# Chapter 2
# Multifunctional Nanoparticles

The functionalization of nanoparticles with one or more specific chemical moieties, so-called ligands, results in multifunctional nanoparticles. They are widely used in biomedical applications, especially drug delivery, cancer therapy, diagnostics, tissue engineering, and molecular biology (Svenson and Prudhomme 2012). Ligands are named based on their functions, such as stabilization, targeting, imaging, anti-immunogenics, and biocompatibility improvement (Table 2.1). Therefore, it is important to discuss the ligands used for the functionalization of nanoparticles.

## 2.1 Stabilizing Ligands

Generally, surfactants are used for stabilizing nanoparticles. These ligand molecules adhere to the nanoparticles in situ during the synthesis process itself, usually by chemisorption, electrostatic attraction, or hydrophobic interaction. Various chemical functional groups possess a certain affinity for inorganic surfaces, the most common example being thiol-gold affinity. These molecules exert repulsive forces due to electrostatic repulsion, steric exclusion, or the hydration layer on the surface; they serve to prevent the aggregation of the particles and stabilize them. This is an important aspect because the stability of the drug or the drug carrier influences the efficacy of the therapy. For example, the surface charge of a gold nanoparticle becomes neutral, causing aggregation. Therefore, the color changes from ruby red to blue. However, surface modification with ligands such as polymers, small molecules, and biological recognition molecules prevents aggregation. Gold nanoparticles can be stabilized using thiol surface functions. Surface-stabilizing ligands are of three types (Table 2.2): polar, nonpolar, and amphiphilic (Sperling and Parak 2010).

The stability factor, the reducing factor, and part of the therapeutic factor are one and the same if the nanoparticles are generated using a green synthesis protocol.



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**Table 2.1** Ligands used for biomedical applications

| S. No | Ligand type | Function | Examples |
|---|---|---|---|
| 1 | Stabilizing ligand | Stabilizes the drug or the drug delivery system | Flavonoid-stabilized metal nanoparticles |
| 2 | Targeting ligand | Site-specific binding of the drug delivery/imaging system | Lung targeting peptide (LCP), hyaluronic acid |
| 3 | Imaging ligand | Monitoring and diagnosis of tumor and drug distribution | Indocyanin green, fluorophores |
| 4 | Biocompatibility ligand | Decreasing the host–implant or host–drug carrier interaction | Self-assembled monolayers, carboxyl groups, hydroxyl groups, amino groups, plasma filming |
| 5 | Anti-immunogenic ligand | Preventing an immune response against biomedical agents, enhancing the circulatory time, restricting the clearance by the reticuloendothelial system (RES) | Polyethylene glycol (PEG) |

**Table 2.2** Surface-stabilizing ligands

| Stabilizing ligand type | Example |
|---|---|
| Polar | Carboxylic<br>Sulphonic acid groups |
| Nonpolar | Trioctylphosphine oxide (TOPO)<br>Triphenylphosphine (TPP)<br>Dodecanethiol (DDT)<br>Tetraoctylammonium bromide (TOAB)<br>Oleic acid (OA) |
| Amphiphilic | Poly(ethylene imine) (PEI)<br>Poly(acrylic acid) |

This is the advantage of a green synthesis approach. For example, silver nanorods synthesized using germinated fenugreek seed extract utilized phytochemicals for reducing the substrate silver nitrate, for stabilizing the nanoparticles, and also in the therapy by acting as an anticancer agent (Suganya and Devasena 2015). Similarly, during the synthesis of gold nanocubes, the polyphenol curcumin analog served a dual role of reduction and stabilization (Devi et al. 2014).

Polyethylene glycol (PEG), also called poly(ethylene oxide) or polyoxyethylene, is an amphiphilic polymer that is widely used as a ligand for drug delivery. The process of the coupling of PEG to a host molecule is called PEGylation; the modified molecules can be referred as PEGylated carriers. The following advantages and unique properties of PEG make it an excellent ligand for biomedical applications:

- High stability and inertness
- High biocompatibility
- Nontoxic nature
- High steric effects
- High hydrophilicity, leading to an increase in the solubility of the nanocarrier
- Decreased immunogenicity and lesser probability to bind to the antibody molecules
- Ability to confer higher circulatory half-life to the host molecules
- Ability to shield the core of nanocarriers from degradation by steric hindrance
- Capacity to increase the hydrodynamic size in order to reduce the renal clearance, increasing the solubility of nanocarriers as a result of its hydrophilicity
- When the cargo is a protein molecule, PEG is useful in preventing the enzymatic attack by proteases.

To conjugate PEG with the drug or the drug carrier, the reacting end of the PEG should be pre-activated. This can be done by using cyanuric chloride, or by the method of succinimidyl succinate, imidazoyl formate, succinimidyl carbonates, or succinimidyl esters. The activated PEG can form conjugates with drugs such as proteins, peptides, enzymes, and cytokines or with carriers such as liposomes, polymers, micelles, hydrogels, nanoparticles, or antibody-conjugated nanoparticles. For example, PEG can be attached to the $\alpha$- or $\varepsilon$- amino groups of lysine, the thiol moiety of the cysteine, or the N-terminal amino groups of protein drugs.

PEGylated interferons were synthesized for the treatment of hepatitis C and hepatitis B viruses. PEG-conjugated human growth hormone antagonist has potential for treating acromegaly. PEG molecules were reported to increase the thrombopoietic activity of interferon-6 and the antitumor activity of tumor necrosis factor by several fold. PEGylation is known to increase the penetration of polymeric nanocarriers across the blood-brain barrier for drug delivery into the brain. PEGylated liposomes show greater circulatory half-life than the unPEGylated ones. Polymeric hydrogels formed with PEG exhibit superior wound-healing activity and biodegradability. PEG has the potential to enhance the gene delivery efficacy of vectors. The circulatory half-life of insulin can be enhanced by conjugation with PEGylated nanoparticles for biological and pharmaceutical applications (Otsuka et al. 2003).

### *2.1.1 Biomolecules*

Biomolecules such as lipids, vitamins, peptides, and sugars and biopolymers such as proteins, enzymes, DNA and RNA molecules can be used as ligands and can be attached to the nanoparticles (so-called bioconjugation). The resulting product is referred to as a nano-bioconjugate or a nano-biohybrid. Such hybrids will combine the unique properties of both the components—that is, the biological specificity (the

molecular recognition property) of the biomolecule and the fluorescent/magnetic property of the nanoparticles (Sperling and Parak 2010).

Bioconjugation can be carried out by following methods:

- Chemisorption, where the ligand binds to the core surface without establishing covalent bonds
- Electrostatic adsorption, which can be established due to attraction between the oppositely charged moieties in the core and the ligand
- Covalent bonding
- Molecular affinity as in the case of biotin-avidin system and protein tags or a polyhistidine system.

### *2.1.2 Avidin-Biotin Conjugate*

The avidin-biotin system is used to attach biomolecules to nanoparticles. Biotin, a small molecule (vitamin H) with one free carboxylic function is first attached to the nanoparticles via conjugation chemistry or through ligands. Biotin-modified nanoparticles can bind to avidin via covalent interaction. Avidin is a tetramer in which each subunit has stronger binding affinity for biotin. At pH below the Pi, avidin has a positive charge, thus enabling electrostatic interaction with negatively charged nanoparticles. Streptavidin can be conjugated through its carboxyl or primary amine function to the quantum dots or alternatively adsorbed directly via a polyhistidine tag (Sperling and Parak 2010). This would help in targeted imaging. The avidin/biotin-liposome system is used for sustained peritoneal drug delivery and also delivery into associating lymph nodes in an ovarian cancer xenograft model (Zavaleta et al. 2007).

## 2.2 Targeting Ligands

Cancer treatment by cytotoxic drugs is usually associated with a risk of non-specific off-target damaging and collateral toxicity. Hence, there is a need for selective targeting of cancer cells based on the recognition of cancer-specific antigens (the tumor-associated antigens), which are overexpressed in the cancer cells alone. This can be achieved by conjugating the drug with another molecule that has affinity for the surface antigens. Consequently, the drugs will hamper the proliferation and induce apoptosis of cancer cells. These molecules are called targeting ligands. The ligand is usually attached to a spacer, which in turn is linked to the drug-loaded nanoparticles by means of a dissociable bridge, thus forming an assembly (Fig. 2.1). The ligand will direct the assembly towards the cancer cell, thereafter

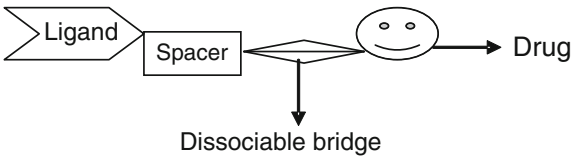


**Fig. 2.1** Targeting ligand-drug assembly

entering into the cell by endocytosis. The bridge is capable of dissociating and releasing the drug once the assembly is engulfed after endocytosis. This is called the "magic bullet approach" of drug targeting, as first proposed by Paul Ehrlich (Muro 2012). The most important criteria for a targeting ligand are (i) high binding affinity to the target, (ii) low immunogenicity to the host, and (iii) high penetrating capacity into the target cell.

Table 2.3 shows the classification of targeting ligands. Monoclonal antibodies require a more detailed explanation because they are the best targeting ligands in view of their specificity and selectivity towards tumor cells. Other targeting ligands include antibody derivatives, peptide, aptamers, and proteins such as DARPins, transferrin, lactoferrin, and lectins, as well as small targeting molecules such as folates and mannose derivatives.

**Table 2.3** Summary of targeting ligands

| Targeting ligand type | Examples | Target |
|---|---|---|
| Antibodies | Cetuximab | Epidermal growth factor receptors overexpressed on the surface of certain cancer cells |
| | Herceptin or rituxumab | CD20 proteins expressed on the surface of B cells |
| Antibody fragments/antibody derivatives | Fab fragment | Used to target drug-loaded liposomal vesicles Also used for targeting specific receptors in the cells of breast, colon, lung and ovary |
| Peptides | DARPins | Targeting the amyloid β protein to treat Alzheimer disease |
| | Arginine–glycine–aspartate (RGD) | Targeting the integrins of endothelial cells, epithelial cells, and glioblastoma cells and delivery of paclitaxel and doxorubicin |
| Aptamers | Oligonucleotides of DNA | Diagnosis and treatment of viral infection |
| | Oligonucleotides of RNA | Diagnosis and treatment of viral infection |
| Small targeting molecules | Transferrin | Transferrin receptors upregulated on the surface of cancer cells |
| | Lectin | Luminal surface of small intestine |
| | Folate | Folate receptors expressed in many malignancies |

### 2.2.1 Antibodies

Among antibodies, IgG is mostly used. Antibodies can be used as such, in the form of fragments (e.g., Fab fragment obtained by enzymatic cleavage of antibodies or by genetic engineering), or as immunoconjugates.

### 2.2.2 Antibody Fragments/Antibody Derivatives

Fab fragments of antibodies (Fig. 2.2) can be covalently cross-linked to a drug carrier for targeting. The Fab fragment of antibody may be coupled to a nanocarrier encapsulated with the drug. This may result in site-specific drug release. For example, a Fab fragment with a projected thiol group forms a stable disulphide bridging with the pyridothiol derivative of phosphotidyl ethanolamine, which constitutes the liposome carrier (Attarwala 2010).

Immunoconjugates are antibodies linked to an effector molecule, which is the cytotoxic agent. The immunoconjugates are either an immune-drug conjugate, immunotoxin, or radioimmuno-conjugate, depending on whether the effector molecule is a drug, protein, or radionuclide, respectively (Attarwala 2010). An immune-drug conjugate is internalized into the cells by endocytosis and thereafter enzymatically hydrolysed by the lysosomal hydrolases to release the drug. The effector proteins of immunotoxins are usually cytotoxic enzymes of plant or bacterial origin or proapoptotic proteins. After recognition and internalization, the toxin induces cell death. A radio-immunoconjugate induces cell death after being engulfed into the cells, due to the toxicity of its constituent radioactive materials.

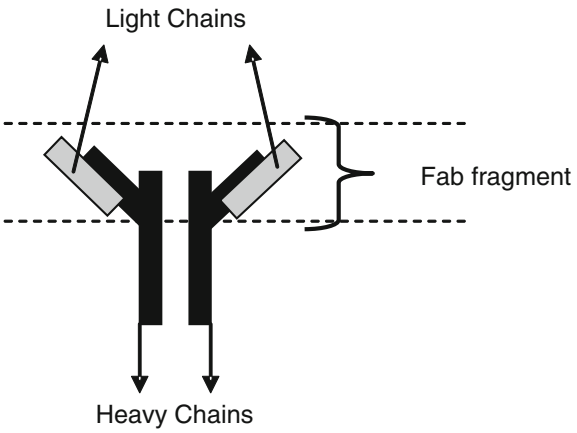


**Fig. 2.2** The Fab fragment of an antibody

### 2.2.3 Peptides

RGD peptide is a synthetic peptide (Arginyl-glycyl-aspartic acid) with binding affinity for cell surface integrins. RGD can therefore be used for the targeted delivery of drugs, drug-loaded nanoparticles, and imaging agents into cells. RGD functions as an apoptotic anticancer agent by activating procaspase-3. It is usually PEGYlated and linked to the drug via an amide or hydrazone spacer (Fig. 2.3). RGD has the advantages of rapid cellular uptake and ease of production by solid-phase peptide synthesis; they are widely used for targeting doxorubicin and paclitaxel. Proteins containing an RGD motif include fibronectin, fibrinogen alpha chain, *E. coli* lambda receptor, sindbis coat protein, alpha lytic protease, and testis-specific basic protein (Schaffner and Dard 2003).

Designed ankyrin repeat proteins (DARPins) are genetically tailored antibody-like proteins (i.e. antibody mimetics) consisting of three to five repeated motifs of ankyrin proteins (Fig. 2.4). The repeats are tightly packed with a hydrophobic core, resulting in high stability, solubility, and dispersibility. DARPins possess specific affinity towards their target protein, thus enabling protein-protein interactions; they have diagnostic and therapeutic applications.

DARPins are capable of effectively crossing the blood-brain barrier, thus emerging as a therapeutic tool for treating neurodegenerative disorders. For example, they are used for treating Alzheimer disease by targeting the amyloid-β peptide (ABP). The ABP plays a pivotal role in the initiation and progression of Alzheimer disease, which is characterized by cognitive defects. ABP-specific DARPins treat Alzheimer disease by preventing the aggregation of ABP, reducing soluble ABP levels, and ameliorating ABP-mediated neurotoxicity in vivo.

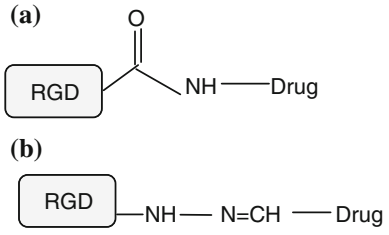


**Fig. 2.3** RGD peptide-based targeting assembly formed by **a** an amide linker and **b** a hydrazone linker

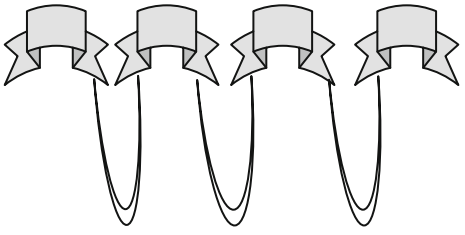

**Fig. 2.4** DARPin with three repeated motifs

Vascular endothelial growth factor (VEGF) is another good example of a therapeutic DARPin. It is used in the treatment of wet macular degeneration (Hanenberg et al. 2014).

### 2.2.4 Aptamers

In Latin, *Aptus* means 'to fit' and *meros* means 'part'. Aptamers are short strands of DNA or RNA that are capable of fitting into a specific part of a target molecule. Aptamers are produced by a method called *systematic evolution of ligands by exponential enrichment* (SELEX). They are competent with monoclonal antibodies. Aptamers are used in the treatment of cancer because they can bind to cancer-specific proteins and nucleic acid targets. The binding affinity between aptamers and their target proteins is useful in fabricating biosensors for detecting cancer markers. Aptamers can conjugate with effector molecules such as drugs, photosensitizers, imaging agents, or Si RNA and are used for theranostic purposes (Wu et al. 2015; Keefe et al. 2010).

In addition, aptamers exhibit affinity for molecules such as proteins and nucleic acids of viral origin. Hence, they are used in the diagnosis and treatment of viral infections. Aptamers are useful for the early detection of viral genes, viral proteins, and host infection markers (i.e., antibodies raised against the virus). For example, H5N1 viral infection is detected using hemagglutinin-specific DNA aptamers. Hepatitis C virus infection can also be detected by the recognition of glycoprotein E2 by DNA aptamers. Aptamers help to treat viral infections by conjugating and delivering the drugs to the virus-infected cells, preventing the entry of virions into the cells, and inhibiting viral replication enzymes.

Macugen is the first therapeutic aptamer approved by the U.S. Food and Drug Administration for the treatment of age-related macular degeneration. Moreover, DNA aptamers are used to treat influenza viruses H5N1 and H9N2. RNA aptamers are used to treat the infections caused by hepatitis B and C viruses, SCV, HMCV, and Ebola. Infections caused by human immunodeficiency virus, hepatitis B virus, hepatitis C virus, severe acute respiratory syndrome, H5N1 avian influenza, and Ebola can be diagnosed and treated by using aptamers (Wandtke et al. 2015).

### 2.2.5 Small Targeting Molecules

Apart from the major targeting ligands discussed previously, some small molecules such as transferrin, lectin and folates have also been reported to exhibit targeting abilities.

Transferrin is an iron-binding protein with a molecular weight of 80 kDa. Receptors to transferrin are overexpressed in cancer cells due to their enhanced iron requirement as compared to normal cells. Hence, transferrin can easily be attracted

towards the cancer cell surface along with chemotherapeutic drugs, cytotoxic proteins, or cytotoxic enzymes. For example, transferrin is useful for targeting CD71 antigens overexpressed on the cancer cell surface. Transferrin has been reported to deliver adriamycin to HL60 and K562 cells and to mice. The targeted delivery of other drugs such as doxorubicin, ricin A-chain-toxic protein, and therapeutic genes (for gene therapy) have also been reported.

Lectins are proteins found on the surface of certain cell types as receptors, such as galactose-specific lectins and mannose-6-phosphate-specific lectins in the hepatic cells of mammals. Another lectin, the mannan-binding lectin, is distributed on the surface of immune cells. Although these lectins have their own functions in the liver and immune system, they may be exploited for drug delivery. Similar to lectin, carbohydrate residues also exist as cell surface molecules, such as glycoproteins and glycolipids. Lectins have high affinity for carbohydrate residues. Taken together, carbohydrates can provide a port of entry for lectinized drugs or drug–nanoparticle conjugates. In the same way, carbohydrate-based therapeutic molecules can be targeted into cells via endogenous ligands of the cells. Hence, the ligand-carbohydrate interaction can be used in the drug delivery application in two ways (Kaszuba and Jones 1998).

There are two strategies to target lectin:

(i) In direct lectin targeting, the nanoparticle-bound drug or the free drug itself is conjugated to a carbohydrate residue (forming a glyconanoparticle or glycosylated drug). The carbohydrate residue, in turn, is allowed to target cell surface lectins to achieve better efficacy of the drug. For example, intraperitoneal administration of a mannan-methotrexate conjugate in leukemic mice showed enhanced anti-tumor potential compared with free methotrexate (Budzynska et al. 2007).

(ii) In reverse lectin targeting, the nanoparticle is conjugated to a lectin (i.e., the lectinized nanoparticles), which is allowed to target cell surface carbohydrate residues. Lectinized gliadan nanoparticles are a useful system for the delivery of acetohydroxamic acid to inhibit *Helicobacter pylori*. Lectinized liposomes are used for targeting alveolar type II epithelial cells. Lectin-modified solid lipid nanoparticles (SLNs) are used in the delivery of insulin (Gupta et al. 2009).

Folate-mediated drug delivery is a good example of vitamin-aided targeting. Folate receptors are overexpressed in cancer cells. Folate, a vitamin B9 molecule, can be conjugated to the drug or the nanoparticle-conjugated drug and targeted toward the cancer cells (Fig. 2.5). Its low molecular weight and high affinity for folate receptors have made folate an excellent ligand for the delivery of protein toxins, immune stimulants, chemotherapeutic agents, liposomes, nanoparticles, and imaging agents. Folate is used to inhibit the proliferation of ovarian, brain, head and neck, renal, and breast cancer cells (Hilgenbrink and Low 2005).

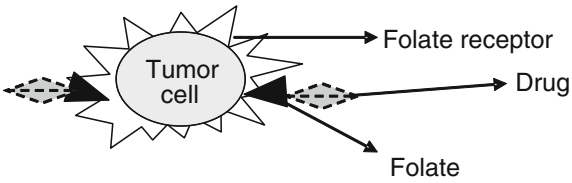


**Fig. 2.5** Folate-mediated drug targeting

## 2.3 Imaging Ligands

Imaging ligands or, more commonly, imaging agents are molecules capable of demonstrating internal structure and monitoring a treatment regimen, keeping track of the internalized drug molecules. Usually, imaging molecules are constructed to be a part of nanoparticle construct or sometimes nanoparticles themselves, such as quantum dots. Magnetic nanoparticles (MNPs), fluorescent probes (fluorophores), radioactive tracers, and mixed lanthanide oxide nanoparticles are used for imaging tissues via magnetic resonance imaging (MRI), fluorescence imaging (FI), or positron emission tomography (PET) techniques.

Magnetic nanoparticles (MNPs) are conventionally used as imaging agents through MRI (see Chap. 4). MNPs are widely used for imaging cardiovascular disease, such as atherosclerosis, myocardial injury, and stem cell therapy (Sosnovik et al. 2008).

Fluorodeoxyglucose (FDG) and fluorine-18 (F-18) are used as tracers for imaging cancer cells, especially lung cancer and lymphoma. 11C-Metomidate has been used to image adrenocortical tumors. Fluorescent radiotracers have extensive applications in neuroimaging, such as in monitoring Alzheimer disease as well as in cardiovascular disease such as atherosclerosis. Clinically, bacterial infections can also be identified using PET with the help of [$^{18}$F] maltose, [$^{18}$F] maltohexaose, and [$^{18}$F]2-fluorodeoxysorbitol (FDS). Gadolinium oxysulfide nanoparticles doped with other lanthanides [Eu(3+), Er(3+), Yb(3+)] function as new multimodal nanoplatforms for MRI, X-ray, and photoluminescence imaging in vitro (Osseni et al. 2014).

Dual molecular imaging provides us with more information about diseased cells and finds immense use in diagnosis. MRI and FI on a single modality would be an ideal dual imaging system for biomedical diagnosis. A mixed lanthanide oxide nanosystem in which one lanthanide exhibits MRI capability and the other exhibits FI capability would give a successful diagnosis. Dy, Ho, Gd, Tb, and Er are MRI candidates, whereas Eu and Tb are fluorescent candidates. Hence, the mixed ultrasmall nanoparticles Dy/Eu, Ho/Eu, and Ho/Tb are dual imaging modalities. The advantages of mixed lanthanum oxide T2 MRI–FI agents include the following, as proven in vitro (DU145 cells, a PC3 human prostate cancer cell line) and in vivo (mouse) (Xu et al. 2013):

- Facile synthesis condition
- Stable and robust
- Controllable composition in terms of the lanthanide oxides

- High $r_2$ values and magnetization
- High negative contrast enhancement
- Highly resolved confocal image
- Feasibility of intravenous administration into the mammalian model.

## 2.4 Biocompatibility Ligands

The biocompatibility of a material is its ability to exist in harmony with the living system without producing adverse side effects. In the context of nanotherapy, biocompatibility is a crucial factor when implants and drug carriers are used for treatment. Inflammation, fibrosis, thrombosis, and infection are some of the adverse effects associated with implantable medical chips, which are mediated via protein adsorption, cell adhesion, and tissue adhesion. Hence, biocompatibility should be enhanced by modifying the surface chemistry of the implant. The biocompatibility of a medical device such as an implant or a drug carrier, can be enhanced when functionalized with suitable molecules—biocompatibility ligands—to minimize the protein adsorption and host-cell adhesion effects. This approach showed success in vitro, but more investigation is needed to validate its biocompatibility in vivo. For example, the biocompatibility of synthetic polymers, such as polyvinyl chloride, can be enhanced using collagen (Lungu et al. 1997). Other methods of increasing surface biocompatibility (Thevenot et al. 2008) include the following:

- Enhancing hydrophobicity to decrease protein adsorption
- Altering surface charges
- Forming flat, chemically homogenous, and well-defined surfaces by activating the bulk material surface, grafting with the polymer, and fabricating self-assembled monolayers (SAMs). SAMs are suitable for gold- and silver-coated surfaces only
- Using the plasma modification method. Gases generate highly excited atomic, molecular, ionic, and radical species called "plasma" upon irradiation with radiofrequency, microwave, or electrons from a hot filament discharge. Plasma modification of an implant or biomedical materials such as metals, polymers, and ceramics results in a uniform surface, which is very essential for tissue engineering and artificial organs
- Adding functional groups as biocompatible ligands. For example, carboxyl (–COOH), hydroxyl (–OH), amino ($–NH_2$), and methyl ($–CH_3$) groups are capable of influencing the interaction of protein and cells with the surface.

## 2.5 Anti-immunogenic Ligands

The biological system (the host) may consider the drug carriers or the implants to be foreign material, resulting in an immune response that would impact the desired effect of the biomedical constituents. This should be prevented by a suitable molecule capable of evading the attack by immune cells. Polyethylene glycol (PEG) is a suitable anti-immunogenic ligand capable of evading the immune response. PEG was reported to decrease the immune response by reducing interleukin-2 and tumor necrosis factor-$\alpha$ secretion from lymphocytes (Jang et al. 2003). PEG is useful for the escape of nanoparticles from RES and endosomes during gene delivery. The final section of this book discusses the application of Si RNA delivery in treating multi-drug resistance cancer, viral infections, and genetic diseases. In spite of these applications, Si RNA delivery has certain demerits: First, they are easily cleared by the RES after systemic administration. Second, they are trapped and subjected to enzymatic hydrolysis in endosomes and lysosomes. This results in decreased accumulation of the therapeutic molecule in the tumor. A PEG graft can overcome these disadvantages to a certain extent (Guo and Huang 2011).

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