Chapter 15
Recent Progress on Nanostructured Materials for Biomedical Applications

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Abstract The focus of this chapter is to explore the progress of nanostructured materials and their potential biomedical applications. Nanotechnology offers incredible opportunities in manipulating chemical and biological entities at the nano scale level. The nanoscience plays a key role in technological development for biomedical applications, especially in the areas of preclinical diagnosis, non- or minimal invasive biomedical imaging, drug discovery, and drug delivery. This research work discusses a brief history of nanotechnology, different synthetic routes, characterizations, fundamental concepts regarding morphologies, characteristics, biological interactions, and clinical applications. A few nanoparticles such as metal nanoparticles (Au, Ag, Pt, etc.), magnetic and metal oxide nanoparticles (Fe_3O_4, Fe_2O_3, ZnO, TiO_2, etc.), quantum dots (CdTe, Cds, etc.), mesoporous silica nanoparticles, carbon nano tubes (CNT, SWNT, etc.), ceramics nano materials (apatite, hydroxyapatite, bio-glass, etc.), polymeric nanoparticles (polypyrrole,

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β-cyclodextrin, chitosan, fucoidan, etc.) are widely used in biomedical field. In this article, we present the recent trend and challenges in the advances of nanomaterials for clinical applications. This review might be considered as a general guide and will help the readers to find key information regarding the recent advances in nanomedicine.

Keywords Nanomaterials · Metal nanoparticles · Ceramics nanoparticles · Polymeric nanoparticles · Cancer treatment · Tissue engineering · Biomedical application

15.1 A Brief History of Nanotechnology

The advances in nanomaterials research and applications with pharmaceutical and biomedical applications have been increased remarkably. To realize the importance of nanotechnology, the chronological achievements of this science need to be considered always. The journey of nanoscience and technology begins since the fourth century (The Lycurgus Cup stained with colloidal gold silver), ninth–seventeenth century which evidenced on in the of Europe's medieval stained windows glass in cathedrals. With progress in time, the development of nanotechnology tremendously accelerated to a new dimension where a new era of nanotechnology started. Nanotechnology represents an escalating research area, including materials, objects, and systems with improved characteristics and functions due to the special tailored preparation in 1–100 nm scale usually. A chronological development of nanoscience and technology has been represented in a tabular form (Table 15.1). The nanoscience and technology grow its arms to multifunctional application starting from energy, healthcare, environment, space, oceans, information and communication, optical, materials, and applied field of research. Recently, a steadily growth observed in nanotechnology for different multidisciplinary healthcare applications such as targeted drug delivery, hyperthermia, photothermal and photodynamic therapy, bioimaging, biosensors, and so on (Mondal and Oh 2019).

15.2 Introduction to Nanoparticles for Biomedical Applications

Nanotechnology is subject to contribute in every field of science, including physics, chemistry, materials science, biology, medical science, computer science, and engineering. With the swift advancement of nanotechnology, drug delivery study extends its opportunities for enhanced therapeutic delivery. Due to their exclusive structure and superior properties, nanomaterials can successfully deliver therapeutics such as drugs, proteins, biomolecules, peptides, genes, nucleic acids, etc. In the field

Table 15.1 A chronological development of nanoscience and nanotechnology (https://www.nano.gov/timeline)

Year	Progress on nanoscience and nanotechnology
Fourth century	The Roman Lycurgus cup found stained in this ancient era with colloidal gold silver nanoparticles.
Ninth–seventeenth century	The vibrant colors of stained glass in the windows of Europe's medieval cathedrals are due to metallic nanoparticles.
1857	Michael Faraday discovered nano ruby gold colloidal solution.
1936	Invention of the field emission microscope by Erwin Müller, which explore the future of nano.
1947	The semiconductor transistor by J. Bardeen, W. Shockley, and W. Brattain.
1950	The process for monodisperse colloidal materials reported by Victor La Mer and R. Dinegar.
1951	Discovery of the field ion microscope by Erwin Müller.
1958	Design and fabrication of the first integrated circuit by Kilby (Nobel Prize winner 2000).
1959	Richard Feynman gave the first lecture on atomic scale, "There's Plenty of Room at the Bottom" at an American Physical Society meeting at Caltech.
1974	Professor Norio Taniguchi coined the term nanotechnology.
1981	Gerd Binnig and Heinrich Rohrer (Nobel prize winner 1986) at IBM's Zurich lab invented the scanning tunneling microscope.
1981	Alexei Ekimov discovered nanocrystalline, semiconductor quantum dots.
1985	Rice University researchers Harold Kroto, Sean O'Brien, Robert Curl, and Richard Smalley (Nobel prize winner 1996) discovered the Buckminsterfullerene (C60).
1985	Louis Brus discovered colloidal semiconductor quantum dots.
1986	The atomic force microscope invented by G. Binnig, C. Quate, and C. Gerber.
1990	Nanotechnology companies starts. To name a few Nanophase Technologies (1989), Helix Energy Solutions Group (1990), Zyvex (1997), Nano-Tex (1998) etc. and so on.
1991	Discovery of the carbon nanotube (CNT) by Sumio Iijima.
1992	Invention of nanostructured catalytic materials MCM-41 and MCM-48.
1993	Controlled synthesis of quantum dots was reported by Moungi Bawendi.
1998	National Science and Technology Council established the Interagency Working Group on Nanotechnology (IWGN).
1999	Dip-pen nanolithography® (DPN®) was invented by Chad Mirkin. The application of this tool was meant for "writing" electronic circuits for biomedical research.
2000	National Nanotechnology Initiative (NNI) was initiated by President Clinton.
2004	Britain published "Nanoscience and Nanotechnologies: Opportunities and Uncertainties" by Royal Society and the Royal Academy of Engineering.
2005	DNA-based computation was proposed by Erik Winfree and Paul Rothemund.

(continued)

Table 15.1 (continued)

Year	Progress on nanoscience and nanotechnology
2006	First nanoscale car was made by James Tour and colleagues built with oligo (phenylene ethynylene), alkynyl axles, and four spherical C60 fullerene wheels.
2007	First report of non-harmful virus mediated lithium-ion battery by Angela Belcher and colleagues at MIT.
2008	Nanotechnology-Related first Environmental, Health, and Safety (EHS) Research was published by NNI.
2010	DNA-like robotic nanoscale assembly devices was fabricated by Nadrian Seeman and colleagues.
2012	Nanotechnology Signature Initiatives (NSIs) Nanosensors, and the Nanotechnology Knowledge Infrastructure (NKI) was initiated by NNI.
2014	The updated 2014 strategic plan was released by NNI on environmental, health, and safety.
2015–2020	An era of tremendous development and improvement of techniques for medical diagnosis and imaging, targeted drug delivery, and hyperthermia (magnetic/photothermal) for biomedical application. Application of nanotechnology for military aid such as battle suits with advanced material as bulletproof or resistant to bacterial chemical attacks. Environmental technology by empowering catalysis mediated reactions which might reduce the toxic materials as effluents. In space technology by building heat proof tiles, optoelectronic instruments for communication, etc.
Future of nano	Converging technologies with multidisciplinary fields to initiate nanoscale or nano-system based foundation for future requirements. To explain such plan, we can consider nanorobot mediated molecular level therapeutic agent which can pre-diagnose and cure the problems. Such ideas are non-exhaustive, for example, carbon nanotube cables for space elevator, advanced nano-opto electronics device for faster communication, nano level replicators help to build exact atomic level mimicry, etc.

of nanotechnology research many nanoparticles already approved by FDA for clinical applications. To name a few superparamagnetic iron oxide nanoparticles (SPION), gadolinium nanoparticles, etc. are already approved for MRI contrast agents. Gold, silver, palladium nanoparticles with tailored shapes and sizes have been extensively studied for bioimaging, biosensing, drug targeting, photothermal therapy applications for cancer treatment (Fig. 15.1) (Bharathiraja et al. 2018; Manivasagan et al. 2019a, b; Phan et al. 2020; Prasad et al. 2016, 2020).

The definition of nanoparticles is depending upon its application and properties. But the most common characteristics for all nanomaterial are its size range. According to the National Nanotechnology Initiative (NNI) nanoparticles sizes are considered in between the range of 1 and 100 nm in general. Whereas many researchers claimed up to 1000 nm might be considered in the range of nano. The foremost benefits of nanostructured materials are its enhanced surface-to-volume ratio. For the last two decades, a steady development in biomedical application of nanoparticles specifically in photoablation therapy, targeted drug delivery, and

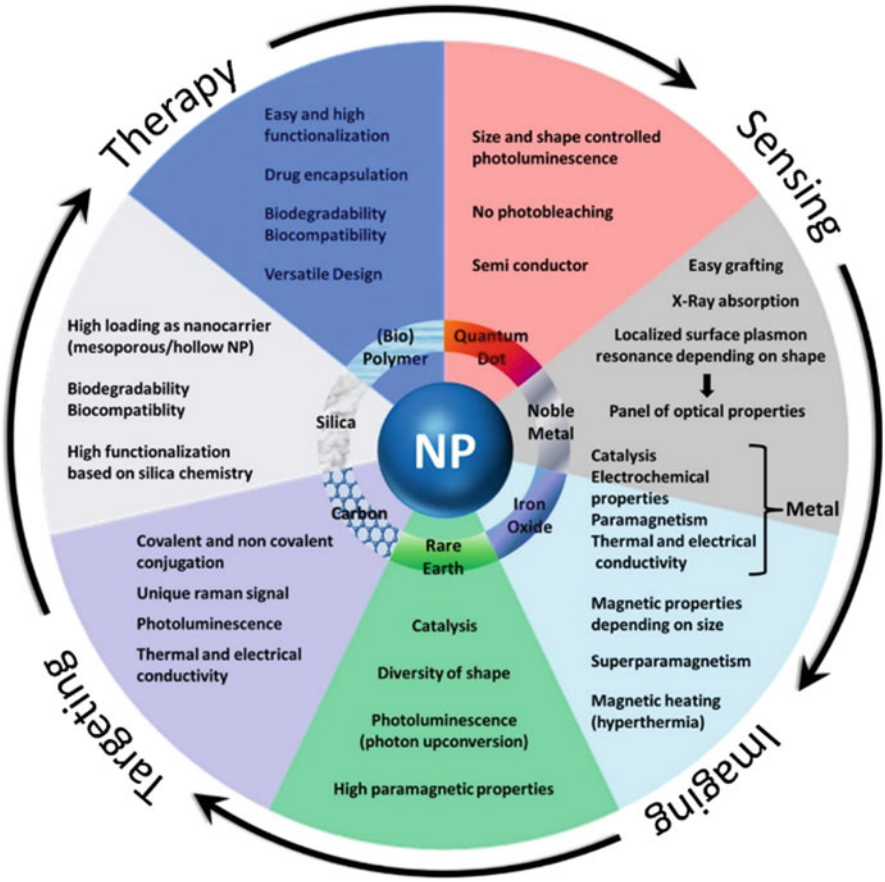

Fig. 15.1 Nanostructured materials for biomedical applications (De Crozals et al. 2016)

bioimaging purposes is observed (Thangadurai et al. 2020a, b). Different ceramics, metallic, and polymeric nanoparticles have shown successful promising results with excellent biocompatibility, chemical stability, non-toxicity, and other associated properties (Prasad et al. 2017). The reliability of nanostructured inorganic materials is much better due to its efficiency, low toxicity, targeted delivery, and tailored morphology. Till date any gene delivery agent has not approved by Food and Drug Administration (FDA) due to its uncertain long-term toxicity. Different synthesis techniques such as chemical, physical, biological approaches were adopted to synthesize tailored nanoparticles (Prasad et al. 2016, 2018; Srivastava et al. 2021). Although researchers have already reported a large number of synthetic routes but most of the techniques lack of reproducibility, and low yield. Moreover, difficult synthesis routes are often making limitations to get better nanoparticles. In this article we have classified nanoparticles in six groups and discussed their different synthesis routes.

15.3 Classification of Nano-systems

Nanoparticles could be classified into six different nano-systems metal nanoparticles, metal oxide nanoparticles, polymeric nanoparticles, ceramics nanoparticles, carbon-based nanoparticles, and composite nanoparticles (Table 15.2).

15.3.1 Synthesis

The last decade evidenced the extensive research on advanced functional materials for nanomedicine application. Due to the unique physical, chemical, biological, and optical properties new synthetic methods have been employed to control and tailored their characteristics (Prasad et al. 2016). Different synthetic routes can produce different characteristics such as varied morphology (spherical, rod, star, cube, triangle, hollow, etc.), and different size ranges (Fig. 15.2). The synthesis of nanoparticles strategies could be broadly categorized into two approaches: (1) top down and (2) bottom up. In "top down" approach, from a primary bulk material, nanoparticles could be synthesized by means of different mechanical, thermal, optical, chemical process. Whereas "bottom up" approach helps to synthesize nanoparticles from atomic or molecular level. Different synthesis procedures such as chemical precipitation, sol-gel, chemical vapor deposition, atomic molecular condensation, arc discharge, and evaporation (Bachilo et al. 2002; Hafner et al. 1998) were successfully employed.

Table 15.2 Classifications of nanoparticles

Nanoparticle type	Examples	Reference
Metal nanoparticles	Au, Ag, Pt, Fe, Zn, Cu, Mn, Co, etc.	Kim et al. (2018a), McNamara and Tofail (2017)
Metal oxide nanoparticles	TiO_2, Al_2O_3, SiO_2, ZnO, Fe_3O_4, Fe_2O_3, etc.	McNamara and Tofail (2017), Qin et al. (2011)
Polymeric nanoparticles	Polypyrrole, chitosan, dendrimer, liposome, etc.	Bharathiraja et al. (2018), Manivasagan et al. (2018), Mondal et al. (2020a) Phan et al. (2018)
Ceramics nanoparticles	Calcium phosphate, hydroxyapatite, bio-glass, etc.	Mondal et al. (2018a, 2020c)
Carbon-based nanoparticles	Carbon nanotube, SWNT, MWNT, etc.	Cherukuri et al. (2004), Mondal et al. (2019a)
Composite nanoparticles	Composite of above materials together	McNamara and Tofail (2017), Mondal et al. (2016b)

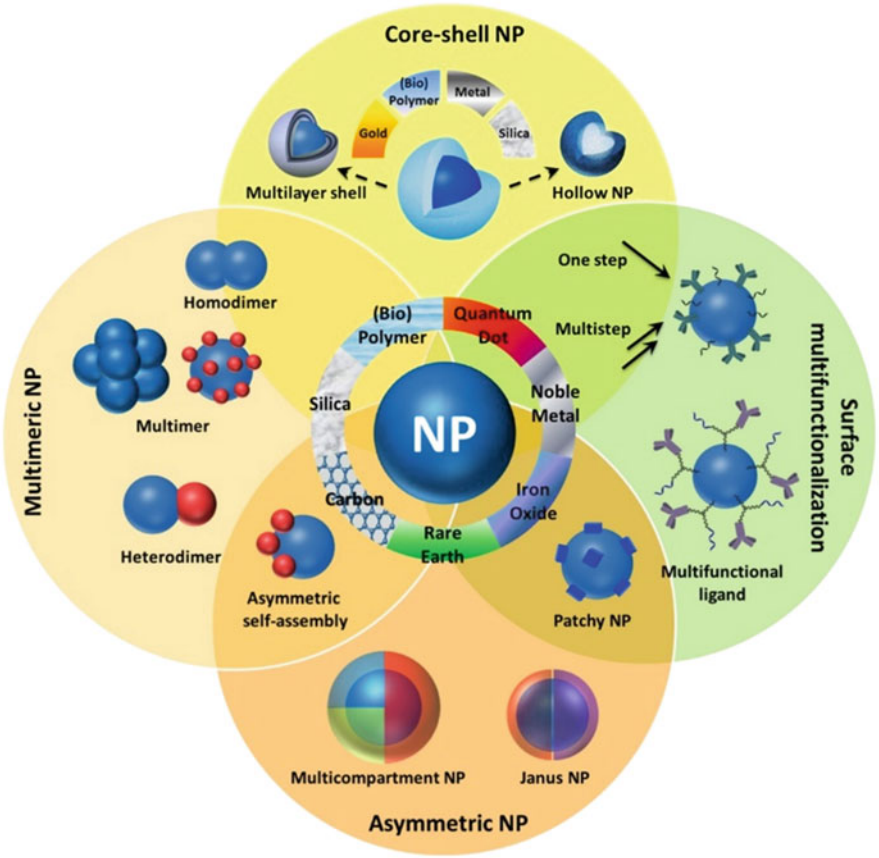

Fig. 15.2 Different morphologies for nanostructured materials and their multifunctional applications (De Crozals et al. 2016)

15.3.2 Metallic Nanoparticles

As long as for 5000 years ago gold served as novel metal for different medicinal purposes. Gold (Au) categorized under metallic nanoparticles exhibits exclusive electronic and optical properties along with strong chemical stability. Gold also possess most active surface functionality which allows different positively charged materials to bind on its surface by strong ionic interactions (Manivasagan et al. 2019c, d). For fabricating contrast agents strong optical absorption of noble metals with surface plasmon resonance (SPR) property is important (Liao et al. 2006). The fundamental phenomenon of metal based nanoparticle for biomedical application is its surface plasmon resonance (Mondal et al. 2017b). With different morphologies (rod, cube, caged, star, triangle, spherical, etc.) the absorption spectra also changed, and due to this property, the application of gold nanoparticle is always demanding.

The absorption in the visible and near-infrared regions already utilized for several photothermal therapy for cancer ablation, as a sensor, and biomedical imaging purpose (Bhattacharya and Mukherjee 2008). The most important factor is its versatile morphologies with unique stability makes gold is a first choice for metal based medicinal application. The second most important metal nanoparticle is silver nanoparticles which exhibit almost equal optical property compared to similar group of metals and additional functional properties such as antibacterial and anti-inflammatory which makes silver as the important metal for biomedical application. Due to this antibacterial property silver is also used for textile industry, food industry, medical devices industry such as antibacterial cream, surgical instruments coating, wound healing materials, etc. (Kim et al. 2018b; Aziz et al. 2014, 2015, 2016). Several other important metals such as Zn, Mg, Cu, Pt, Fe, Co, Cr are also used in medical industry for different biomedical applications such as micronutrients in drugs, coating agents, or doping agents, etc. Similar to single metal bimetallic or more than two metal (alloys) are also used for enhancing individual metal property or to produce a completely new property for different biomedical application such as enhancing chemical stability, or thermal stability, increased enzymatic activity a prosthetic group, enhancing drug loading efficiency etc.

15.3.3 Metal Oxide Nanoparticles

Metal oxides are derivative of metals with unique chemical properties. Among widely used metal oxide nanoparticles titanium dioxide (TiO_2), zinc oxide (ZnO), mesoporous silica (SiO_2), cerium oxide (CeO_2) are the most important. The application of those material is not only restricted in a particular field, whereas a wide application is observed including food color agent, sunscreen, tooth paste, pharmaceutical and cosmetics industry. Recently, CeO_2 nanoparticles are as potential biological antioxidant and anticancer agent along with its extended application in biosensor (Alpaslan et al. 2015). Another important nanoparticle is silica-based hybrid nanomaterials.

The use of SiO_2 nanoparticles is well known for greater surface area which could accommodate large number of drug molecules. This type of nanoparticles also could be useful for triggered and controlled drug delivery application due to its tailored morphology including variable pore structure, particle size, and tunable biocompatibility (Moorthy et al. 2018, 2019). Research study suggested that silica particles can successfully carry and deliver the therapeutic or imaging cargoes (Moorthy et al. 2017). As a biomolecule carrier agent ZnO is also in the priority list. Its unique electronic properties make this molecule a bioimaging contrast enhancer. Though its only drawback is its solubility in biological fluids. To overcome such limitations different coating materials are employed to coat the ZnO surface to protect them in biological system (Ngo et al. 2009).

15.3.4 Quantum Dots

Quantum dots (QDs) are tiny fluorescent semiconductor nanocrystals (specifically 1–10 nm in range) with exclusive optical properties (Choi et al. 2007). QDs possess more stability compared with organic dyes and fluorescent proteins, while their brightness could be controlled by different synthetic process. The other exclusive characteristics are narrow linewidth emission spectra, comparatively long (5 to >100 ns) fluorescence lifetime (1–5 ns for organic dyes), and negligible photobleaching over minutes to hours (Resch-Genger et al. 2008). The luminescence property of QDs is widely used as a tagging molecule for medical imaging applications. Synthetic techniques directly control the absorption and emission characteristics and optical properties of QDs. Different synthetic routes were reported by researchers for the synthesis of cadmium selenide (CdSe), cadmium sulfide (CdS), or cadmium telluride (CdTe) QDs (Murray et al. 1993). QDs photoluminescence efficiency could be enhanced by different core shell techniques such as CdSe core and a ZnS shell that shields the core (Talapin et al. 2004). Use of ZnS capping also enhances the stability of QDs by decreasing the oxidative photobleaching.

15.3.5 Iron Oxide Nanoparticles

One of the most commonly used nanoparticles in biomedical research is iron oxide nanoparticles. Iron oxide is a common name, whereas different oxidation states of the nanoparticles may change its property and corresponding applications. To discuss the oxidation levels, we can categorize including iron (II) oxide (FeO), iron (III) oxide Fe_2O_3 and Fe_3O_4. Different crystalline polymorphs are observed for iron (III) oxide (Fe_2O_3) [α-Fe_2O_3, β-Fe_2O_3, γ-Fe_2O_3 and ε-Fe_2O_3]. For biomedical application maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) are the most suitable material, whereas in terms of super paramagnetic iron oxide (SPION) nanomaterial magnetite (Fe_3O_4) is the best choice as its facile synthesis process and high magnetic saturation with low remanence and coercivity (Mondal et al. 2017a; Abd-Elsalam et al. 2019). Different doping activities reported to enhance the magnetic as well as biological properties. Such doping is accompanied with magnetically susceptible elements such as cobalt (Co), manganese (Mn), and nickel (Ni) (McNamara and Tofail 2017).

15.3.6 Carbon-Based Nanoparticles

The main constituent of organic molecule is carbon. So, for biomedical application there is no substitute of carbon in respect of favorable biochemical properties. The advanced nanotechnology research helps us to tailor the morphology of carbon

nanomaterials with superior characteristics. Different morphologies with carbon nanoparticles such as carbon nanotubes (CNTs) have expand their application in multidisciplinary fields. The advanced research reports different surface modification of carbon-based nanoparticles with biological molecules has increased their use in drug delivery, and bioimaging research. CNTs are the most discussed and promising nanostructure which is basically a monolayered graphite sheet rolled into tubes. Single and multi-walled CNTs structure could be useful for different applications. The CNTs are the most important carbon-based nanostructure due to its exclusive high electrical and thermal conductivity and enhanced tensile strength properties.

15.3.7 Liposomes

Bangham and Horne (Bangham and Horne 1964) first reported about small artificial lipid-bilayer spherical vesicles called "Liposomes." Liposomes are a promising drug delivery carrier especially used in ophthalmic therapy. The synthesis of liposome is also highly tunable compared to size, surface charge, shape, etc. By changing different lipid molecules liposome fluidity and rigidity could easily be controllable. There are several classifications already reported for different liposomes. The classification is primarily based on their size (diameter). The size of liposomes ranges between 10 and 100 nm diameter considered as small uni-lamellar vesicles (SUVs) and ranges above 100–1000 nm considered as large uni-lamellar vesicles (LUVs). There are other classifications also considered for liposomes based on the number of lipid bilayers. Different multiple phospholipid bilayers could be used for multilamellar liposome vesicles in aqueous media with a comparatively bigger size range of 400–3500 nm in diameter (Akbarzadeh et al. 2013). Liposomes have been engineered to deliver a wide range of therapeutic agent or target molecules which could not be possible for conventional nanoparticle system. For example, liposomes can transport a wide range of compounds, such as aqueous soluble or insoluble drugs, antibiotics, enzymes, antioxidants, proteins etc. for different vaccination, therapeutic purposes. Due to protective lipid bilayers the functionality of these carrier molecules is well preserved and the efficiency or circulating time enhanced dramatically even in harsh conditions (Akbarzadeh et al. 2013).

15.3.7.1 Dendrimers

In modern drug delivery application polymeric biomaterials are most promising (Fig. 15.3). Among different polymeric materials dendrimers are the new carriers with highly branched molecules and variable morphologies. The molecular structure could be tailored according to the demand with low polydispersity. The wide range molecular cargo trafficking with tunable size and shape makes dendrimers as a promising biomolecule. The other advantage of this molecule is to carry more than

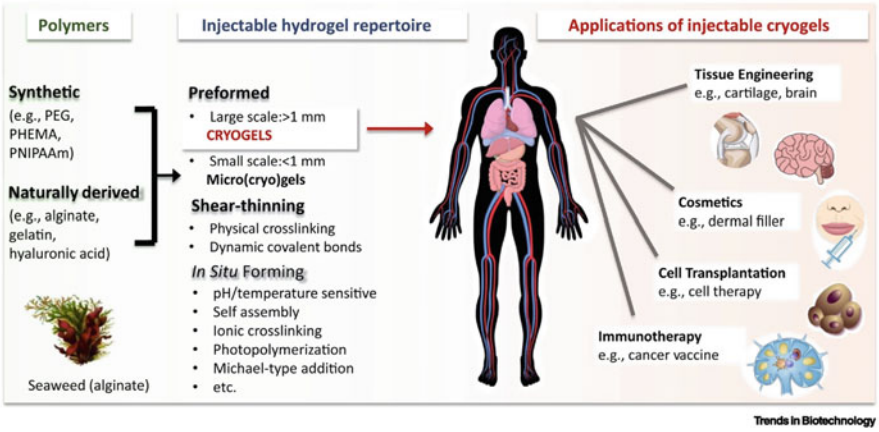

Fig. 15.3 Different biomedical applications of polymeric nanoparticles (Eggermont et al. 2020)

one type of target molecules in specific site. Gadolinium-polyamidoamine (PAMAM) starburst dendrimers were first reported by Wiener et al. which could be useful for MRI contrast agents (Wiener et al. 1994). The long-term effects of dendrimers in body system were studied by Kobayashi et al., who reported that the different sizes of dendrimer show variable blood retention, circulation, and clearance rates (Kobayashi et al. 2003).

15.3.7.2 Lipid-Based Nanoparticles

Most of the oral drugs are based on lipid-based nanoparticles such as liposomes and micelles (Muchow et al. 2008). Lipids contain both hydrophobic and hydrophilic parts with a unique property of self-assembling in aqueous environments. Lipid-based nanoparticle is comparatively a new field of research for bioimaging application. There are very few and small number of successful research work reported till date. To address this relatively new technique Muller et al. first reported the lipid-based nanoparticles for contrast enhancing agent for MRI application (Mulder et al. 2006). Another study was performed by Koole et al. on silica nanoparticles coated with paramagnetic lipid molecule for multimodal imaging purpose. The fabricated nanostructure contains a core quantum dot which acts as a contrast agent for MRI and fluorescence imaging (Koole et al. 2008). Among the few successful study Cressman et al. reported lipid incorporated liposomal nanoparticles labeled with RGD on its surface for imaging biomolecular movements in endothelial cells (Cressman et al. 2009).

15.3.7.3 Apatite Nanoparticles

The most reliable and widely used nanoparticle is calcium phosphate material which received its attention due to extremely low or no toxicity, excellent biocompatibility and bio-absorbability (Liu et al. 2005; Mondal et al. 2016a, 2018a; Mondal and Pal 2019). The most widely used apatite material as bone tissue engineering application is hydroxyapatite. Other different types of apatites are calcium phosphate (CP) dicalcium phosphate (DCP), tri calcium phosphate (TCP), tetra calcium phosphate, etc. Calcium phosphate is mostly used for biomedical purposes such as delivery vehicle for drugs, biotherapeutics, gene, proteins, peptide, DNA, etc. (Maitra 2005). The study with calcium phosphate is not exhaustive as delivery agent only, whereas recent studies suggested its potential use for biomedical imaging and contrast agent also (Mondal et al. 2020d, e).

Mondal et al. reported a rapid microwave assisted facile synthetic technique to synthesize gold loaded HAp nanoparticles (Au-HAp). Further the Au-HAp nanoparticles were coated with collagen and used for doxorubicin drug delivery applications. Though the authors reported different concentration Au loaded HAp but the DOX loading and releasing study was performed with optimized for 0.1 wt% Au–HAp–Col nanoparticles. A high drug loading efficiency of ~58.22% and a pH responsive releasing of ~53% (at pH 4.5) were observed. To evaluate the cytotoxicity osteoblast-like MG-63 cells were studied for AO/PI and MTT assay. The promising nontoxic results extend with scaffold fabrication and cellular attachment study (Fig. 15.4). The overall result qualifies the Au-HAp nanoparticles for drug delivery and tissue engineering application (Mondal et al. 2019b).

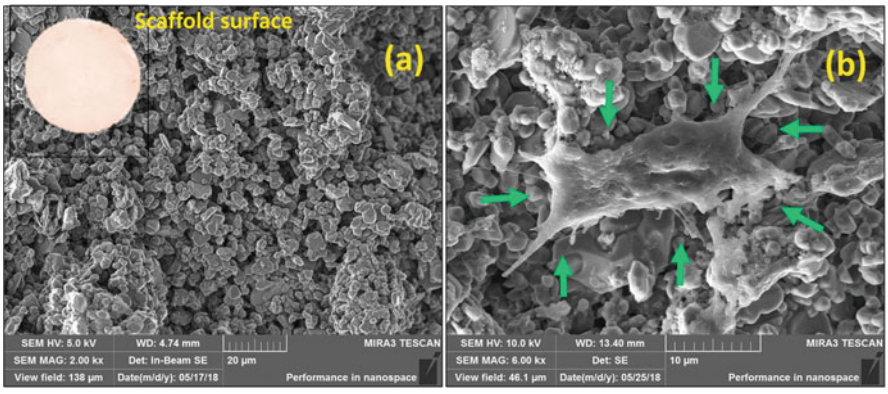

Fig. 15.4 FE-SEM study of (a) 0.1 wt.% Au-HAp-Col scaffold prior to MG-63 cell treatment (b) attached MG-63 cells (green arrow) on 0.1 wt.% Au-HAp-Col fabricated scaffold (Mondal et al. 2019b)

15.4 Biomedical Applications

15.4.1 Sensing

Due to its variable color property with different shape and morphology gold nanoparticles are widely used as a colorimetric sensing agent (Zhao et al. 2008). Different biochemical reactions associated with colloidal gold solution produce different color intensity due to gold nanoparticles unique plasmon resonance effects and that help to clue the sensing property of Au nanoparticles. In simple words the assay is directly depend upon the formation of color due to surface plasmon resonance of Au nanoparticles. The plasmon resonance frequency is controlled by different factors such as shape, morphology, sizes, average distance between gold particles and this might change the color from red to purple or even blue. Mirkin and co-workers first reported the DNA-gold sensors which rely the same color changing phenomenon (Mirkin 2000). This biosensing property is used for detecting various biomolecules, including different proteins, peptides, metals, enzymes, nucleic acids, etc. (Liu and Lu 2004; Singh et al. 2020).

15.4.2 Imaging

Kee and Danila et al. demonstrated that gold nanoparticle is an excellent blood pool contrast agent and targeted imaging of myocardial scar in a rat model of myocardial infarction with CNA35-gold nanoparticles (Fig. 15.5). A molecular imaging approach was taken by gold nanoparticles contrast agent which successfully detects the CT-based specific imaging for myocardial scar.

Magnetic resonance imaging is a noninvasive extremely efficient tool for imaging deep tissues inside body system. Nowadays clinician highly depends upon imaging modules for diagnosis and treatment. With the advances of therapeutic approach deep tissue penetration imaging could be possible by using nanoparticles. Noninvasive is a non-painful technique which could visualize the structure and morphologies of tissues. To better visualize nowadays different nanoparticles have been used as contrast in noninvasive imaging. Among all different nanoparticles iron oxide is the most widely used and FDA approved due to its superparamagnetic property with adequate biocompatibility. To enhance its biocompatibility surface modification could be performed by different polymeric coating agents with antibody, peptide, or small molecule conjugation for active targeting in affected tissues (Wunderbaldinger et al. 2002). Hainfeld et al. reported 1.9 nm size gold nanoparticles mediated contrast agent for detecting tumors in mice by X-ray CT (Hainfeld et al. 2006). After 24 h post injection the gold nanoparticles were not traced in the blood, whereas significant accumulation observed in kidney. Due to extreme small size of gold nanoparticles there was no accumulation evidence found inside liver or spleen.

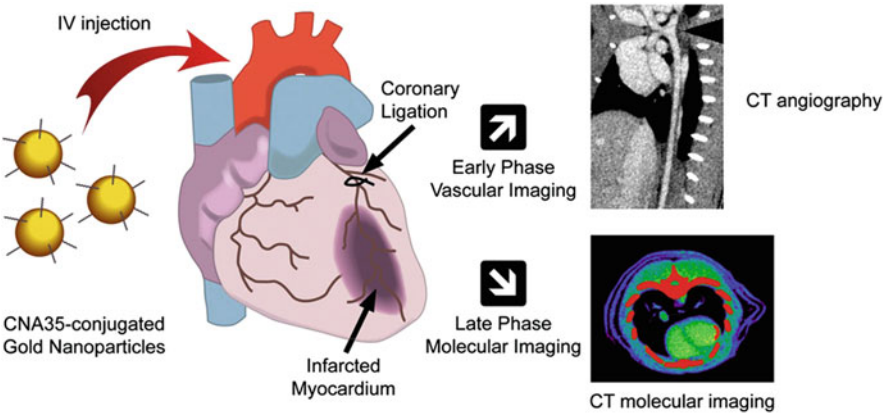

Fig. 15.5 Management of patients suffering from myocardial infarction is based on the extent of coronary artery stenosis and myocardial scar burden. (Upper panel) Gold nanoparticles (AuNPs) functionalized with collagen-binding adhesion protein 35 (CNA35) perform vascular imaging at early phase and molecular imaging at late phase. (Lower panel) Myocardial infarction imaging at 6 hours after injection. Reproduced with permission. Copyright 2018. Elsevier. (Kee and Danila 2018)

For cancer treatment and diagnosis purposes carbon nanotubes successfully synthesized and applied. Several researchers have reported CNTs based bioimaging system applied for detection and destruction for cancer cells. Different fluoroprobes have already been successfully linked with single wall nanotubes (SWNTs) by means of covalent bonding which make possible visible wavelength imaging (Kam et al. 2004). Kam et al. conjugated SWNTs with streptavidin to detect human T cells and promyelocytic leukemia cells by confocal microscopy. Another study reported by Pantarotto et al. synthesized amino-modified SWNTs with FITC in dimethylformamide (Pantarotto et al. 2004) *to detect cancer cells*. The capacity of the FITC-labeled SWNTs confirms after successful images captured by confocal microscopy. Cherukuri et al. also reported the cytotoxicity study of pristine SWNTs. In the reported article NIR imaging was performed by fluorescence microscope and spectrofluorometer (Cherukuri et al. 2004). The fluorescence property of SWNTs has been opened the paves for nanoparticle based promising imaging techniques which could be useful as a powerful tool for tracing diseased or damaged tissues conjugated with CNTs.

15.4.3 Drug Delivery

Drug delivery is an important characteristic for nanomaterials in biomedical application. The affinity between nanoparticles and drug molecule is very important for drug loading and releasing purposes. The strong attraction between drug molecules

and the nanocarriers is mainly due to covalent and ionic interactions. With strong interactions drug loading and stability will enhance, whereas for drug releasing purpose these interactions may hamper the releasing efficiency. On the other hand, carrier molecules could give stability and long circulating time inside body system. Drug loading and releasing could be externally controlled by different characteristics such as for releasing purposes external stimuli by ultrasound, heat, magnetic effects, etc. and for loading purposes pH, heat, morphologies, etc. In targeted drug delivery a special type of carrier molecule is necessary such as magnetic nanoparticles. To be specific superparamagnetic nanoparticles are most important. When the external stimuli are applied by magnetic fields the SPIONs will be activated and targeted to specific direction, whereas in absence of the external magnetic field the nanoparticle will behave like nonmagnetic particles. This strategy could help nanoparticles to target in specific location. Also, iron oxide nanoparticles sometime cause toxic effect when circulating inside body system, and to overcome such unwanted toxic effects, nanoparticles are coated with biomolecules such as polymers, ceramics, etc. In general iron oxide nanoparticles are coated with biopolymers such as collagen, poly ethylene glycol, polyvinylpyrrolidone, chitosan, fucoidan, dextran, etc. Moreover, the nanoparticles are also loaded with specific drug to treat and target specific disease to control. Several research studies demonstrate pH dependent drug release capability to target specific tumor cells. The tumor cells have acidic pH compared to normal healthy cells. In this respect mesoporous silica, nano HAp, mediated drug delivery agents are investigated and reported. The release efficiency is also studied by different enzymatic activity, changes in temperature, or in different osmolality environment (Chatterjee et al. 2014). It is always recommended that specific target-oriented drug delivery is most beneficial to manage disease control and treatment. For favorable tumor targeting nanoparticles are always conjugated with target ligands, or receptor molecules complementary to target site. A large number of different targeting receptor and ligand molecules are already studied and reported by several researchers. Nowadays, selection and modification of nanoparticle surface with specific target-oriented biological molecules are well practiced and pharmaceutical companies are running phase II and III clinical trials on this drugs (De Crozals et al. 2016).

15.4.4 Magnetic Hyperthermia

Hyperthermia is a heat mediated therapeutic approach where heat is applied to destroy affected cells and tissues without damaging the healthy cells. The fundamental phenomenon of hyperthermia relies on 41–46 °C mediated cell apoptosis of cancerous cells when heated specifically. Thermal ablation is also another type of hyperthermia where temperature rises more than 50 °C for treatment of affected tissues. In general, three different types (local, regional, and whole-body hyperthermia) were performed to treat cancer. In local hyperthermia, radio frequency, microwave, or ultrasound mediated heat is generated to specific small target site. Large

tissue areas are being treated with regional hyperthermia, whereas whole-body hyperthermia is rarely used for treat cancers to encounter metastatic phase. For all this hyperthermia mediated treatment the use of nanoparticle enhances the success rate of treatment. Different magnetic nanoparticles generate different heat energy, so application specific nanomaterials need to be selected for treatment purpose. Nanoparticles are sometime coated with different polymeric materials to enhance its biocompatibility. Magnetic nanoparticles might be injected directly to the tumor or cancer region or might be targeted to specific region by binding with specific target molecules such as specific antibody or peptides.

15.4.5 Photoablation Therapy: Photodynamic and Photothermal Therapy

Different approaches are invented to inhibit cancer cells activity and photoablation therapy is one of the most promising techniques to counter act. Photodynamic therapy (PDT) and photothermal therapy (PTT) are the two classification of photoablation therapy. PDT uses photosensitizers a nontoxic light sensitive material or complex which become toxic to targeted cells or tissues upon light exposure. To activate the sensitizer a specific excitation wavelength is required. This therapeutic approach is mainly used for cancer cells management. In the PDT procedure photosensitizers (TiO_2, Ce6, etc., nanoparticles) are exposed to excitation wavelength, which results in formation of photo-induced electrons and holes. The subsequent electron and hole react with system surrounding water molecules which generates hydroxyl ions, oxidative radicals [reactive oxygen species (ROS)], and singlet oxygen. The final step of this PDT is free radical mediated cell organelles damage to targeted or affected cells which results in cell death.

Photothermal therapy uses a suitable near-infrared (NIR-I: 700–900 nm, NIR-II: 1000–1700 nm) light source to irradiate cancer cells. The exposure of this light energy subsequently converted to heat energy due to surface plasmon resonance (SPR) effect which can cause hyperthermia mediated cell death. Manivasagan et al. reported a dual modal multifunctional theragnostic agent for imaging-guided photothermal treatment (Fig. 15.6). In this study gold nano shell was wrapped with chitosan conjugated with paclitaxel drug and anti-EGFR antibody for specific targeting tumor cells. The promising in vivo results show successful thermal ablation of tumors from nude mice model.

With gold the second most widely used nano metal is silver (Ag). There are many promising characteristics of Ag nanoparticles and the most important is its near equal optical characteristics like gold. The other advantage is its low cost and antibacterial activity and easy synthesis process. In spite of having excellent opportunities the main limitation of Ag is its low stability. Though with different approaches such as coating the stability of Ag nanoparticles enhanced. Therefore, Ag could act as a promising material for different therapeutic applications. Different research activities

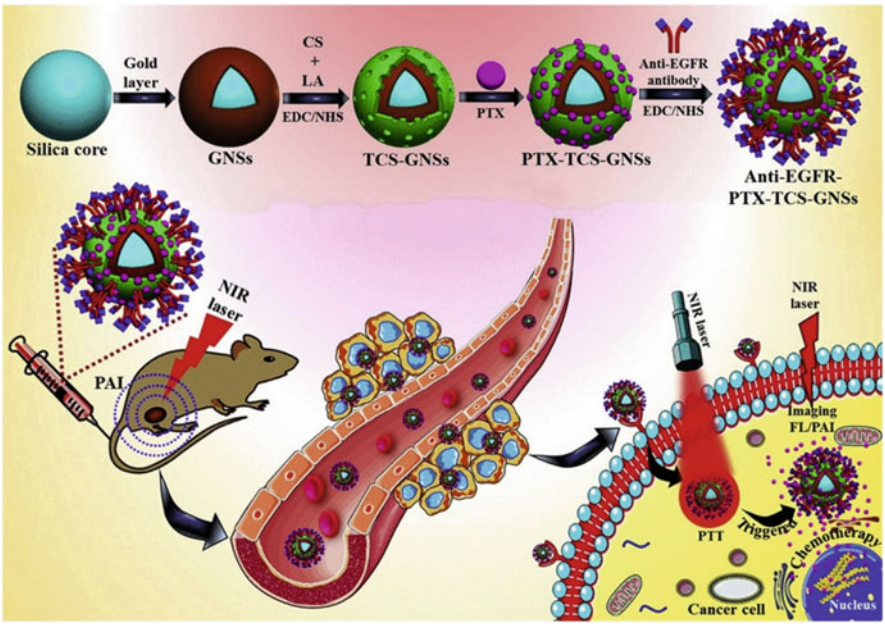

Fig. 15.6 Representation of anti-EGFR-PTX-TCS-GNSs mediated near-infrared fluorescence/photoacoustic imaging-guided chemo-photothermal therapy for cancer treatment (Manivasagan et al. 2019d)

have reported the promising performance of Ag nanoparticles in different clinical activities such as drug delivery, diagnosis, imaging, antibacterial activity, etc. (Prasad 2014). Franco-Molina et al. reported the anticancer activity of colloidal silver nanoparticles with MCF-7 human breast cancer cells (Franco-Molina et al. 2010). MCF-7 cells were incubated with different concentrations colloidal Ag nanoparticles to determine its cytotoxic efficacy. The trypan blue cell exclusion assay was performed to determine cell viability. The results suggested that colloidal Ag had a concentration dependent cytotoxic effect on MCF-7 cell line. The apoptotic cell death confirms the anticancer activity of the colloidal Ag nanoparticles (Franco-Molina et al. 2010; Aziz et al. 2019).

Qin et al. (Qin et al. 2011) reported two different methods to load TiO_2 nanoparticles with doxorubicin (DOX). The two methods non-covalent complexation (TiO_2/DOX) and the covalent conjugation (TiO_2–DOX) were employed to load drugs. Further studies were performed to evaluate the best outcomes in respect with cellular uptake, cytotoxicity, and glioma (C6) cell line mediated intracellular distribution. TiO_2 nanoparticles are widely used for sunscreen agent. The UV light is harmful for human skin due to its mutagenic effect. Fortunately, TiO_2 nanoparticles have unique absorption capability which could be helpful for protecting from direct sunlight. On the other hand, researchers are using this unique property of nanoparticles as photosensitizers for PDT treatment to treat cancer.

Bimetallic nanoparticles could show unique property combining the effect of individual element. Among these bimetallic nanoparticles Fe–Pt is widely studied as contrast agents for diagnosis of tumors. Liang et al. reported the potential application of Fe–Pt nanoparticles coated with L-cysteine for MRI/CT imaging. The study was performed with three different glioma cell lines (SGH44 and U251 from humans, C6 from rat). The results concluded with nontoxic effect of Fe-Pt-Cys nanoparticles strong contrast signals could be useful for potential biomedical imaging application (McNamara and Tofail 2017).

15.4.6 Nanotechnology to Engineer the Surface of Metallic Implants

Another major application of nanotechnology is found in tissue engineering and prosthetic implantation. The surface modification of implants is very important to make the materials biocompatible and favorable to accommodate on its host environment. Nanoparticle mediated surface modification of implant may play a crucial role for tissue engineering application. Attachment of cells on implant surface is a big challenge in tissue engineering. For example, poly lactic acid (PLA) is an example of excellent biomaterials but its major drawback is its smooth surface which cannot allow cells to attach or grow. To overcome such situation, we need to modify the surface of the scaffold or implant by means of chemical, physical, or structural modifications (Mondal et al. 2020b). The enhanced surface activity may facilitate the cells to attach and grow firmly. Till date titanium (Ti) and its alloys are considered one of the best materials for bone replacement applications due to its adequate mechanical properties, high resistance to corrosion, and bioinert property. The limitation of Ti implant is a thin fibrous layer which separates the scaffold from the host bone causing loose bonding and subsequent implant failure. In this situation, for more successful bone implant surgery, a better bone–scaffold interaction is necessary by improving scaffold surface (Le Guéhennec et al. 2007). Mondal et al. reported a composite biomaterial formulation with HAp, Al_2O_3, bio glass, and starch for enhanced mechanical support and better biocompatibility (Fig. 15.7). The scaffold was fabricated by gel-casting and achieved compressive strength of ~157 ± 2 MPa and tensile strength of ~83 ± 2 MPa with 20–25% porosity when sintered after 1200 °C for 2 h. The study extends with successful MG-63 mediated cytotoxicity evaluation and cell attachment and proliferation study on its surface. The result confirms the nontoxic behavior of the scaffold formulation which facilitates cell attachment and proliferation on its surface (Mondal et al. 2018b).

Due to excellent bioactivity CaP nanoparticles were used as a coating material over different implant surface. Kokubo et al. reported that simulated body fluid (SBF) is most commonly used biomimetic solution (Kokubo et al. 1990) which consists of a precursor Ca and P ionic formulation that mimic human body fluids. This biomimetic procedure helps to promote immobilization of apatite

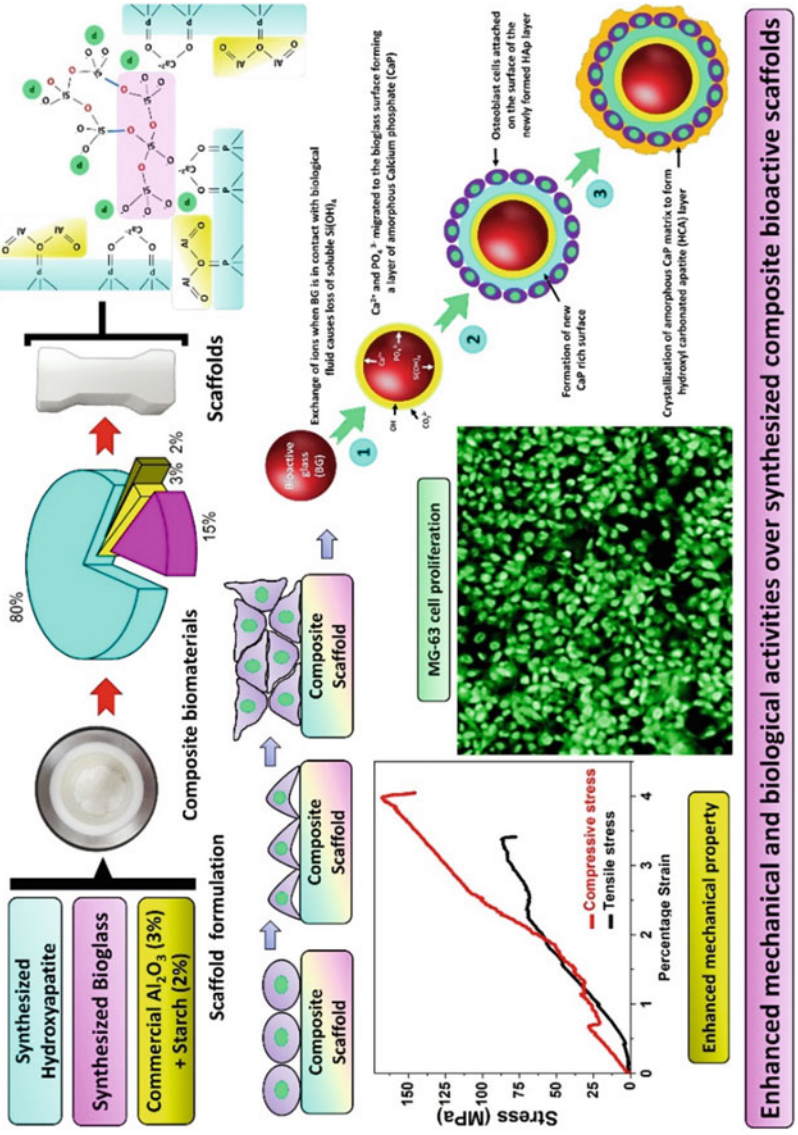

Fig. 15.7 Fabrication of composite scaffold with enhanced mechanical and biological performance for tissue engineering application (Mondal et al. 2018b)

structure, growth factors, therapeutic agents, drugs, proteins, etc. on its surface along with paving its way to promote new cell generation.

15.5 Limitations and Challenges

Several materials, including ceramics, polymers, metal, metal oxide nanoparticles, bio glasses, and polymers, are in top priorities for biomedical applications. However, each of these materials also has exclusive limitations. Poor shape holding, low mechanical strength, inadequate cell adhesion, and in vivo toxicity are the key features for experimental failure. To date, no such absolute nontoxic biomaterials can be used without further modifications. The prime limitations associated with the failure of present approaches are toxicity for in vivo application. The use of suitable dose of nanoparticles as drug needs to be prudently measured. The toxicity of nanomaterials is associated with multiple factors such as morphology, surface charge, sizes, chemical structure, and obviously on dose and composition. Low contrast efficiency for bioimaging application, synthesis reproducibility is another concern regarding synthesis of nanoparticles. Therefore, it is always be prime concern to choose the biomaterials according to the specific target region with tailored shape and biological properties. The limitations of nanoparticles as a drug delivery agent depend upon its payload capacity, drug intake, and release efficiency. Also, specific targeting (to avoid killing healthy cells) is the most important characteristics of nanoparticles. Therefore, targeted drug delivery is one of the biggest challenges. Nanoparticle colloid stability, aggregations, and storage in clinical locations remain a big challenge to consider. Reproducible large-scale production for clinical application with a cost-effective way is also a big challenge. Establishing the real consequences of nanomaterials in body system is an extremely important, challenging, and in the similar way interesting task.

15.6 Summary

Nanotechnology, a multidisciplinary field of research brings all the concepts from physics, chemistry, biology, medicine, engineering, and others under a single roof of science and technology. The future of nanotechnology for biomedical application must integrate a multiple factors-based technology to promote a strong host materials interaction with all chemical, biological, and physiological supports. Though the current trends of nano-research in biomedical application appear promising, till there are many miles to go to achieve the direct benefits. This study recapitulates emerging research and their promising results for healthcare applications. Different nanoparticles with diverse characteristics are aimed to employ for noninvasive imaging, drug delivery, photothermal/photodynamic therapy for different cancer treatment. The developed nanoparticle will cross the limits for conventional

materials which restricts their application for therapeutic approaches. Till date many nanomaterials such as quantum dots, gold, silver nano particles are most promising for fluorescence, photoacoustic, X-ray, CT imaging applications. The rich surface chemistry and precise control over size and composition of iron oxide nanoparticles are useful and FDA approved contrast agents for MRI. As a most reliable bioactive biomaterial hydroxyapatite nanoparticles win the race since 1970s and till going on. Nonetheless, in order to take advantage of the potential application of nanomaterials, extensive safety and toxicology studies will need to consider along with its clinical trials.

Conflicts of Interests The author declares no conflict of interest.

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