Chapter 1
Introduction to Nanomedicine

Abstract A brief introduction is given to nanomedicine, an emerging paradigm intersecting two burgeoning fields of nanotechnology and medicine. It covers the application of nanomedicine in diagnostics and therapy of a wide range of diseases such as cancer, cardiovascular, orthopaedics, and neurodegenerative disorders. A wide range of nanomaterials, nanoparticles and biomaterials for these applications are discussed.

Keywords Nanoparticles · Nanomedicine · 2D nanomaterials · Quantum dots · Diagnostics · Therapy · Cancer · Neurodegenerative disorders · Cardiovascular diseases · Orthopaedics

1.1 Nanomedicine

Nanomedicine is a field of interdisciplinary science that integrates physical, chemical, and engineering sciences, utilizing nanotechnology (functional nanomaterials, and structures at the nanometer scale between 1 and 100 nm) and medicine (drugs, imaging tools and delivery devices) for disease diagnosis and therapy.

Today, nanomedicine is a buzzword for a variety of diseases including cancer (Chow and Ho 2013; Min et al. 2015; Chen et al. 2017; Liu et al. 2017; Nam et al. 2019), cardiovascular (PA Ferreira et al. 2015; Di Mauro et al. 2016), orthopaedics (Mazaheri et al. 2015; Perli et al. 2017), dental (Besinis et al. 2015; Padovani et al. 2015; Chieruzzi et al. 2016; Priyadarshini et al. 2016; Fawzy et al. 2017; Priyadarshini et al. 2017), kidney (Marom et al. 2012; Kamaly et al. 2016; Williams et al. 2016), and neurodegenerative diseases (Goldsmith et al. 2014; Saraiva et al. 2016; Tapeinos et al. 2017; Teleanu et al. 2019a).

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1.1.1 Nanomaterials for Cancer Nanomedicine

In cancer nanomedicine, a wide range of nanomaterials including two-dimensional 2D MoS_2/Bi_2S_3 (Liu et al. 2014; Wang et al. 2015a, b; Song et al. 2016), MnO_2 nanosheets (Chen et al. 2014f), graphene oxide (Chen et al. 2014e), transition metal dichalcogenide nanomaterials (Gong et al. 2017) have been developed extensively for therapeutic and diagnostic (i.e. theranostics) applications of cancer (Peng et al. 2017). Nanotechnology assisted approaches for stem cell differentiation, tracking, labelling, and therapy have been delineated in recent reviews by our group (Nanda et al. 2017; Yi et al. 2017).

Different nanoparticles (NPs) have been designed for nanomedicine over the last decade. Metallic NPs (e.g. Au, Ag, Pd, Pt, Cu) have been used as plasmonic nanosensors or surface-enhanced Raman scattering (SERS) probes for label-free ultrasensitive molecular detection of body fluids (Kosaka et al. 2014; Bui et al. 2015; Lane et al. 2015; Langer et al. 2015; Jeong et al. 2016; Yang et al. 2016b; Xie et al. 2017). Conversely, semiconductor quantum dots (QDs) have been extensively used for biological applications (Mattoussi et al. 2000; Gao et al. 2004; Medintz et al. 2005; Chang and Rosenthal 2012).

Despite toxicity issues related to heavy metal cadmium, even today, semiconducting NPs such as CdSe/ZnS QDs are the best diagnostic agents for in-vitro cell labelling and in-vivo animal imaging studies, thanks to their excellent optical properties and stabilities (Yen and Selvan 2015; Freyer et al. 2019; Hanifi et al. 2019; Ondry et al. 2019) Alternate non-cadmium based QDs have emerged in response to combat heavy metal Cd-based cytotoxicity (Xu et al. 2016). For example, Mn-doped ZnS QDs have been used as protein sensors (Wu et al. 2013), used for detection of H_2S (Wu et al. 2014) and dopamine (Diaz-Diestra et al. 2017) in biological samples, and as imaging probes for intracellular Zn^{2+} ions (Ren et al. 2011). Earlier, our group contributed to the grafting of Mn-doped ZnS nanocrystals and anticancer drug (doxorubicin) onto graphene oxide for cell labelling and delivery (Dinda et al. 2016). Conversely, molybdenum disulfide QDs (Liu et al. 2018) has been used for the detection of dopamine.

Recently, ZnO nanowires and nanocomposites (e.g., Ag–ZnO) have shown great potentials in the detection of cancer biomarkers such as RNA, DNA, proteins, and extracellular vesicles (Guo et al. 2018; Paisrisarn et al. 2022; Chattrairat et al. 2023; Huang et al. 2023; Jung et al. 2023). It is worth mentioning here the application of ZnO and TiO_2 nanostructures for the biosensing of proteins using the surface-enhanced Raman scattering (SERS) approach (Adesoye and Dellinger 2022).

Multifunctional NPs for multimodal bioimaging incorporating optical imaging using NIR emitting QDs or up-conversion luminescence, computed tomography (CT) and magnetic resonance imaging (MRI), and therapy (Lee et al. 2012) (photodynamic, photothermal, targeted drug delivery (Liu et al. 2015), pH-triggered on-demand drug release (Wang et al. 2015c) etc.), have attracted immense interest (Chen et al. 2014d; Wu et al. 2015; Li and Chen 2016; Duan et al. 2017; Amirav et al.

2019). We have also pioneered the synthesis of bifunctional nanomaterials (fluorescent QDs, magnetic iron oxide, up-conversion, and magnetic/antibacterial NPs) for bimodal imaging (optical and MRI) and therapeutic applications (Selvan et al. 2007; Ang et al. 2009; Selvan et al. 2009; Das et al. 2010; Selvan 2010; Zhang et al. 2014). Carbon nanodots (Bhunia et al. 2013; Shi et al. 2015; Xu et al. 2015) and graphene QDs (Zhang et al. 2012; Zheng et al. 2015a, b; Yang et al. 2016a; Yao et al. 2016; Yan et al. 2019) have been extensively explored as bioimaging probes. Interestingly, carbon dots have recently emerged as a potential candidate system in nanomedicine to protect the cells from oxidative stress, eliminating intracellular reactive oxygen species (ROS) (Xu et al. 2015). It is worth mentioning here the use of ceria–zirconia NPs as a therapeutic nanomedicine for treating ROS-related inflammatory diseases such as sepsis (Soh et al. 2017). Several ROS-mediated nanomedicine systems have been delineated recently (Yang et al. 2019; Ding et al. 2023; Naik and David 2023).

Notable advances have been made in the synthesis of different magnetic NPs (MNPs) (e.g., Fe_3O_4, Fe_2O_3, FePt, Co), and their nanostructures and composites. (Yen et al. 2013b; Yen et al. 2015; Kang et al. 2017; Wang et al. 2018; Yang et al. 2018; Ray et al. 2019; Satpathy et al. 2019; Esthar et al. 2023; Liu et al. 2023).

These magnetic nanocomposites can be used as drug carriers (Farmanbar et al. 2022; Turrina et al. 2022; Esthar et al. 2023; Liu et al. 2023), hyperthermia agents (Ansari et al. 2022; Shabalkin et al. 2023), and MRI contrast agents (Cheraghali et al. 2023; Jiang et al. 2023) in cancer diagnosis/bioimaging (Mohapatra et al. 2023) and therapy (Su et al. 2023; Vangijzegem et al. 2023). Iron oxide NPs combined radioisotopes (e.g., Tc-99 m) can be used as dual modality contrast agents for the high spatial resolution of MRI applications combined with high sensitivity single photon emission computed tomography (SPECT), and positron emission tomography (PET) (Karageorgou et al. 2023).

Upconversion NPs (UCNPs) (e.g. $NaYF_4$:Er, $NaGdF_4$:Er) are another interesting class of materials utilized extensively for bioimaging, owing to their stable luminescence; and fabricated as core–shell NPs (Dou et al. 2015) or multifunctional NPs for bioimaging, and photodynamic therapy (PDT) (Idris et al. 2012; Chen et al. 2014a; Wang et al. 2015b; Zhou et al. 2015; Zhou et al. 2016; Xu et al. 2017; Liu et al. 2019b; Zhang et al. 2019). Other polymeric NPs (Ang et al. 2014), hybrid NPs (Nguyen and Zhao 2015; Zhang et al. 2017), and multifunctional NPs derived from small organic building blocks (Xing and Zhao 2016) have considerably contributed to nanomedicine. Conversely, rare-earth oxide NPs (e.g. gadolinium oxide) found their potential uses in MRI and chemotherapy (Wu et al. 2019).

Although metallic NPs such as Au, Ag are synthesized in water directly, most of other NPs such QDs, UCNPs, MNPs are synthesized in presence of organic ligands at temperatures over 200 °C, resulting in hydrophobic NPs. Different coating methods have been developed to make these hydrophobic NPs water soluble. Today, the stabilization of NPs in water and biological media has become a matured strategy, thanks to a wide variety of coating strategies that exist in the literature. This includes silica (Mulvaney et al. 2000; Gerion et al. 2001; Selvan et al. 2004; Darbandi et al. 2005; Selvan et al. 2005; Yi et al. 2005; Zhelev et al. 2006; Tan et al. 2007), polymer (Hong et al. 2012; Wang et al. 2013; Yen et al. 2013a; Chen et al. 2014b; Topete et al. 2014;

Palui et al. 2015), peptides (Narayanan et al. 2013; Chen, Li et al. 2014c; Yang et al. 2017; Zhang et al. 2018), lipids/liposomes (Medintz et al. 2005; Murcia et al. 2008; Weng et al. 2008; Al-Jamal et al. 2009; Tian et al. 2011), proteins (Mattoussi et al. 2000; Chithrani and Chan 2007; Yang et al. 2013; Hu et al. 2014; Tay et al. 2014; Sasaki et al. 2015; Scaletti et al. 2018), antibodies (Goldman et al. 2002; Medintz et al. 2005; Snyder et al. 2009), and enzymes (Kong et al. 2016) for the stabilization of NPs. Hydrophobic ligands such as HDA can also be used for the stabilization of Au NRs and heterostructures (Cheng et al. 2014; He et al. 2014).

1.2 Challenges and Advancements of Nanomaterials for Nanomedicine

In general, nanomaterials in biomedical applications pose an important concern: what are the safety concerns of nanomaterials? How do we address the growing needs of ageing population with neurodegenerative disorders, and early diagnosis and therapeutic measures for diseases like cancer? This Book attempts to address the above concerns with the advent of nanomedicine. Compared to cancer nanomedicine, the application of nanomedicine in neurodegenerative diseases is still in its infancy state. The biggest challenge in neurodegenerative diseases is to tackle the permeability of blood-brain-barrier (BBB) and deliver therapeutic drugs to the brain (Ramanathan et al. 2018). Toward this goal, nanoscale materials have been developed and used either as bio-labelling agents or as therapeutic carriers, and in some cases as neuroprotective agents for neurodegenerative diseases (Goldsmith et al. 2014; Saraiva et al. 2016; Teleanu et al. 2019b; Liu et al. 2019a; Le Floc'h et al. 2019).

This Brief focuses mainly on the application of nanomedicine in cancer and neurodegenerative diseases. It also attempts to cover the application of nanomedicine in other emerging areas such as orthopaedics, and cardiac diseases (Fig. 1.1).

1.2.1 Nanomedicine Advancements in Cancer and Neurodegenerative Diseases

Some of the recent advancements (See Chap. 2) in cancer diagnosis (e.g., multimodal tumor imaging) and therapy (e.g., combined therapies involving either photothermal, chemotherapy, photodynamic or immunotherapy) have been made using 2D nanomaterials (Chen et al. 2020; Ding et al. 2020) (e.g., MoS_2/Bi_2S_3 nanocomposites (Wang et al. 2015a; Wang et al. 2019), molybdenum oxide nanosheets (Song et al. 2016; Wang et al. 2023b), MoS_2 nanosheets (Liu et al. 2014; Murugan and Park 2023), MnO_2 nanomaterials (Chen et al. 2014f; Tan et al. 2017; Ding et al. 2020), doped graphene nanosheets (Lu et al. 2022), graphene oxide-based multifunctional nanomaterials (Gonçalves et al. 2013; Chen, Xu et al. 2014e; Gu et al. 2019; Itoo

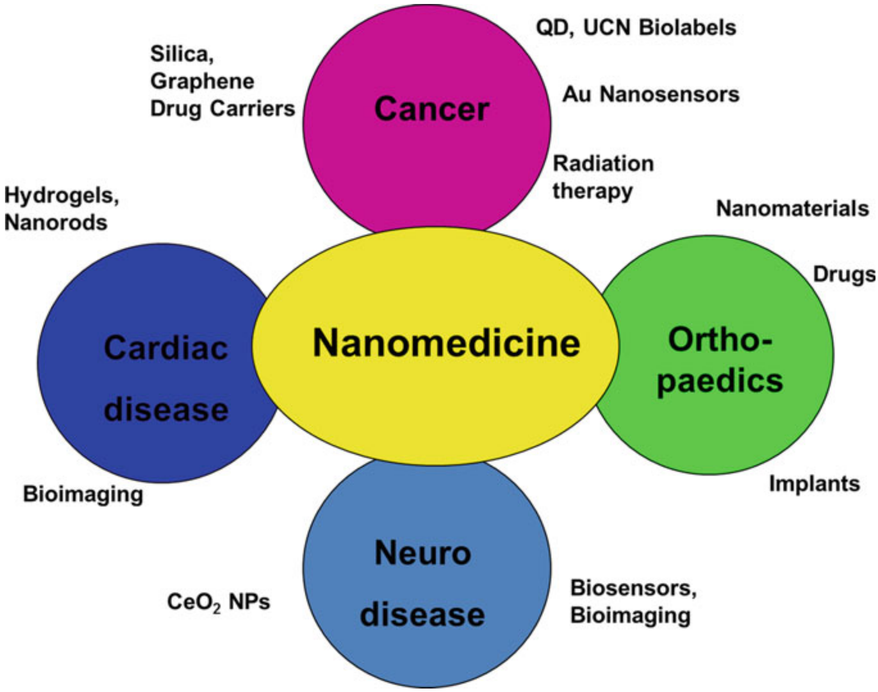

Fig. 1.1 Applications of nanomedicine in cancer, orthopaedics, neurodegenerative, and cardiac diseases

et al. 2022), and multifunctional Au-based nanomaterials (Ouyang et al. 2023; Wang et al. 2023c), and magnetic nanomaterials (Mukherjee et al. 2020; Liu et al. 2021).

Chapter 3 deals with different nanomedicine approaches for neurodegenerative diseases such as Alzheimer's disease (AD). Design of inorganic NPs (e.g., Au, ZnO, MoS_2, CeO_2) and organic NPs (e.g., curcumin, green tea polyphenol- EGCG) for inhibiting the amyloid aggregation and tau hyperphosphorylation associated with the AD are discussed (Han et al. 2017; Shukla et al. 2021; Tamil Selvan et al. 2021). Different NP-based drug delivery approaches (e.g., apolipoprotein, peptides, dendrimers) to the delivery of CNS drugs across the blood–brain barrier (BBB) are also discussed (Tapeinos et al. 2017; Arvanitis et al. 2020; Loch et al. 2023).

1.2.2 Nanomedicine Advancements in Orthopaedics and Cardiovascular Diseases

Chapter 4 addresses nanomedicine and tissue engineering approaches for orthopaedics. Bone mimicking scaffolds composed of polymers (e.g., polycaprolactone, polylactic acid, chitosan) and inorganic nanomaterials (e.g., reduced graphene oxide rGO, hydroxyapatite) (Seyedsalehi et al. 2020), and zwitterionic chitosan/β-tricalcium phosphate hydrogel/GO scaffolds (Wang et al. 2023a) for bone tissue engineering applications are covered. Orthopaedic drug delivery systems using dextran/β-tricalcium phosphate nanocomposite hydrogel scaffolds (Ghaffari et al. 2020), and chitosan-vancomycin hydrogel bone repair scaffold (Gao et al. 2023) are also delineated.

Chapter 5 delineates the applications of nanomedicine in diagnostics and treatment of cardiovascular diseases (CVDs). Recent developments in multifunctional NPs (Kleinstreuer et al. 2018), nano/biomaterials and devices to diagnose and treat a variety of CVDs with the attributes of mechanical, conductive, and biological requirements are discussed (Liu et al. 2020; Saeed et al. 2023).

Chapter 6 provides conclusions and perspectives on different types of emerging nanomaterials and NPs as theranostic tools for cancer, neurodegenerative, orthopaedic, and cardiac diseases.

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