Chapter 9
Flexibility in the Design of Nanomedicine Using Biomimetic Immunomodulatory

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9.1 Overview of Immune System and Immunomodulators

From invertebrates to humans, the immune system (IS) is essential to the health of all living things and can either prevent or cause disease. The immune system is a sophisticated, interconnected system of cells, tissues, organs, and soluble mediators that protects the body from outside threats to its integrity. The majority of the IS's cells, such as neutrophils, macrophages, and monocytes, are phagocytic. Pathogens and foreign substances can be absorbed and digested by these cells.

The body's normal immune response to infections and cancers, as well as auto-immunity, are mediated by lymphocytes, the second-most numerous cells in the IS (Yatim & Lakkis, 2015). They can be divided into two groups known as T- and B-cells. Following haematopoiesis, common hematopoietic stem cells (HSCs) in the bone marrow give rise to all immune cells. Lymphocytes multiply and diversify exponentially as the immune response is activated. B cells develop into plasma cells, which are a type of antibody factory that release hundreds of antibodies into the bloodstream, while T cells differentiate into numerous subgroups with various specialties (Yatim & Lakkis, 2015).

Two traditional categories of the immune response are innate and adaptive immunity, which serve various and diverse roles in the immunological defence responses.

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- A short-term memoryless innate immune system that offers a quick but insufficient defence against a foreign insult (Netea et al., 2011).
- Long-lived lymphocytes (memory cells) and their highly specialised receptors are part of an adaptive immune response, which is an antigen-specific system (Pancer & Cooper, 2006).
- Unbalanced immune responses can be the cause of a wide range of problems, including allergies, autoimmune diseases, immunosuppression, and AIDS, despite their high effectiveness and specificity (Yatim & Lakkis, 2015; Lerner et al., 2016).

Epidemiological data show that immunological disorders are becoming more prevalent nowadays, which has led to the development of a specific class of chemicals called immunomodulators that can either stimulate or decrease the immune response in diseases involving the immune system. While immunosuppressive medicines are used to reduce the immune response in many immunological-mediated disorders, immunostimulatory therapies may be useful for treating infections, immunodeficiency, and cancer (i.e., in organ transplantation and autoimmune diseases). The creation of new vaccines, therapies for autoimmune illnesses and allergies, regenerative medicine techniques, and immunotherapies for cancer are just a few biomedical applications where attempts to boost, decrease, or qualitatively change the immune response are crucial.

Since the beginning of time, people have been known to get ideas and inspiration from the natural world and its surroundings. This practise is known as "biomimetics," which is derived from the Greek words "bios" (life) and "mimesis" (to copy). It is the most sophisticated approach for applying biological principles—which underlie the structures, morphology, and performance characteristics of biological entities—to man-made designs or models in order to determine the most efficient way to tackle current issues through revolutionary urban design and innovative information technologies. Using structural and genetic methods, researchers are only now learning about the fine ways through which proteins, nucleic acids, metal ions, carbohydrates, and steroids interact with one another (Perera & Coppens, 2019). Researchers create materials with improved properties such as peptide-functionalised gold nanoparticles (NPs), protein-functionalised nanoparticles, and carbohydrate-functionalised nanoparticles by studying and simulating the complex biological structures and processes (Speck & Speck, 2019). This can offer solutions to basic issues in cell biology, biophysics, pharmacology, medicine, and more.

The three types of biomimetic systems are biological (Fig. 9.1), bio-hybrid, and synthetic. Natural biological molecules like proteins, DNA, and RNA, as well as synthetic biomolecules assembled or synthesised by biological systems, including synthetic amino acids created by genetic engineering, are the building blocks of biological structures. Materials that mix synthetic elements (such as metal particles, polymeric chains, and so on) with organic living molecules make up the biohybrid structures. Last but not least, synthetic elements are materials based on artificial building blocks, such as artificial amino acids and synthetic polymers (i.e., prepared in vitro such as solid-phase synthesised peptides). Where the underlying molecular

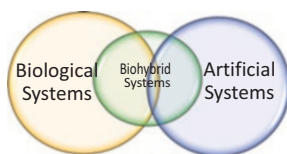**Fig. 9.1** Biomimetic system classification: The three types of biomimetic systems are biological, synthetic, and biohybrid. The interface between artificial and biological systems is where biohybrid systems live. Applications of biomimetic systems in drug delivery

principles are known, one can use and mimic biological processes and interactions to develop biomimetic systems.

Nanomedicine and nano delivery systems, which use materials in the nanoscale range, offer new technological advancements in the development of new and revolutionary pharmaceuticals as well as in the reformulation of currently available drugs to boost their efficacy, improve delivery, and reduce adverse effects. Nanomaterials' potential to more easily pass through biological barriers, persistence in the environment and the body, toxic qualities as well as their physicochemical properties that can cause changes to pharmacokinetics, including the absorption, distribution, elimination, and metabolism, are all causes for concern. Nanotechnology offers many benefits in the treatment of chronic human diseases by delivering precise drugs to designated areas and targets. It has also been shown to bridge the gap between biological and physical sciences by employing nanostructures and nanophases in a range of scientific domains (Liu et al., 2009). Nanoparticles have spurred the discipline of biomedicine, which includes medication delivery, nanobiotechnology, biosensors, and tissue engineering (Mirza & Siddiqui, 2014).

- To achieve their drug delivery goal of achieving the therapeutic concentration of a specific medication at the site of disorder while limiting off-target effects, nanoparticles (NPs) must complete the following crucial requirements.
- NPs need to circulate with enough time to get to the desired location (Yoo et al., 2010).
- NPs need to be able to only affect diseased tissue while insensitive to healthy tissues unaffected (Moghimi et al., 2001; Friedman et al., 2013).
- NPs must be synthesised from a biodegradable material that can be eliminated from the body safely (Naahidi et al., 2013).
- NPs engage with the complex biological environment of the human body.

Numerous immunotherapeutic approaches have produced outstanding results in the therapy of a variety of diseases (Gordon et al., 2014), however immune regulatory drugs' performances can be harmed by significant immune-mediated toxicity, poor solubility, and loss of bioactivity on prolonged circulation (Shen et al., 2018). It is encouraging to note that nanotechnology has the potential to address the issues at hand and so produce the anticipated therapeutic outcome. Studies have revealed that the nanoplatforms exhibit a variety of beneficial characteristics, including;

1. The simultaneous administration of antigens and adjuvants to intracellular spaces or antigen-presenting cells (APCs) (Tazaki et al., 2018).
2. Extended half-lives of molecules carrying bioactive payload by preventing their enzymatic oxidation during blood circulation (Kim et al., 2018).
3. Enhanced permeability and retention (EPR) effect, which is size-dependent, results in increased accumulation in tumour tissues (Xu et al., 2015; Li et al., 2016).
4. Surface modification to target particular cells or tissues (Ding et al., 2013; Chen et al., 2017).
5. Stimuli-sensitive behaviour for secure drug distribution and safe trafficking (Zhang et al., 2018a; Xu et al., 2017; Gao et al., 2019).
6. Higher tolerated doses of medication due to decreased buildup at tissues and organs that are off-target (Musetti & Huang, 2018).
7. Antigen and costimulatory surface interaction Antigen and costimulatory molecule surface coupling to create artificial APCs (aAPCs) with strong T-cell activation potential (Steenblock & Fahmy, 2008).
8. A variety of medication delivery methods, such as subcutaneous microneedle patch delivery or intranasal administration (Tazaki et al., 2018; Kim et al., 2012; Yang et al., 2017)
9. How artificial nanoparticles' inherent immunomodulatory properties work (Chahal et al., 2016; Li et al., 2018).

9.2 Nanoparticles for Immunostimulation

Immunotherapy is the idea that a disease can be treated by either stimulating or inhibiting the immune system. Engineering of immunostimulatory nanoparticles and immunosuppressive nanoparticles based on functional nanoplatforms, and their applications in the treatment of various diseases by regulating immune-related cells, cytokines, and enzymes.

9.3 Emergence of Biomimetic Nanoparticles

Specifically, nanomedicine has witnessed the evolution of multiple NP generations during the past few decades. Scientists have created significant progress in enhancing the medicinal effectiveness of these platforms with each iteration.

NPs in their early years as a generation (Fig. 9.2) were spent developing them with the sole goal of limiting interactions with the body's biological components while passively transporting NPs from site of injection to the illness location. This first generation of NPs was created primarily to test various chemical contents, non-fouling coatings, and sizes (Faraji & Wipf, 2009; Albanese et al., 2012). But it soon became clear that it was difficult to create NPs that are fully unaffected by the in vivo
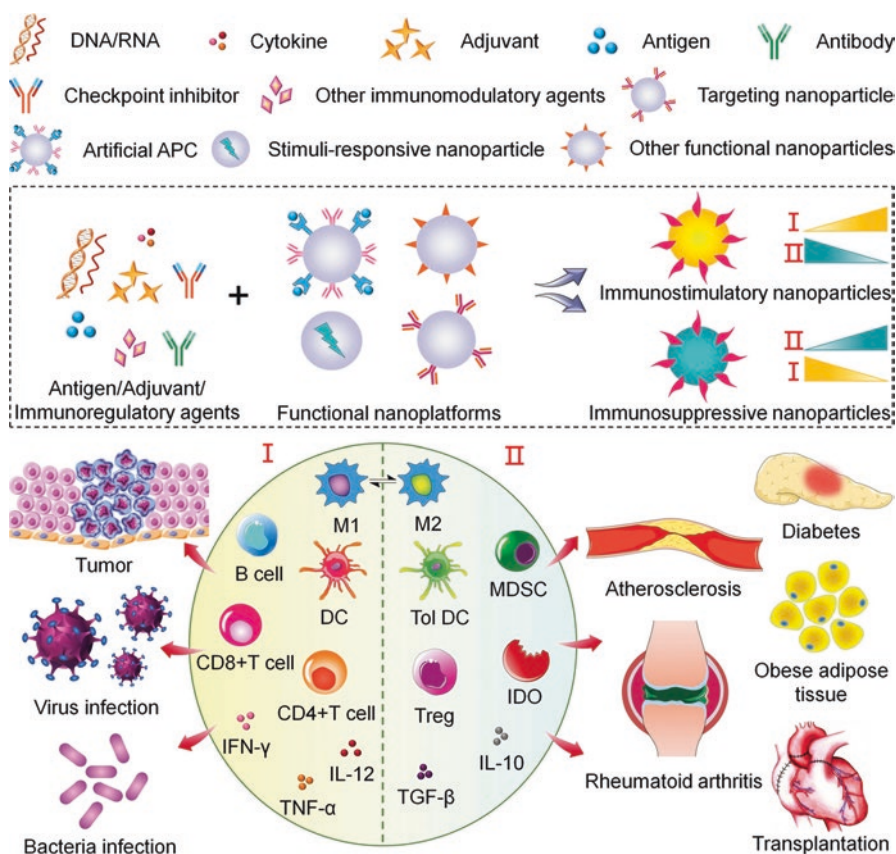
Fig. 9.2 Generations of nanoparticles. Early incarnations of the particles had non-fouling coatings to stop them from interacting with the cells they came into contact with in vivo and were biologically inactive. The subsequent generation of nanoparticles then evolved into active targeting molecules, allowing them to travel to the site of the disease and interact with the surrounding environment. The third generation of cell membrane-based biomimetic nanoparticles uses complete cell membrane or membrane protein functionalisation onto synthetic carriers to imitate the surface characteristics of real cells made with Biorender (Sushnitha et al., 2020)

environment. As a result, the second group of NPs began to concentrate on more specialised, bioactive carriers. These delivery systems were created specifically to allow drugs to access the specific ailment and lessen quasi biodistribution (Mout et al., 2012). Utilising binding ligands, such as peptides, antibodies, and small compounds, was a frequent technique (Friedman et al., 2013). This developing tendency in surface functionalisation was first seen in early attempts to direct active contact between a particle and the cells around it at the nano-bio interface. This second generation of NPs, in contrast to the first, consisted of particles with signals imprinted on their surfaces that allowed them to operate as a mediator in cell interactions. This approach has two variations that handle the two sides of the coin in this scenario of communicating with immune cells. NPs were functionalised with markers on one

side, reducing MPS uptake and clearance (Zhou & Dai, 2018). However, studies have also shown how the addition of affinity ligands makes it possible for NPs to target the area while activating the immune cells that are already present there (Chen et al., 2012; Schmid et al., 2017). Despite using these compounds has shown expected outcomes, by affixing them as solo molecules in their non-native state can prevent them from performing to their full potential. These molecules' arrangement and density on the surface of NP can alter as a result of the conjugation chemistries employed to bind them, changing or completely eliminating their function (Rambukwella et al., 2018).

Because the second generation of active targeted NPs has shortcomings, scientists turned to nature for ideas when creating NP formulations for particular uses. Here, we have witnessed the rise of the third phase NPs, known as biomimetic NPs, which imitate the characteristics of nature to improve their in vivo therapeutic benefits. In addition, a group of biomimetic NPs focused on mimicking the behaviour and function of real cells has arisen to improve these biomimetic NPs' ability to interact and connect with the biological environment. Biomaterials can also be created as instruments to influence the tissue, cell, and molecular interactions that affect immune cells in order to provide fresh insight on the operation of the immune system, just like in other fields of cell biology. This emerging field of immune engineering utilising biomaterials is producing innovative and potentially effective new approaches for vaccination, cancer immunotherapy, the therapy of autoimmune diseases, and the development of organ transplant tolerance. With this technology at their disposal, researchers have investigated the potential therapeutic uses for these biomimetic NPs.

Biomimetic nanoparticles based on cell membranes have become one method for achieving targeted medication administration by active association and interaction with the biological environment. "The surface features of NPs control their in vivo fate at the nano-bio interface, which serves as the primary interface for communication exchange. The interactions at the nano-bio interface, which is the area where the nanoparticle surface comes into direct contact with its surrounding biological environment, regulate the interaction between immune cells and NPs (Nel et al., 2009). This procedure is especially important while circulation because firstly an immune cell interacts with the NP surface. In the succeeding sequence of interactions at this nano-bio interface, direct and indirect signalling cues are used to regulate how the immune cell would respond to their presence in the bloodstream". As a result, the NP surface's physicochemical characteristics and composition considerably influence how the immune system perceives them and, consequently, can control their capacity to transcend the immune system's biological barriers (Wang & Wang, 2014; Liu & Tang, 2017).

9.4   Disease Applications of Biomimetic Nanoparticles

Immunostimulatory therapy should be utilised to immune system activation in the treatment of cancer and infectious diseases in order to identify non-self antigens, eradicate them, and build sustainable results for various disorders. Contrarily,
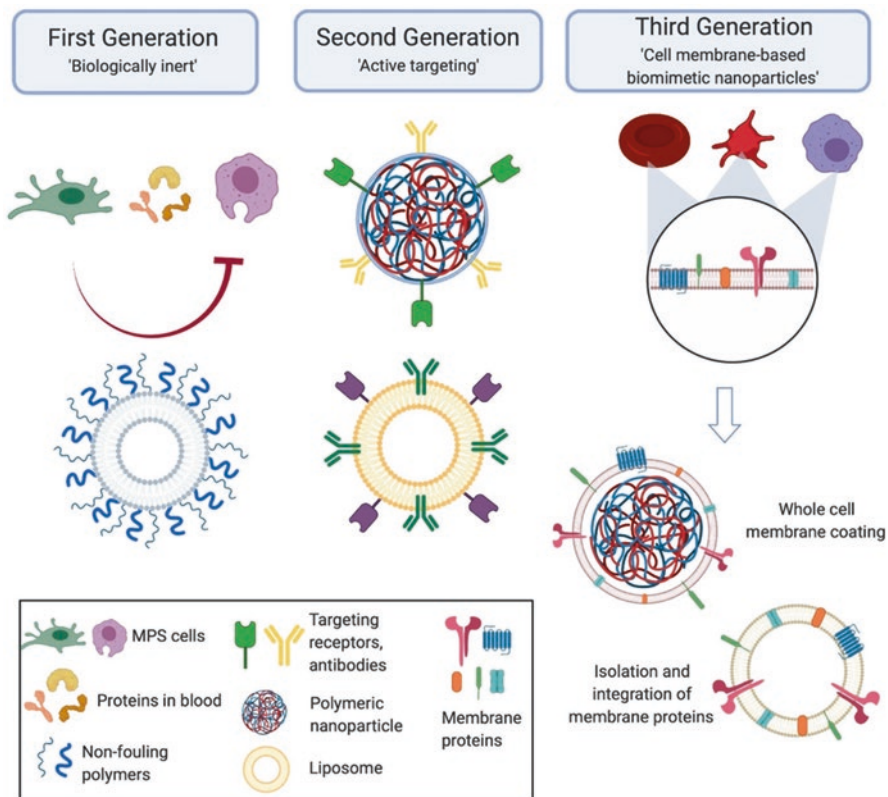
Fig. 9.3 Applications for treating numerous diseases by controlling cytokines, immune-related cells, and enzymes using immunosuppressive nanoparticles built on functional nanoplatforms (Feng et al., 2019)

immunosuppressive medication is required to reduce immune response and create specific immune tolerance for overactive immune response in disorders like rheumatoid arthritis (RA), atherosclerosis, diabetes, transplantation, and obesity (Fig. 9.3). Some immunotherapeutic approaches that have demonstrated impressive results in the treatment of different diseases are listed below;

9.4.1   Cancer

Biomimetic nanoparticles (NPs) based on cell membranes that target tumours have techniques that imitate numerous native cell types. The expression of "don't eat me" markers such as CD47 was used by RBC-based NPs, to accelerate circulation times and get to the target tumour without being affected by MPS. Similar techniques have been utilised to impart these properties to NPs using leukocyte membranes.
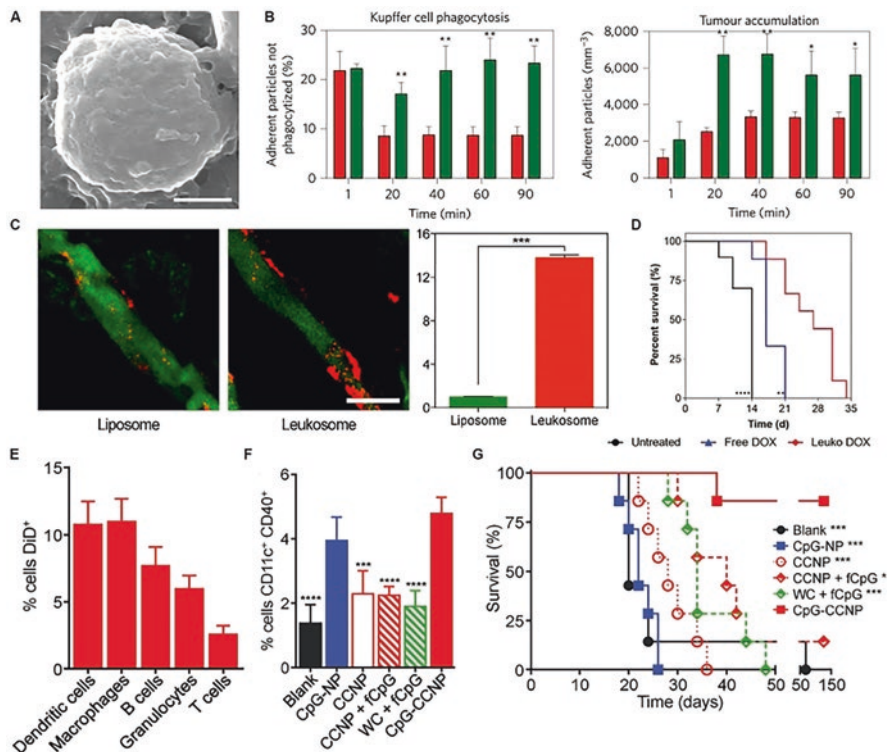
Fig. 9.4 Targeting tumours with bioinspired nanoparticles. Leukocyte mimicking nanoparticles exhibit decreased mononuclear phagocyte system uptake and enhanced tumour targeting in (**a**, **b**). Leukocyte membrane (LVV) is covering a porous silica nanoparticle in (**a**) SEM imagery. Scale bar: 1 mm (**b**) When compared to bare nanoparticles, LLV showed decreased absorption by Kupffer cells (left) and enhanced targeting to melanoma tumours (right). Leukocyte-based liposomes (Leukosomes), which have a stronger affinity for inflammatory tumour vasculature, are (**c**). Scale bar: 50 μm (**d**) Extended lifespan of tumour-bearing mice following administration of doxorubicin-loaded leukosomes. CpG-encapsulated nanoparticles with melanoma cell coating (**e–g**) for immunotherapy (**e**) Immune cells' in vitro uptake of CpG-CCNPs (**f**) In vivo maturation of dendritic cells after exposure to NPs and other controls (**g**) Mice inoculated with CpG-CCNPs and other control formulations both survived overall. (With permission, the images in (a, b) have been copied from (Parodi et al., 2013). Images in (c) have been copied from with permission (Martinez et al., 2018). With permission, the photo in (d) has been copied from (Molinaro et al., 2020). With permission, the images in (e–g) have been copied from (Kroll et al., 2017))

The circulating monocytes do not interact with these biomimetic NPs and identify them for removal by the MPS because they resemble native immune cells in appearance (Parodi et al., 2013; Corbo et al., 2017a) (Fig. 9.4a, b). Due to this, these NPs have a higher chance of reaching the tumour since they imitate the circulatory behaviour of these cells. Along with using these natural coatings for NPs to target the tumour more effectively while in circulation, researchers have also taken

advantage of these membrane-based NPs. For instance, when compared to naked liposomes, integrating liposomes with the leukocyte membrane proteins demonstrated a 14-times enhancement in attraction to inflammatory vasculature associated with triple-negative breast cancer tumours (Martinez et al., 2018) (Fig. 9.4c).

It has been found that the superior targeting is caused by "the presence of leukocyte proteins like LFA-1 and Mac-1. These essential signals give these NPs the potential to act like natural leukocytes that target regions of inflammation, and blocking these proteins on the NPs greatly decreased their ability to selectively accumulate within the tumour (Martinez et al., 2018). This leukocyte-based NP was also demonstrated to enhance doxorubicin administration in two cancer models, melanoma and breast cancer, leading to an improvement (64% and 142%, respectively) in median survival over untreated mice (Molinaro et al., 2020) (Fig. 9.4d). As a result, these NPs imitated the targeting capabilities of leukocytes to target the tumour and deliver the enclosed payload". Others have used activated platelet membranes coated silica NPs to target the circulating tumour cells (CTCs) responsible for the development of metastatic disease by utilising the connections between tumour cells and platelets (Li et al., 2016).

Another study discovered that primary breast cancer tumours accumulated more platelet-coated nanovesicles that were functionalised with TRAIL ('tumour necrosis factor-related apoptosis-inducing ligand') and loaded with the chemotherapy drug doxorubicin (Hu et al., 2015a). The effectiveness of employing cancer cell membrane-coated NPs was demonstrated, for instance, polymeric NPs coated with 4 T1 breast cancer cell membrane, which showed increased homotypic tumour targeting and longer circulation times (Sun et al., 2016). In this case, as the protein profiles of the NPs and cancer cells were similar, the cancer cell was able to recognise and internalise the NP. These studies demonstrate the mechanism of biomimetic NPs perform earlier generations by making use of natural cellular surface characteristics to evade clearance by immune cells that prevent tumour formation and interact directly with the cancer cells.

Another study has shown that the PD-1/PD-L1 immune inhibitory axis, which is the target of immune checkpoint drugs that have received clinical approval, can be disrupted using cancer nanovesicles (Zhang et al., 2018b). Studies also looked into the possibility of using biomimetic NPs as cancer vaccines, whereby the administration of the NP guards against the growth of a tumour when exposed to tumour cells. The same was demonstrated in a study, where pro-inflammatory cytokines were secreted in vitro by immune cells employing PLGA NPs coated with cancer cell membranes as an antigen-presenting material and an immunological adjuvant (Kroll et al., 2017). The study showed that these particles were picked up by a variety of immune cells and were also able to increase Dendritic cell (DC) maturation and overall lifespan of mice by 60% during the course of 5 months using a mouse melanoma model (Fig. 9.4e–g). Additionally, this biomimetic NP platform proved to be an excellent cancer vaccination and treatment option for existing tumours.

9.4.2   Cardiovascular Disease

Cell membrane-based biomimetic NPs can be developed to treat and target several aspects of the pathophysiology of cardiovascular diseases. Researchers have developed novel technologies that imitate the behaviour of innate cells while controlling the inflammatory response common to all of these by drawing inspiration from how native cells behave in this illness scenario.

Myocardial infarction, high blood pressure, and stroke are just a few of the ailments that fall within the broad category of cardiovascular diseases. These conditions are all connected to the heart and blood vessels' regular activities (Stewart et al., 2017). High levels of inflammation have been a defining feature of the pathophysiology of cardiovascular disease from its origin (Golia et al., 2014). However, an accumulation of atherosclerotic plaque is the root cause of many of these disorders (Bobryshev et al., 2016). In a healthy state, lipid and macrophage buildup is resisted by artery walls. However, factors that cause atherosclerosis, such as obesity, hypertension, and high saturated fat diet, start the development of adhesion molecules, which then allow lipids to enter the arterial wall and draw leukocytes to the damaged area; for these applications, biomimetic NPs based on cell membrane have been employed primarily to imitate different cell membranes, such as those of leukocytes platelets and protein complexes crucial for cardiovascular health, such as high-density lipoprotein (HDL) (Park et al., 2020). The body uses HDL, a native lipid carrier "NP, to move lipids with a natural affinity towards atherosclerotic plaque (Feig et al., 2014). Such interactions aid in the movement of macrophagial cholesterol that have accumulated plaque to the liver for processing. This molecule serves as a model complex whose functions NPs can imitate in order to enhance the pathophysiology related to plaques".

Additionally, researchers used artificial HDL-mimicking NPs to stop the growth of atherosclerotic plaque macrophages in an in vivo study with advanced atherosclerotic plaques (Tang et al., 2018). This consequently resulted in a 45% reduction in macrophage proliferation in the aortic roots throughout the course of the 8-week treatment period, a reduction in the inflammatory gene expression, and a reduction in atherosclerosis (Fig. 9.5a, b). Similar to normal HDL, these NPs changed the flow of cholesterol to the liver and prevented the growth of macrophages that feed atherosclerotic plaque.

Additionally, platelets have been strongly associated with the onset of cardiovascular disease and have shown a preference for adhering to blood vessel injury (Kinlough-Rathbone et al., 1983). Using this behaviour as the basis for targeting, NPs coated with platelet-membrane have been created using a freeze and thaw procedure, and after which the extracted membranes were adhered to PLGA cores (Hu et al., 2015a). In a model of rat coronary stenosis, these biomimetic NPs showed enhanced binding to damaged arteries in addition to inhibiting the growth of neo-intima (i.e., the creation of scar tissue).

NPs that imitate leukocytes and RBCs have also been created to transport therapeutic compounds to help treat cardiovascular disorders. For instance, in a model of
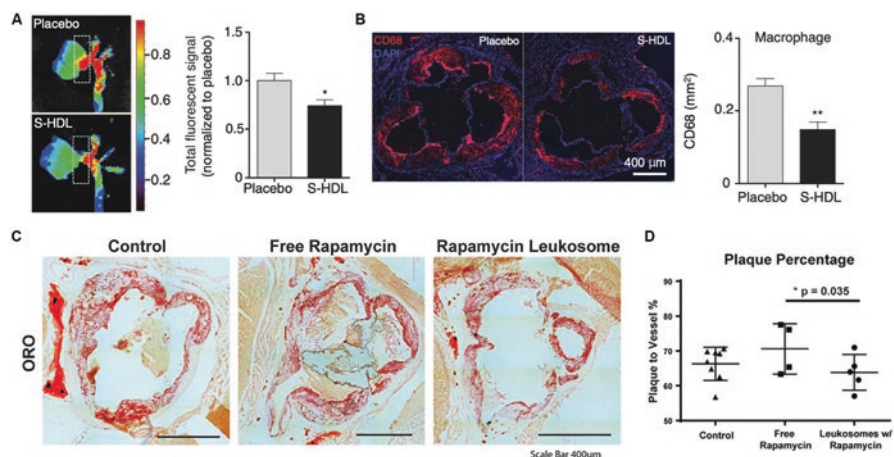
Fig. 9.5 Cardiovascular disease treatments using biomimetic nanoparticles. (**a**, **b**) Mice with atherosclerotic arteries have less plaque buildup and less macrophage infiltration (red) in the aortic roots when HDL-mimicking nanoparticles are used. (**c**, **d**) Leukocyte-based nanoparticles infused with rapamycin to cure atherosclerosis. (**c**) Mice with atherosclerosis treated with or without nanoparticles had lipid deposition stained with oil red O in their aortas. (**d**) Measurement of the plaque area in the image with the vessels. (With permission, the images in (a, b) have been copied from (Tang et al., 2015). Images in (c, d) have been copied from with the permission of (Boada et al., 2020))

cerebral artery occlusion, the circulation of a neuroprotective medication was prolonged by dextran polymer NPs coated with RBC membrane while ischaemic brain damage was reduced (Lv et al., 2018). In a mouse model, NPs based on leukocyte which were loaded with Rapamycin similarly showed enhanced accumulation in atherosclerotic plaques, lowering macrophage proliferation and reducing local inflammation (Boada et al., 2020). Additionally, the vessels' plaque load was decreased as a result of Rapamycin release from these particles (Fig. 9.5c, d). In this instance, the leukocyte proteins were included into the NP to increase targeting of the inflamed location as well as to cause effects that were anti-inflammatory and reduced the localised inflammation at the disease site (Boada et al., 2020).

9.4.3   Infectious Disease

An innovative family of medications that treat infections with three main strategies—targeting the infection's source, neutralising the pathogens' mechanisms for inactivating natural immune defences, and modulating the immune cells which are responsible for anti-pathogen response has been made possible by biomimetic NPs based on cell membrane. To reach this level of targeted precision, NPs that resemble epithelial cells, platelets, and also bacteria themselves have been utilised. For instance, it has been demonstrated that bacteria can invade platelets and cause

platelet aggregation (Fitzgerald et al., 2006). However, platelets are essential to the host's defence mechanism; excessive activation can result in the formation of difficult-to-treat thrombi, which can serve as a haven for germs that are immune to the host's defences. Utilising this characteristic of bacteria, investigators formulated platelet-coated nanoparticles to efficiently transport antibiotics (Hu et al., 2015b). Mice treated with these biomimetic NPs and systemically exposed to a methicillin-resistant strain of bacteria showed significant antibacterial efficacy. In other methods, antibiotics have been delivered through stomach epithelial cell membrane nanoparticles (Angsantikul et al., 2018). This strategy is particularly new because the NPs delivered the surface antigens that the bacteria would ordinarily recognise on the host's cells. The bacteria unintentionally ingest these NPs containing fatal antibiotics due to the identification of these particular proteins on the NP surface. Another strategy is to employ biomimetic NPs to bind the target locations to stop bacteria from adhering to the host's cells in a competitive manner (Zhang et al., 2019).This approach was demonstrated to be successful in a study, H. pylori bacteria were wrapped in polymeric nanoparticles (NPs) to prevent the bacteria from sticking to the stomach lining (Fig. 9.6a, b). Binding sites which were typically used by the pathogen to colonise and cause infection were occupied by bacteria that mimicked NPs. In vitro binding of H. pylori to intestinal cells was reduced by these biomimetic NPs by a factor of six, while in vivo, bacterial colonisation of murine stomach tissue was diminished by over 50%. These illustrations show how the biomimetic NPs' surface characteristics deftly mediate contact with the target pathogen or block the pathogen's interacting with the host cells, which eventually results in the bacterium's death.

Cell membrane-based biomimetic NPs have been investigated as toxin-neutralising platforms to shield immune cells from apoptosis and provide them the capacity to neutralise the pathogen (Fang et al., 2015). This strategy has been demonstrated largely employing RBC-coated NPs due to their long durations of circulation and their capacity to interact with the pathogens in the circulation. Multiple pore-forming toxins, including melittin, a-hemolysin, and streptolysin-O were demonstrated to be sequestered by polymeric NPs that were coated around the membranes of RBCs, protecting hemolysis cells (Hu et al., 2013). Additionally, these NPs, also known as "nanosponges," did not transport these poisons to host cells, illustrating the platform is generally safe.

It has also been demonstrated that biomimetic NPs based on cell membranes can alter the immune response required to treat an infection (Angsantikul et al., 2015). This was demonstrated in sepsis models, which occur when the infection spreads beyond the local tissue and results in systemic organ dysfunction, in particular (Delano & Ward, 2016).

By embedding macrophage membrane proteins into a liposome formulation, Molinaro et al. were able to minimise the impact of proinflammatory genes like IL-1ß and TNF-a while enhancing the expression of anti-inflammatory genes like TGF-ß and IL-10 (Molinaro et al., 2019) (Fig. 9.6e, f). Despite the fact that it ought to be emphasised that earlier research has demonstrated the ability of pure, artificial NPs in the therapy of sepsis, this research has only focused on physicochemical properties as a mechanism of interacting with the surroundings (Casey et al., 2019).
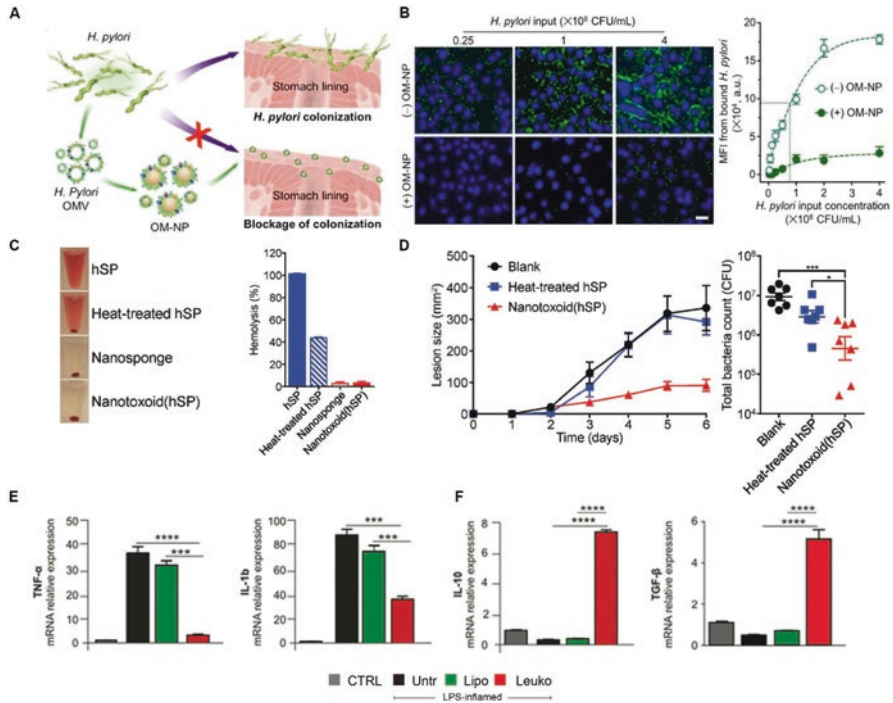
Fig. 9.6 To destroy, neutralise, and control the immune response to pathogens in infectious diseases, biomimetic nanoparticles are used. Nanoparticles with bacterial membrane coatings hinder binding to host cells (**a**, **b**). (**a**) Diagram showing the use of bacterial nanoparticles (NPs) to stop *H. pylori* from colonising stomach tissue. (**b**) Confocal pictures of *H. pylori* (green) adhering to gastric epithelial cells (blue) with or without treatment with NPs, and quantification of those images (right). Scale bar: 25 m (**c**, **d**) RBC-coated nanosponges (Nanotoxoid hSP) as bacterial infection toxoid vaccinations Following NP treatment, sample pictures (left) and haemolysis quantification are shown in (**c**). (**d**) Mice vaccinated with NPs and controls showed differences in lesion size (on the left) and overall bacterial count (on the right). (**e**, **f**) Using liposomes that imitate leukocytes to treat sepsis resulted in decreased expression of pro-inflammatory genes (**e**) and increased expression of anti-inflammatory genes (**f**). (With permission, the images in (a, b) have been copied from (Zhang et al., 2019) Images in (c, d) have been copied from with the permission of (Wei et al., 2017). With permission, the images in (e, f) have been copied from (Molinaro et al., 2019))

9.4.4 Autoimmune Disease

Numerous illnesses fall under the umbrella of autoimmune disorders, including rheumatoid arthritis, systemic lupus, and type 1 diabetes (Theofilopoulos et al., 2017). These illnesses are characterised by autoimmunity, a condition in which the immune system starts to begin to fight the body's own cells in a variety of ways, such as by producing antibodies against them (Wang et al., 2015). These illnesses are also characterised by a persistent inflammatory state in which the immune system keeps trying to fix the harm that has been done. However, these illnesses are

now thought to be incurable. "Research using biomimetic cell membrane-based NPs has demonstrated the growing potential these technologies offer to intervene and mediate the behaviour of the immune system in several illness states. Biomimetic NPs have been demonstrated to mimic native cells, which are capable of resolving inflammation and healing tissue damage and to act as binding decoys for systems that cause the chronic inflammatory state". Engineered leukocyte membranes imitating NPs were developed to bind to inflamed mucosal tissue by overexpressing a4b7, a key integrin protein on T-lymphocytes in order to exploit the processes of T-cell activation in the course of IBD pathogenesis (Berlin et al., 1993). These "specialised leukosomes" showed more firm adherence to inflamed endothelia as a result of this overexpression. Additionally, these biomimetic NPs enhanced the crypt shape, decreased CD45+ immune cells, and inhibited edoema in DSS-induced IBD mice (Corbo et al., 2017b). It was hypothesised that the therapeutic effects seen after therapy with these customised NPs resulted from NPs binding to receptors that would normally be bound by the immune cells causing this disorder. With RBC-mimicking NPs, this method was also used to illustrate how to remove pathogenic antibodies. These RBC-based biomimetic NPs were very effective at acting as binding stooges for antibodies that would otherwise bind to native RBCs and mark them for extravascular haemolysis (Copp et al., 2014). In a model of induced anaemia, RBC numbers and haemoglobin levels returned to normal in mice given these RBC-NPs. The RBC count was reduced by 60% in mice that did not get the NPs, and the levels of haemoglobin were reduced by twofold. Finally, it has been demonstrated that neutrophil-mimicking NPs have important effects on rheumatoid arthritis treatment. In actuality, these NPs reduced joint degeneration and suppressed proinflammatory cytokines in two mouse models of arthritis. These results highlight the adaptability of biomimetic NPs in focusing on and fine-tuning the underlying pathways that underlie and fuel a variety of autoimmune disorders.

9.4.5 Vaccination

A vaccine consists of an antigen, which serves as the immune system's target, and an adjuvant, which is injected along with the antigen to boost the immune system's reaction. Nanoparticles (NPs) have recently drawn a lot of attention as vaccine delivery systems. In addition to improved immunogenicity and antigen stability, nanovaccine formulations also offer targeted distribution and protracted release. Additionally, NPs aid in preventing the antigen and adjuvant from being prematurely degraded by enzymatic and proteolytic processes (Bishop et al., 2015). Although NPs have the benefits listed above, they also have drawbacks, including an unfavourable interaction with the reticuloendothelial system and a lack of colloidal stability under physiological conditions caused by protein corona forms (RES) (Corbo et al., 2016, 2017c).

A unique type of nanoparticles known as biomimetic NPs effectively avoids unfavourable interactions with immune cells like RES and prolongs blood circulation

Table 9.1 Some of the reported biomimetic nanovaccines and their applications

Nanoparticles	Components	Application	References
Liposomes	PLGA NPs with lipid antigens	Malarial vaccine delivery	Moon et al. (2012)
	Liposome-polycation-DNA NPs	DNA vaccine delivery	Li et al. (1998)
VLPs	Genetically modified VLP	Anti-viral protection	Wu et al. (2012)
	Avian retrovirus with Gag fusion proteins	Intracellular protein delivery	Kaczmarczyk et al. (2011)
Self-assembling proteins	Hollow vault protein	Self-assembling protein with Flagellin scaffold	Champion et al. (2009)

(Angsantikul et al., 2015; Gao et al., 2013; Rao, 2013). When given to the body, these nano vaccines' carrier NPs, which resemble biological membranes, allow for longer circulation and the evasion of immunological reactions (Vijayan et al., 2018). A different kind of biomimetic carrier system with a "core-shell" shape is a cell-membrane-coated NP. A thin layer of plasma membrane serves as the shell, with the NP acting as the hydrophobic core (Hu et al., 2012) (Table 9.1).

An extruded polymeric NP was covered with red blood cell (RBC) membranes to create the first membrane-coated nanoparticles, according to Hu et al (Hu et al., 2012). The creation of membrane-coated NPs has made use of a variety of membranes from various sources, including RBCs (Hu et al., 2012; Gao et al., 2017) leukocytes (Wei et al., 2019; He et al., 2016, 2018), cytotoxic T-cells (Wei et al., 2018). Self-assembling proteins can also be utilised to make biomimetic nanovaccines since they have excellent symmetry and stability and can be structurally organised into particles with diameters between 10 and 150 nm (Kang et al., 2009). Due to their capacity to self-assemble and deploy into a specific shape that replicates the architecture of real microbes, these self-assembling protein NPs serve a variety of physiological functions and are chosen as vaccine carriers (Castón & Carrascosa, 2013).

9.5   Conclusion and Future Prospects

The area of biomimetic nanoparticle engineering has made enormous strides in the previous 10 years and is currently under rapid development. The bioinspired nanoparticles have a variety of functions, involving increased accumulation at infected locations, extended circulation, and less off-target effects in healthy tissues. They do this by utilising the many transport and translocation strategies that viruses and mammalian cells have devised. Therefore, thorough anti-infective investigations are required to verify the efficacy and long-term safety concerns of emerging bioengineered nanotherapies. The cellular and molecular events that dominate the in vivo pharmacokinetic and biopharmaceutical profiles of the biomimetic

nanotherapies now being produced should also be the subject of mechanistic studies. In light of recent developments in the life sciences and biological as well as the modernisation of nanotechnology, it is essential to increase the variety and utility of biomimetic nanoplatforms. Other state-of-the-art technologies, such as materials genome, artificial intelligence, and computational design can be incorporated to find more effective and beneficial nanoparticles based on bioengineering methodologies.

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