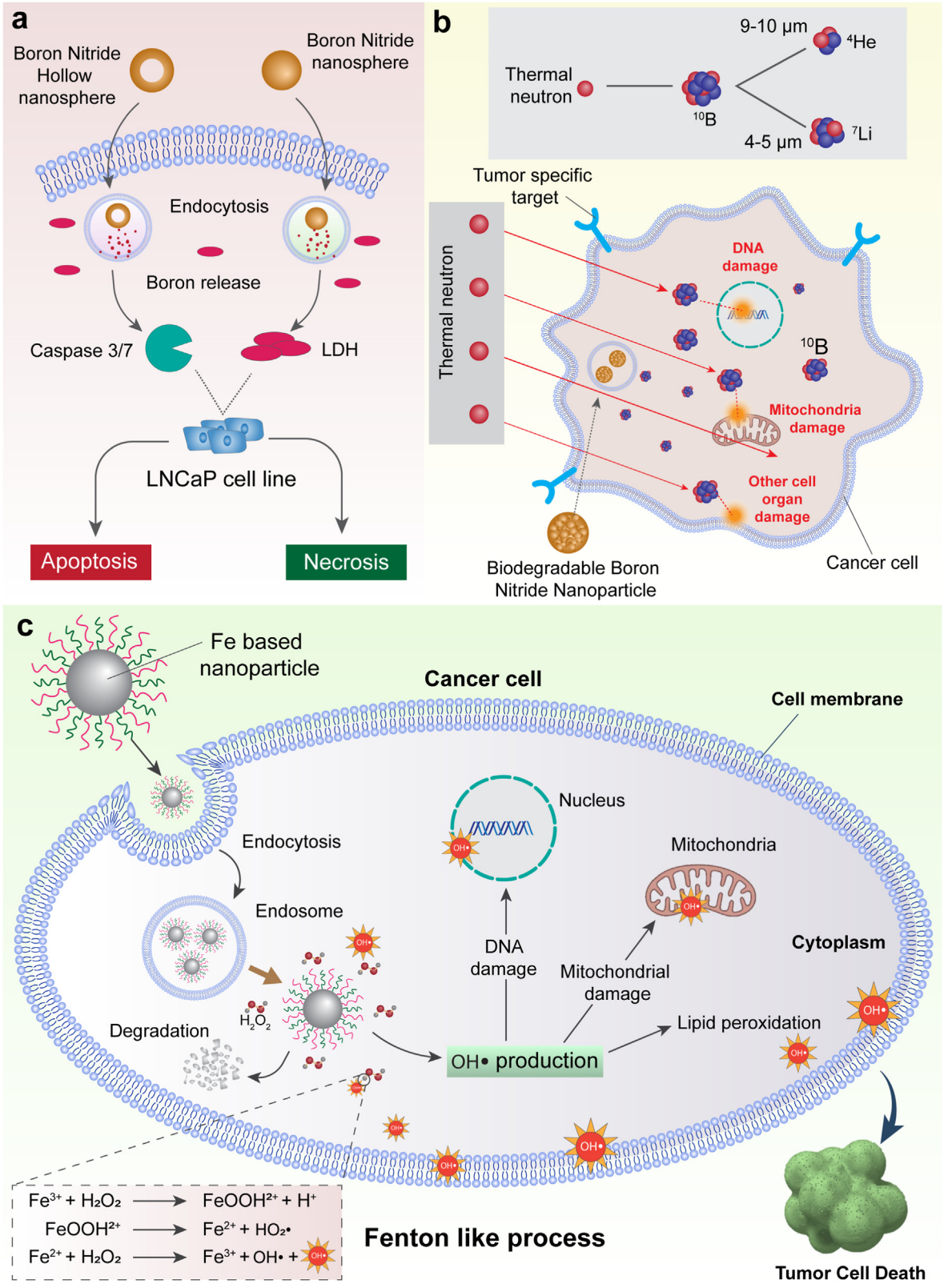



**Fig. 6.** **(a)** Boron Nitride hollow nanospheres (BNS) initiate apoptosis and necrosis by the Caspase-3/7 pathway (Shown above in Fig. 2 (a)) and Lactate dehydrogenase (LDH) release, respectively. **(b)** Biodegradable boron nitride nanoparticles lead to cancer cell death. The use of the thermal neutron approach leads to DNA, mitochondria, and cell organelle damage. **(c)**Iron-based nanoparticles cause tumor cell death by converting $H_2O_2$ to $OH^-$ Free radicals in Fenton chemical process. The release of excessive free radicals leads to DNA and mitochondrial damage. {Concept generated from Refs. [192,203]}.

Their primary method of action was based on the generation of reactive oxygen species (ROS), which led to membrane lipid, protein, and DNA damage, initiating the apoptotic process (Fig. 6). A Fenton chemical technique that changes $H_2O_2$ into the hydroxyl free radical ($OH^{\cdot}$) can be utilized to destroy cancer cells in addition to the boron inhibition approach. The tumor microenvironment contains a much higher concentration of $H_2O_2$ that upon conversion to $OH^{\cdot}$ can inhibit the tumor growth. Several nanoparticles synthesized to kill cancer cells using the Fenton chemical method are $Fe_2O_3$, $MnFe_2O_4$ [196], $FeO_x$-MSNs [197], silver [198], gold [199] and α-$Fe_2O_3$ [192,200]. low efficiency of the Fenton mechanism to release OH- led to the addition of a few other therapeutic approaches like chemotherapy, photothermal therapy (PTT), and photo-fenton to the reaction [201] (Fig. 6). Apart from iron few other compounds with the help of cations such as Mn2+, Cu+, and Cr4+ could produce a Fenton-like reaction. For instance, the amorphous iron nanoparticles (AFeNPs) developed by Zhang et al. [202], in presence of Fe2+ and Fe3+ induced excessive free radical ($OH^{\cdot}$) production in the tumor microenvironment.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\cdot} + H^{+}$$

Creating unfavorable conditions like hypoxia, high redox stress and inflammation using the therapeutic nanobiomaterials seems promising and could lead to targeting and killing the tumor cells in the future [192].

## 5. Translational applications of nanobiomaterials

Nowadays, monitoring air in the workplace, in an urban environment, and on battlefields has become a major requisite. Also, exhaled air from medical patients; air in packaged food containers; and all of these can be achieved using different analytical instruments. Vapor sensors have their niche in these measurements when unobtrusive, low-power and cost-effective technical solutions are required. Unfortunately, available vapor sensors tend to lose their accuracy often in the presence of high levels of interferences and cannot quantitate several components in complex gaseous mixtures, thus leading to degradation. Hence, new approaches with improved quality of sensor selectivity are required. By carefully designing sensing materials with new performance properties, and by coupling these materials with the suitable type of transducers, this technological task can be accomplished. The assessment of the capabilities of nanobiomaterials along with bioinspired nanostructures for selective vapor sensing needs to be focused. These sensing materials can run with several physical transducers based on their electrical, mechanical, and optical principles and also can provide vapor response selectivity which was previously unattainable by the use of other sensing materials. The ability of these vapor sensing systems to selectively detect signals, provide opportunities in major directions and advancements in applications of different vapor sensors.

There are multiple operational advantages of vapor sensors over other field-portable analytical instruments. These include low power consumption; modest form factors; operation without consumables; and real-time determination of concentrations of specific sample constituents. Responses of these vapor sensors should be considered on different levels, ranging from responses to all gases and vapors, to responding to only a specific vapor, and ultimately a response to the vapor of interest in the presence of gaseous interferences and uncontrolled operating conditions as mentioned in the figures given [204]. Fig. 7 demonstrates sensor materials, which are not only sensitive to target analysis but also a wide range of vapors and denotes variable or uncontrolled operating conditions, such as temperature fluctuations that further reduce the sensor accuracy [204]. The main aim is to achieve improved qualitative analysis by extracting the response patterns and identifying the types of detected analytes, when multivariate analysis tools process the response of arrays produced by sensors. Jurs et al., [205] and Röck et al. [206], used a technique for multivariate signals, that is implemented as a pattern-recognition system [205]. PCA is a robust, unsupervised technique that significantly reduces the data load dimensionality by presenting the data as its weighted sums of the original inputs from each sensor. Fig. 7 gives an idea about the principle of data processing using the PCA technique and the main aspects of PCA-based pattern recognition [204].

### 5.1. Biosensing with bioinspired nanostructures

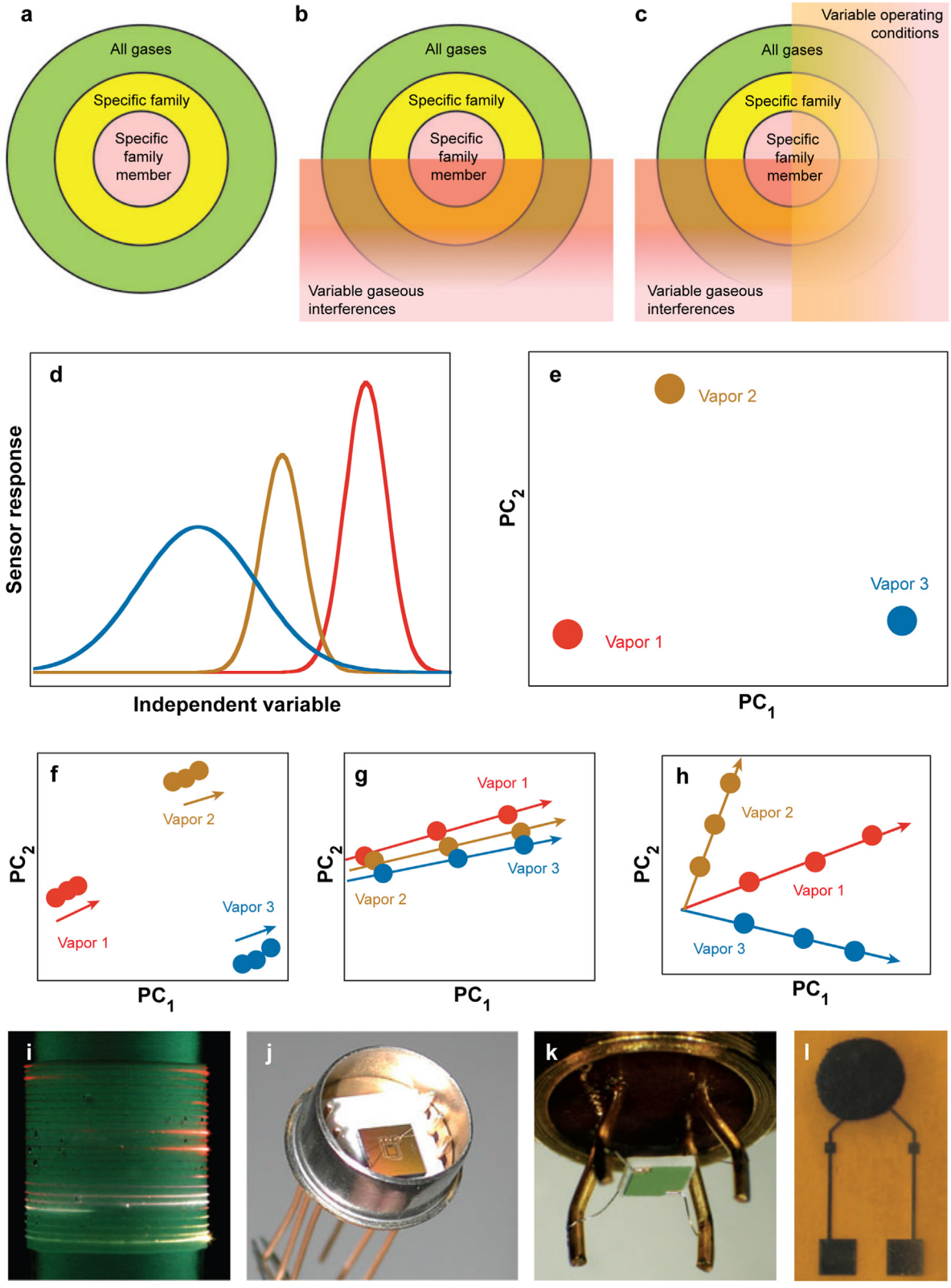
Natural biological nanostructures have recently become the center of growing attention for several sensing applications. Due to this tremendous advancement of biosensing nanostructures, the design features of these nanostructures often provide geometries that are nearly impossible to reproduce by using existing nanofabrication tools. Reported transduction principles using these bioinspired nanostructures include optical [207–209] and natural photonic crystals [210,211]. These photonic crystals may be 1-D, 2-D, or even 3-D in nature and are related to a phenomenon of structural color across the animal kingdom which has been under continuous development for more than 500 million years [212,213]. Examples of natural photonic structures such as morpho butterflies and other array systems demonstrate different types of interactions with light such as scattering, diffraction, interference, etc. [212,214–216]. These results illustrate a vast variety of approaches taken by natural structures to produce structural colors while some structures exhibit intrinsic vapor responses. For instance, a Dynastes Hercules beetle displays a diffractive hygrochromic effect, changing its color from green to black upon increased exposure to its moisture content (above 80%) [217]. Other natural photonic structures, such as scales of butterflies [218], scales of beetles [217], and feathers of birds [219], have been utilized as a source of studies due to their vapor responsiveness, with the motive of exploring the physics of optical effects, selectivity, and sensitivity of vapor responses.

## 6. Contribution of fabricated nanoparticles

Technology enables the fabrication of nanoparticles via chemical or biological methods [222,223]. Modified nanoparticles have gained recognition in a variety of domains of advancing nanobiotechnology including biomedicine, sensors, and wastewater management due to their unique physical, chemical, structural, electrical, and magnetic properties (Fig. 8). Several physical, chemical, and biological approaches are utilized to synthesize different coated nanoparticles as they are environmentally friendly and cost-effective. However, the green synthesis of these fabricated nanoparticles such as magnetic nanoparticles is gaining rapid momentum and researchers are more focused on biological synthesis due to many advantageous aspects [224] (Fig. 8). Physical and chemical methods have major drawbacks such as the high cost, and use of hazardous chemicals that may cause toxicity to humans, and harm our ecosystem consequently [225]. In contrast, the biological method is more natural for example enzymes such as nitrate reductase naturally play the role of reducing agents and raw materials are easily accessible [226]. For instance, the biosynthesis of silver nanoparticles from silver nitrate salt uses the enzyme nitrate reductase with coenzyme nicotinamide adenine dinucleotide phosphate (NADPH) [227].

$$2Ag^{+} + NADPH \rightarrow 2Ag^{0} + NADP^{+} + 1H^{+}$$

Over recent years several nanoparticles have gained importance in various fields of application. Industrialization and urbanization have caused havoc release of toxic contaminants in the form of harmful by-products like affluence and gases, including both organic and inorganic pollutants [228,229]. Adsorption, filtration, catalysis, and transformations are the four major removal techniques or degradation mechanisms of MNPs for contaminants removal from wastewater [230]. The high surface area and nano-size pores of MNPs can easily functionalize and help in the adsorption of the targeted contaminants [231].




(caption on next page)

**Fig. 7.** Performance level of the sensor system. **(a)** All vapors are detectable by a sensor (Sensitive to all vapors, specific family, and a specific family member of vapors). **(b)** Sensor performance accuracy is degraded by the presence of variable gaseous interference hence creating complications in sensor measurement. **(c)** Sensor performance accuracy is reduced by temperature fluctuation and uncontrolled operating conditions. **(d)** For principal-components analysis (PCA) exemplary processing and PCA-based pattern recognition, three simulated Gaussian curves with varied height and width. The basic features and key points on which the PCA-based pattern recognition system works are: (a) Three stimulated Gaussian curves with variable height and width for PCA exemplary processing. (b) Scores plot of a PCA model, based on the data from the three stimulated Gaussian curves. The general scenarios explained in the figure revolve around sensitivity and selectivity, and how it varies in all three situations. (PC1, PC2, and PC3 denote principal components 1, 2, and 3, respectively) **(e)** A principal-components analysis model scores plot based on data from three generated Gaussian curves. Principal-components analysis score plot with three different scenarios according to sensitivity and selectivity (f–h): **(f)** good selectivity and poor sensitivity, **(g)** good sensitivity and bad selectivity, and **(h)** good selectivity and good sensitivity. (a–h) images are adapted from Ref. [204] (i–l) examples of transducers. **(i)** Radiant energy transduction **(j)** mechanical energy transduction. Adapted from Ref. [204] (i–l) examples of transducers. **(i)** Radiant energy transduction **(j)** mechanical energy transduction. Adapted from Ref. [220] **(k)** electrical energy transduction **(l)** thermal energy transduction. {Adapted from Ref. [221]}.

MNPs are the probability of achieving their optimum efficiency while dispersed in water because of their mobility and close contact with pollutants [232,233]. MNP-based nano filters that act on low pressure also gain water purification, the key benefit of ng momentum for waste water management due to its fixed surface charge and high rate of permeation [234]. Products of daily usage including dyes, pharmaceuticals, and personal products are organic contaminants and are a major source of water pollution. For the degradation of organic contaminants, Fe-MPN is very efficient and highly stable [233,235]. Other variety of contaminants can be removed by magnetic nanoparticles coated with Poly(-ethylenimine) (PEI). In 0.5 L of wastewater, PEI-coated iron MNP can remove 50% of total organic carbon within 60 min. Moreover, the turbidity, microbial content, and color of wastewater are also reduced to a greater extent using the PEI-coated iron MNP [236]. It has been reported that doped MNPs can enhance the $H_2O_2$ activation ability and decompose $H_2O_2$ more rapidly than the undoped copper doped $Fe_3O_4$ MNPs. $H_2O_2$ is the source of OH radicals that can be used in the degradation of a dye such as Rhodamine B. Moreover, OH radicals can be scavenged by $H_2O_2$ if provided in excessive amounts in the solution which eventually lowers the concentration of OH radicals [235].

$$4H_2O_2 + \bullet OH \rightarrow HO_2 \bullet + H_2O$$

Huang et al. [237], synthesized and functionalized $Fe_3O_4$ magnetic nanocomposite with poly (ionic liquid) for the removal of anionic dye from an aqueous solution of mixed dyes [238]. The adsorption performance of the dyes was explained through two widely used adsorption isotherms models, Langmuir and Freundlich, where the Langmuir constant is related to the adsorption site affinity, and the Freundlich constant signifies the adsorption intensity and capacity.

$$\text{Langmuir: } C_e/q_e = C_e/q_{max} + 1/q_{max}K_L$$
$$\text{Freundlich: } \ln q_e = 1/n \ln C_e + \ln K_F$$

$q_e$-adsorption capacity at equilibrium, $q_{max}$-adsorption capacity of the theoretical maximum monolayer, $C_e$ - concentration of adsorbate at equilibrium, $K_L$ - Langmuir constant, $K_F$- Freundlich constant.

The nanocomposite showed ultra-fast adsorption of Alizarin red up to 510.2 mg $g^{-1}$ from the mixed dye of thionin acetate, malachite green, acid orange II, and alizarin red. This poly (ionic liquid) nanocomposite is efficient and durable for wastewater treatment and the collection can be achieved by applying a magnetic field and regenerating it with a salt solution. In a study, Nodehi et al. [239], synthesized a core-shell nanoparticle of $Fe_3O_4$ coated with NiO in the removal of Alizarin from an aqueous solution. By applying the pseudo-second-order kinetic equation and Freundlich isotherm model it was concluded that the NiO core-shell $Fe_3O_4$ magnetic nanoparticle has a maximum adsorption capacity of 223.30 mg/g of Alizarin.

$$Ni(NO_3)_2 / Fe_3O_4 + 2NaOH \rightarrow Ni(OH)2 / Fe_3O_4 + 2NaNO_3$$

The former study further stated that co-anions inversely affect the adsorption capacity, as increasing the co-anions in solution decreases the adsorption capacity. Jiaqi et al. [240], synthesized a carboxylated ethylenediamine functionalized magnetic nanoparticle ($Fe_3O_4$, SiO core-shell magnetic nanoparticle) for removal of and improving the adsorption of methylene blue from an aqueous solution. In accordance to pseudo-second-order kinetic equation and Freundlich isotherm model, equilibrium was attained at 60 min with a maximum adsorption capacity of 43.15 mg/g. It is noteworthy that external magnets can quickly recover adsorbents from aqueous solutions. Several magnetic nanoparticles such as Kaolinite-supported nanoscale zero-valent iron [241], betaine-modified magnetic iron oxide nanoparticles [242,243], $Fe_3O_4$ MNPs [244], and three-dimensional magnetic bacterial cellulose nanofiber [245] are used to remove crystal violet, methylene blue, green/red azo dye, and malachite green respectively.

Inorganic contaminants like metals and heavy metals are toxic to an environment that can also be removed by using MNPs. Heavy metals like mercury, lead, chromium, gold, copper, etc. can be adsorbed using various MNPs [226]. Dil*et al.* [246], synthesized a novel MNP of gamma-$Fe_2O_3$ for $Pb^{2+}$ ion from an aqueous solution. The maximum adsorption capacity of the MNP is 163.57 mg/g in 4 min as described by the second-order kinetic equation and Freundlich isotherm model. $Fe_3O_4$ and porous graphene composite can be synthesized with an environmentally friendly cost-effective hydrothermal process that can remove both organic and inorganic contaminants from the wastewater. $Fe_3O_4$/graphene nanocomposite resulted in ultrahigh adsorption of $Pb^{2+}$, $Cu^{2+}$, and $Cd^{2+}$. The high surface area of graphene and $Fe_3O_4$ magnetic properties helps in easy separation, reusability, and high adsorption capacity of the nanocomposite [247]. In extraction of gold and copper thiosulphate from alkaline gold ore leachate using polyethyleneimine-coated iron oxide MNP, maximum adsorption of gold and minimum of copper was at the adsorbent dose of 35 g/L for 55 min at 23°Ctemperature. The ANOVA test showed that gold adsorption efficacy is affected by adsorbent dosage and copper adsorption efficacy is affected by three parameters, time, temperature, and interaction of adsorbent dosage with temperature [248].

In recent years, *in vivo* targeted delivery of therapeutic compounds in the treatment of profuse diseases using MNPs has gained a lot of interest. The system includes a therapeutic compound such as doxorubicin for chemotherapy in cancer, attached with biocompatible MNP that can be targeted to a specific area *in vivo* by applying an outside magnetic field [249]. The surface coating and magnetic core of MNPs determine their potential in drug delivery systems. Chitosan as a surface coating to MNP is a promising biopolymer that has a large surface-to-volume ratio with antimicrobial, biological, and outstanding physiochemical properties. The surface coating on MNPs provides a large surface area for bioconjugation of functional groups with therapeutic compounds or targeted ligands [250]. Magnetite, maghemite, and cobalt ferrite are the most widely used MNPs in drug delivery systems [251].

Taherian et al. [252], developed a chitosan-coated MNP loaded in black pomegranate extract for the treatment of breast cancer. The result showed that chitosan coated MNP has no *in vivo* cytotoxicity with higher efficiency than the free drug that can significantly eradicate cancerous cells. Another MNP delivery vehicle with a dual-layer, core of doxorubicin-gelatin and shell of Fe3O4-alginate to target the breast cancer cells constituted from Michigan Cancer Foundation-7. The dual-layer MNP efficiently encapsulates, delivers doxorubicin, and

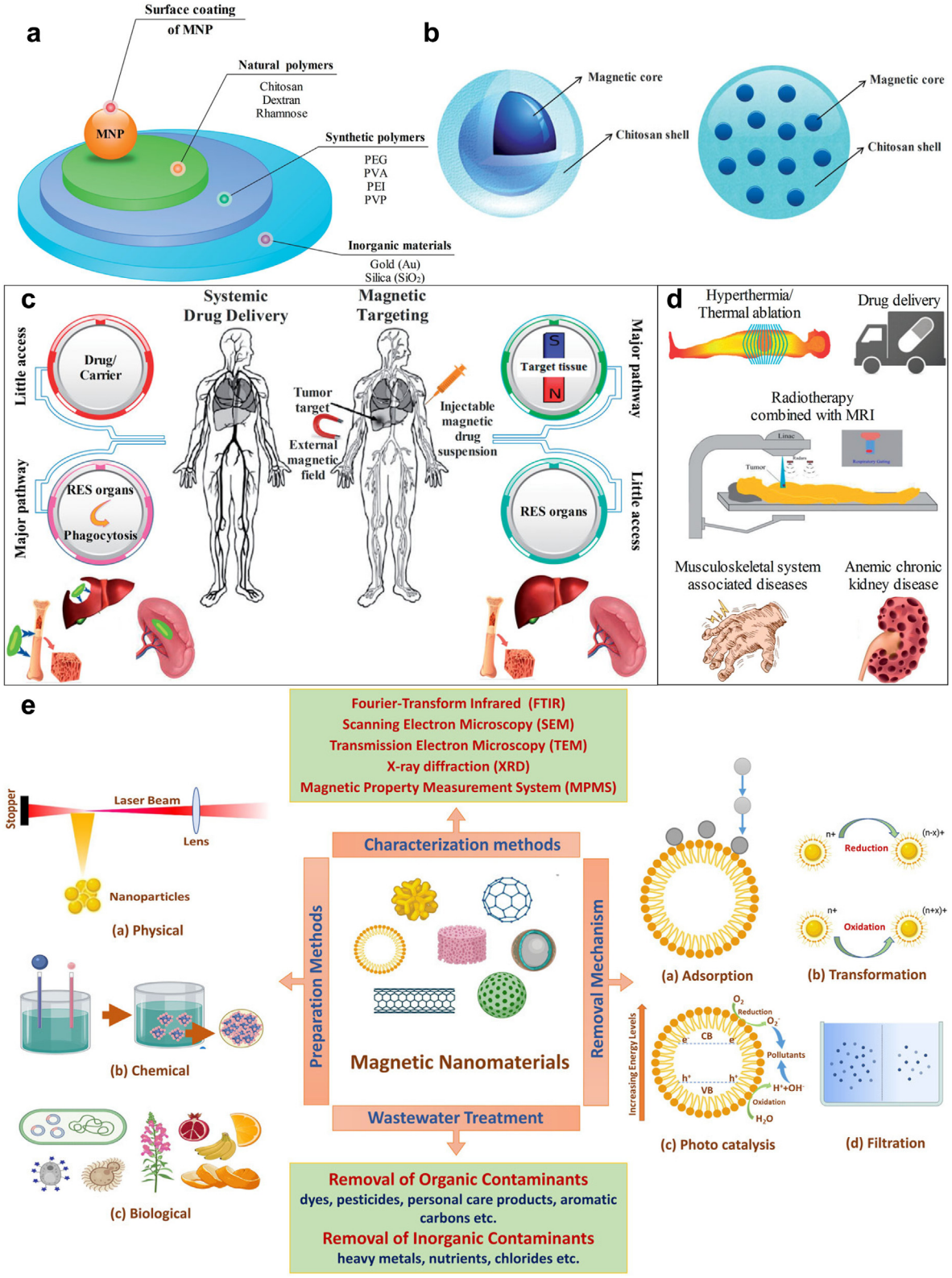



**Fig. 8.** **(a)** Fabricated nanoparticles with various magnetic core coatings for surface modifications. **(b)** Chitosan shell on magnetic core and homogenously dispersed magnetic multi-cores in chitosan. **(c)** Magnetic drug targeting principle (RES: reticuloendothelial system). **(d)** Biomedical applications of the magnetic nanoparticle. (a–d) images adapted from Ref. [250] **(e)** Demonstrating magnetic nanoparticle preparation, characterization methods, and removal mechanism in wastewater treatment. Image adapted from Ref. [226].

targets the specific cell line. In an acidic medium, the release of doxorubicin accelerated which further appeared in the nucleus after 6 h of incubation after manipulation in the magnetic field. Within 12 h of incubation, the Michigan Cancer Foundation-7 breast cancer cell viability was seen to decrease noticeably [253].

Magnetic nanoparticle with less than ~30 nm diameter induces super magnetism where there is no magnetic dipole and the nanoparticles losses their magnetic memory due to thermal fluctuations. Hence, the nanoparticle orients randomly. However, the magnetic dipole can be induced with an external magnetic field. Super magnetism of MNPs is advantageous as the nanoparticle can easily be dispersed in the solution without inducing aggregation and is important for magnetic sensors. The MNPs integrated with analytical tools and methods have opened new doors for analytical chemistry, such as quantitative analysis, bioanalysis, sensors, chemosensors, and imaging techniques. Different sensors such as colorimetric, electrochemical, Giant Magneto resistive Sensors, optical sensors, and other analytical methods such as mass spectroscopy, and magnetic resonance imaging can be integrated with MNPs [254] (Fig. 7). Traditionally, MNPs have been employed for disease imaging via passive targeting (Fig. 6). Recent advancements have been made on MNPs to develop a non-invasive, cellular-specific targeting and multi-modal imaging in magnetic resonance imaging by optimizing designing criteria such as size, coating, and molecular functionalization [255]. For early diagnosis of influenza virus strains, Chou et al. [256], developed iron oxide MNP with H5N2 hemagglutinin targeted antibodies functionalized protein using immunoassay conjugated mass spectroscopy. The result showed the high specificity to the targeted protein by antibody conjugated MNP without cross-reactivity. To eliminate non-specific binding, the conjugate was capped with methoxy-terminated ethylene glycol. For virus screening, MALDI-MS technique was rapid and sensitive. The MALDI-TOF-MS was highly sensitive that can detect the targeted protein within an hour. For the diagnosis of different influenza strains, MNP encapsulation with monoclonal antibodies can be used as a specific probe. Similarly, MALDI-TOF-MS integrated with biomolecules functionalized MNP is effective in bacterial protein detection. Large proteins like penicillin-binding protein can be detected by MALDI-MS using amoxicillin functionalized MNP. As the diagnosis is sensitive, it has high potential in near future for the detection of pathogenic bacterial infections [257].

Microfluidic chips can be integrated with MNP conjugates for the detection of circulating cancer cells. Circulating-cancer cells in the bloodstream are rare and an important indicator of disease progression and survival. T. Y. Lee et al. [258], developed CD45 antibody-coated MNP for the detection of circulating cancer cells with an integrated microfluidic chip using multi vortexing to enhance mixing. T. Y. Lee et al. analyzed 10 blood samples of breast cancer patients from which circulation cancer cells were isolated from 5 samples while 1–3 cells from another 5 blood samples. The integrated microfluidic chip excludes the background cell in the bloodstream and enriches the circulating-cancerous cell for molecular and cellular analysis. Moreover, different tumor types circulating cancerous cell isolation can be expected to be useful with a proposed chip.

## 7. Current challenges and future perspective

Considering the commercial exploration of the nanobiomaterials applications, it is understood that some companies are involved in the development and commercialization of nanomaterials while most companies are miniature sequels of various research institutes. Most companies are developing pharmaceutical applications mainly based on drug delivery approaches. Several companies make the most of quantum size effects in semiconductor nanocrystals for tagging biomolecules or use bio-conjugated gold nanoparticles for labeling different parts of a cell. A wide number of companies are utilizing nano-ceramic materials for tissue engineering and several other medical fields such as orthopedics. Majorly, established pharmaceutical companies have their internal research programs on drug delivery that are either on formulations or dispersions containing components down to nano sizes. Colloidal silver has been substantially used in antimicrobial formulations and dressings. The high reactivity of titanium nanoparticles is also used for bactericidal purposes in filters. Increased catalytic properties on nano-ceramics or noble metal surfaces are used to destruct dangerous toxins and other hazardous organic materials.

For now, most commercial nanoparticle applications in medicine are focused on drug delivery systems. With the advancement of nanoscience nanoparticles, these days are replacing organic dyes in fields that require high photo-stability as well as high multiplexing capabilities. Noticeable development has been observed in directing and remotely controlling the functions of nano-probes, for example, magnetic nanoparticles to the tumor and then making them either to release the drug load or just heating them to destroy the surrounding tissue. The present-day goal is to further develop nanomaterials to make them multifunctional and controllable by external signals or by the local environment thus essentially turning them into mechanized nanoscale devices [19]. The development of 3D-bioprinted tissue constructs for application in drug discovery, assessment of chemical, biological, and toxicological agents, and fundamental research, in addition to transplantation, is a scientific breakthrough. Difficulties associated with like cell and material requirements, tissue maturation and functionality, and appropriate vascularization and innervation will arise as we try to move forward from 2D to 3D tissue development from the skin to hollow tubes like blood vessels, and solid organs like the kidney. To tackle these hurdles and explore the potential of 3D bioprinting, multidisciplinary research is required [119]. Several difficulties are still associated with product development and commercialization despite the field's rapid progress and rising number of publications. One of the most pressing challenges is the health, safety, and environmental impact of some nanobiomaterials, as well as their regulatory status. The regulatory requirements for its monitoring and continued development will influence the responsible use and acceptance of modern technology, either positively or negatively. These legislative constraints can either offer a framework for responsible technology adoption and decision-making, or they can create unwarranted obstacles to innovation and technology use. Regulations are intended to detect possible dangers while preventing excessive data creation, time delays, and cost increases. US government organizations like the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) along with various international governing bodies have evaluated nanobiomaterials regarding their environmental sustainability throughout the life cycle and the risks associated with their development and safety profile [259]. When it comes to nanotherapeutic, the Rule of Five doesn't apply to forecast the toxicity or safety profile of orally administered low molecular weight therapeutics. Thus, manufacturers must use caution and diligence in the development of this remarkable class of novel nanobiomaterials, to avoid the violence of these rules that still happen in the majority of cases [260]. The development of a balanced integrated approach between the regulatory aspect and technology adoption can only lead to meeting its expected return on investment from translational nanotechnology [261].

Since time immemorial our biosphere has been a continuous resource for plenty of substances, starting from plant extracts, vitamins, and peptides to biopolymers, and several other useful materials. Human beings on the other hand never left a scope to discover new topics and fields to study upon. Now and then we are coming across different materials and their usage. These days' bio-synthesized nanomaterials are playing a pivotal role in the field of tissue engineering and biomedical sciences such as drug and gene delivery, using different kinds of nanoparticles derived from green sources. Bio-inspired microstructures are usually nontoxic and many of them are well appreciated as green reduction agents. These nanomaterials are already in use and will be gaining popularity as time prevails. Metals, non-metals, and their respective oxides have been reportedly used in several environmental approaches such as water pollution. Biopolymers and their composites have shown

repeated use in medical-based applications. Articles have reported excellent applications of graphene-based cellulose fibers for the super capacitor applications and stated that such functional materials can be produced at an industrial scale if a substantial amount of research work is done on the extraction of cellulose fibers from wastepaper materials. Similarly, carbohydrates and their derivatives are already in use by numerous businesses and are readily available for real-time applications. For example, countless novel nanocomposites and new materials were developed using chitosan, cellulose, and dextran, which were isolated from natural sources. Although rapid progress was seen in the biomedical engineering sector over the past few decades, a lot of challenges are faced by researchers while designing a new podium that can assimilate new technologies for more innovative and significant commercial output of these biomaterials. Based on the above discussion, it is very clear that plant-based materials have tremendous potential to lead the world of micro and nanomaterials in various applications. The main issues that restrict its growth are mass production, easy availability, purification, and utilization without the help of other matrices. To solve these issues, we must overcome the upscaling ultrapure biomaterials production along with the challenge, which lies in conserving the commercial availability. Throughout the globe, biotechnologists are working hard to find possible solutions to the above-mentioned challenges and to push biomaterials from the patents to the markets. There is still a need for affordable technologies and much innovation in the field of nanomaterials. Hopefully, in near future, all biomaterial-based products will reach all the sectors of this society and benefit every individual [262]. Therefore, using nanoscience-based technologies we might be able to produce more, and the desired biopolymer-inspired micro and nanomaterials for a wide range of applications from medicines to electronics, to food to cosmetics.

## 8. Conclusion

The main goal of bio-nanotechnology is to provide humanity with a healthy and pollution-free lifestyle, and it has brought around many revolutionary inventions to serve this purpose. This review aims at gathering a collection of data demonstrating the developments and applications of bio-nanotechnology at the industrial level. These advancements encourage us to make great strides towards attaining a healthy lifestyle and wellness. Current research has revealed nanoparticle-based diagnostic approaches such as drug delivery, cancer immunotherapy, etc. that have been widely discussed in this chapter. Nanoparticles can improve antigen presentation via efficient delivery of cancer antigens and therapeutic supplements to APCs in immunological organs, for example, lymph nodes. The major trend in the further development of nanomaterials is to make them multifunctional and controllable by external signals or by the local environment thus essentially turning them into nano-devices.

In this review, we have tried to incorporate major details of all the fundamental aspects and recent progress about different kinds of bio-inspired micro and nanomaterials. Special attention has been given to industrial-scale applications of nanotechnology-based systems where nanoparticles have been utilized for a wide range of purposes starting from nacre to vapor sensing applications. These materials are not only abundant on our planet earth but also are bio-compatible and suitable for biomedical applications. In addition of it, the usage of bio-nanomaterials in the field of tissue engineering has also been mentioned which has become very popular in the last decades. The structural aspects of biomaterials and recent advancements are well deliberated in this study. Along with the already existing systems and methods, the future perspective of nanobiomaterials in upcoming years has also been predicted based on their commercial exploration. With the integration of bioprinting and nanomaterials advances, tissues with higher complexity and functionality are anticipated to advance to degrees each time closer to organ replicas. A review by Florczak et al. [137], suggested silk as a promising candidate for developing several nanobiomaterials for biomedical applications. Because of the stability, flexibility, and slow degrading structure of the silk-based scaffolds, they can be used for various biomedical and clinical applications apart from drug delivery, cancer therapy, and their use in electronic devices [132,140]. Apart from these, as per present needs, the main challenges for tissue engineering applied in the COVID-19 pandemic are the translation of clinical research into therapies and the development of scalable manufacturing strategies with commercially attainable measures [263]. Promising advancements of 3D printing have been pronounced at the reproducible, low-cost, and high throughput of scaffolds for tissue engineering, but the period for maturation of tissues and survival rate of cells must be optimized to clinch an appropriate clinical intercession. Biosafety and agencies by regulatory agencies are responsible for the scrutiny of all these biomaterials going under the process of the trial [264]. Controlling and patterning nanomaterials for 3D bioprinting can enable a multiscale and multi-material manufacturing strategy that will aid in the creation of modern designs with diverse applications [118]. Printability, structural integrity, biocompatibility, biosafety, and biofunctions of bioinks should be prioritized for the commercialization of 3D bioprinted products. A more advanced approach to bone tissue engineering may be conceivable with the successful integration of nanotechnology, nano biomaterials, and 3D printing technologies [122]. For instance, an allowable toxicity profile, higher biocompatibility, and biodegradability to verify scaffold removal without any need for an invasive surgery [265] are the utmost criteria for passing such trials. On the other hand, one thing that must be kept in mind is that as much as nanomaterials and nanoparticles are becoming an integral part of our everyday life, their possible toxicity and potential negative impact on the environment and health, in general, are becoming an important subject to study and much-needed research to avoid health hazards. Further investigations and detailed studies can uncover many facts that are yet unknown which might be directed to the future evolution of bio-nanomaterials, henceforth leading nano-biotechnology towards prosperity on medical, pharmaceutical, and an overall industrial scale.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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