Chapter 15
Mannose Receptor and Targeting Strategies

Priyanka Jahagirdar, Amit S. Lokhande, Prajakta Dandekar, and Padma V. Devarajan

Abstract The mannose family receptors are unique multidomain, multifunctional endocytic receptors belonging to the C-type lectin family. These receptors, although structurally similar, exhibit differential binding to discrete ligands. This chapter discusses such similarities and differences between the structures, ligands, the expression, and molecular trafficking among the members of mannose receptor family. Further, targeted drug delivery strategies in infections and cancer to the most widely investigated receptor of the family, the mannose receptor, are comprehensively explained with examples.

Keywords Mannose receptor family · Mannose conjugates · Nanoparticles · Liposomes · Vaccines · Infections · Cancer

Abbreviations

CD	Cluster of differentiation
CTLD	C-type lectin domain
DCs	Dendritic cells
DRV	Dehydration–rehydration vesicle
HIV	Human Immunodeficiency Virus
IFN	Interferon
IL	Interleukin

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LAM	Lipoarabinomannan
LPS	Lipopolysaccharide
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
NPs	Nanoparticles
PEG	Polyethylene glycol
PLA_2	Phospholipase A_2
PLGA	Poly (lactide-co-glycolide)
RES	Reticuloendothelial system
SLA	Soluble leishmanial antigen
SPIONs	Superparamagnetic iron oxide nanoparticles
TAM	Tumor-associated macrophages
TB	Tuberculosis

1 Introduction

The C-type lectin superfamily comprising of transmembrane and soluble proteins like selectins, collectins, and asialoglycoprotein receptor has garnered attention since eons [1]. The family of mannose receptors is an integral part of the C-type lectin family. Multiple lectin domains in a single polypeptide structure make this family an unconventional member of the lectin superfamily [2]. The mannose family receptors are involved in antigen capture, recognition of mannosylated structures of pathogenic cell walls and may be overexpressed in certain diseased states. Targeting the mannose receptor provides an attractive strategy to combat number of infections and certain cancers [3, 4]. A complete understanding of the receptors, ligands, and binding interactions is quintessential for successful targeting applications. This chapter focuses on the mannose receptor family and its physiology in normal state and in pathologies. Drug delivery approaches to harness targeting effectively in the therapy of infectious diseases and cancer are also discussed.

2 Mannose Receptor Family

The family of mannose receptors comprises of four endocytic glycoprotein receptors, namely mannose receptor, M-type receptor for phospholipases A_2 (PLA_2R), DEC-205/CD205/gp200-MR6, and Endo180/uPARAP [5–8]. Mannose receptor, the first member of the family, was identified in the late 1970s. Multiple C-type lectin domains (CTLDs) in a single polypeptide backbone constitute a distinct feature of this receptor family. The members of mannose receptor family share mutual structural features, namely cysteine-rich domain, fibronectin type II domain, and CTLDs which vary from eight to ten. However, C-type lectin activity is not exhibited by all members. The C-type lectin activity for interacting with mannosylated

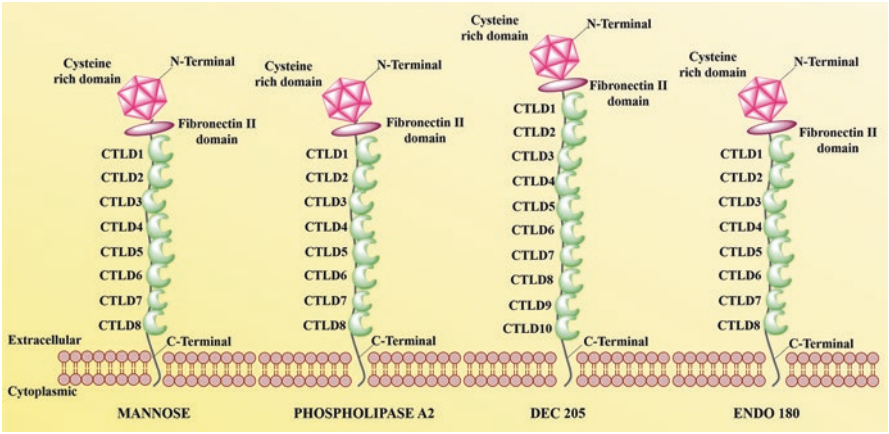

Fig. 15.1 The mannose receptor family

moieties is displayed only by mannose receptor and Endo180. CTLD5 of PLA_2R is involved in protein–protein interactions, a nonlectin activity. The cysteine-rich domain is involved in the recognition of sulfated carbohydrates whereas the fibronectin type II domain internalizes collagen. A functional cysteine-rich domain for binding to sulfated carbohydrates like galactose is present only in the mannose receptor. The receptors of mannose family terminate into short cytoplasmic domains. The receptors are rapidly internalized inside the cell and deliver the extracellular content to the intracellular compartments. Delivery to intracellular locations occurs via interactions between the motifs of terminal cytoplasmic domains and the endocytic machinery. The members of mannose family and their recognition domains are depicted in Fig. 15.1.

2.1 Receptor Recognition Domains

2.1.1 Cysteine-Rich Domain

Although present in all family members, the cysteine-rich domain lacks homology among the mannose receptor family. A 25–30% sequence identity is observed among the family members. Among the four receptors, only the mannose receptor has a functional N-terminal cysteine-rich domain which can exhibit binding to sulfated molecules. The receptor can bind to glycoproteins containing sulfated N-acetylglucosamine and sulfated galactose residues in hormones like lutropin and thyrotropin via this domain [9]. Binding to chondroitin sulfate A, chondroitin sulfate B, sulfated Lewis antigens, CD45, and sulfated transmembrane protein sialoadhesin is also reported [10, 11]. The binding is Ca^{2+} independent and occurs through a neutral binding site. The exact mechanism of binding is beyond the purview of this chapter and is well explained in the literature [2, 12].

2.1.2 Fibronectin Type II Domain

Fibronectin type II domain is the most conserved extracellular domain of mannose receptor family. This domain occurs in different proteins like matrix metalloproteinases (MMP) 2 and 9 [13]. This domain mainly binds to denatured collagen. The collagen binding may be a result of interaction between aromatic structures of the hydrophobic pocket exposed by the solvent with the nonpolar collagen residues leading to disruption of triple helix. The conserved amino acid (Arg^{34} and Asp^{36}) residues can play a role in stabilizing this interaction [2]. Another hypothesis suggests the fibronectin type II domain can bring about N-terminal extension to bring the N-terminal in the vicinity of the C-terminal leading to stabilized interaction with collagen [14]. The binding of fibronectin type II domain of mannose receptor to collagen has been studied. An extended conformation at physiological pH and a compact conformation at acidic pH was reported. At physiological pH, a calcium-dependent binding was observed whereas acidic pH calcium did not affect the collagen binding [15]. This behavior could play a critical role in the intracellular trafficking of cargo delivered through mannose receptor endocytosis.

Mannose receptor demonstrates the ability to bind to collagens I, II, III, and IV while exhibiting a weak binding to collagen V [16]. Fibronectin type II domain of M-type PLA_2 expressing cells binds to collagens I and IV, while Endo180 fibronectin type II domain preferentially binds to collagen V over collagens I and IV. No information is available regarding the ability of DEC-205 to recognize collagen, although this is a likely possibility.

2.1.3 C-Type Lectin Domains

CTLDs contain 120 amino acids. Noncovalent and covalent interactions between two antiparallel β sheets and two α helices lead to the formation of a hydrophobic fold. The carbohydrate interactions in functional CTLDs occur in the hydrophobic fold that imparts stability by hydrophobic core formation. Two disulfide bonds are also formed between cysteine residues. This hydrophobic fold of functional CTLDs permits interactions with sugars by facilitating contact with residues integral for coordination with Ca^{2+} and sugar moieties [2].

In the case of mannose receptor, the binding of terminal carbohydrate residues like mannose, fucose, and N-acetylglucosamine occurs in the presence of Ca^{2+}. A higher affinity is demonstrated by mannose receptor CTLDs toward mannose and fucose whereas the binding affinity to N-acetylglucosamine and glucose is lower. Only the mannose receptor CTLD4 is involved in sugar binding. Similar to mannose receptor, CTLD2 of Endo180 shows binding dependent on Ca^{2+} to glycoconjugates, while CTLD5 of PLA_2R is involved in binding to the nonglycosylated PLA_2 ligand via Ca^{2+}-independent pathways. Further, instead of lectin interactions, CTLD5 mediates protein–protein interactions. DEC-205 is devoid of C-type lectin activity.

2.2 Ligand Binding

In most multidomain receptors, domains which mediate ligand interaction are often stationed at a distance from the membrane. Surprisingly, among the mannose family receptors, CTLD4 and CTLD5 which exhibit a crucial role in binding are found in the central region of the mannose receptor and the PLA_2 receptor, respectively. An extensive study of mannose receptor revealed an extracellular domain with a rigid and extended conformation and close interactions between neighboring CTLDs (CTLDs 1 and 2, CTLDs 4 and 5, CTLDs 7 and 8) with exposed flexible linker regions on either side of CTLDs 3 and 6 [2, 17]. CTLD5 of mannose receptor demonstrates weak binding to sugars in addition to CTLD4, the principal sugar-binding domain. The association of these two CTLDs results in the formation of a protease-resistant core. Such domain disposition enables binding to multiple sugar moieties, enhanced binding of CTLDs, and/or modulates the rigidity of CTLDs.

Closeness of the N- and C-terminal of fibronectin type II domain brings it near to the other domains, as suggested by the sequence analysis. A close association of the cysteine-rich domain, fibronectin type II domain, and C-type lectin domains is seen by protease studies. Such an arrangement stabilizes the interaction with collagen and projects the cysteine-rich domain away from the membrane. This projection is desirable for interactions of cellular sulfated glycoproteins and the domain.

Further, the ligand–receptor binding in mannose receptor is highly pH dependent. Mannose receptor shows poor binding of ligands at pH 5 and optimal binding at pH 7. Such pH dependency is prominent in ligands dissociating in the acidic endosomal compartments. The pH-dependent binding enables separation of the ligand and receptor and recycling of the free receptors to the cell surface. Additionally, the Ca^{2+} dependency in binding may aid in the endosomal dissociation [18].

2.3 Intracellular Internalization

The rapid internalization of mannose receptor family members mainly occurs via clathrin-mediated endocytosis. Internalization by phagocytosis is another pathway mediated by mannose receptor expressed on the macrophages. Under steady state, the cell surface receptors constitute 10–30% whereas remaining 70–90% receptors are intracellular.

2.3.1 Clathrin-Mediated Endocytosis

During endocytic uptake, ligands packed in clathrin-coated vesicles are internalized from the plasma membrane and are delivered in the endosomal system. Smaller particles (<0.2 μm) are taken up by this pathway. The mannose family receptors recycle about 10 times an hour.

Two endocytic motifs, namely tyrosine residue-based motif and dihydrophobic motif, are present in the cytoplasmic domain. Although directed to the same intracellular compartment, the mannose receptor and Endo180 mediate the transport via different motifs. Mannose receptor and PLA_2R recruit tyrosine-based motif whereas Endo180 utilizes the dihydrophobic motif [19]. Internalization occurs from the clathrin-coated pits into the early endosomes. This is followed by transportation to late endosomes and fusion with lysosomes followed by release of cargo into the cytoplasm. A different destination of DEC-205 within the cells is reported. Whereas mannose receptor is located in the early endosomes, localization of DEC-205 is seen in the late endosomes [20].

2.3.2 Phagocytosis

The uptake of particles of >0.2 μm occurs via phagocytosis. Fc receptors and complement receptors, the opsonic receptors, initiate phagocytosis signaling resulting in extension of membrane around the particle via regulation of actin cytoskeleton [21]. A phagosome is formed which then fuses with endosomes/lysosomes leading to exposure of the cargo to hydrolytic enzymes. The direct role of mannose receptor in phagocytosis is questionable. Phagocytic pathway may proceed upon binding to a mannosylated residue which may in turn activate a classical phagocytosis receptor [2]. As PLA_2R and DEC-205 are mainly involved in uptake of macromolecules and are not expressed on phagocytic macrophages, their involvement in phagocytic machinery is unlikely. Although Endo180 is expressed on macrophages, an involvement in phagocytosis analogous to the mannose receptor is not observed in vitro [19].

3 Receptor Location and Expression

Mannose receptor, a 175-kDa type I membrane glycoprotein receptor, was originally isolated in liver and alveolar macrophages [22]. The receptor is predominantly found in most tissue macrophages and dendritic cells (DCs). It is also located in endothelial cells of liver and splenic sinusoids [23]. The receptor is also expressed on the microvascular endothelial cells of the dermis [24], cells of Kaposi's sarcoma [25], human keratinocytes [26], and retinal pigment epithelium [27]. Although initially termed as the macrophage mannose receptor, it is now designated as the mannose receptor, as the occurrence is not exclusively limited to macrophages. The involvement of mannose receptor in phagocytosis of mannosylated structures and pinocytosis of soluble molecules is reported. It also acts as pattern recognition receptor by recognizing the mannosylated ligands of microbes [28–30]. Other functions of this receptor constitute improved presentation of antigens, modulation of cellular trafficking, and maintaining homeostasis by scavenging nonessential mannoglycoproteins and circulating pituitary hormones like lutropin and thyrotropin. PLA_2R is expressed on muscle cell membranes and internalizes PLA_2, the lipolytic

Table 15.1 Mannose receptor family

	Mannose receptor	PLA_2R	DEC-205	Endo180
Occurrence	Macrophages, DCs, few lymphatic or endothelial cells	Muscle cell membranes	DCs, epithelia, B cells, bone marrow stroma, and endothelial cells	Fibroblastic cells, stromal cells, macrophages, and a subset of endothelial cells
Functions	Antigen presentation, phagocytosis of mannosylated structures, homeostasis regulation, modulation of cellular trafficking	Phospholipid digestion, cell proliferation, cell migration, and hormone release	Antigen uptake, presentation of cargo to T cells	Remodeling of cellular membranes
Domain				
Cysteine-rich	Active Enables binding to sulfated carbohydrates like galactose	Inactive	Inactive	Inactive
Fibronectin type II	Binds to collagens I, II, III, and IV and weakly to collagen V	Binds to collagens I and IV	Unknown	Binds to collagen V over collagens I and IV
CTLDs	8 C-type lectin activity	8 Non-lectin activity	10 No C-type lectin activity	8 C-type lectin activity

enzymes required for digestion of phospholipids [5]. DEC-205 which is expressed by dendritic cells has shown involvement in uptake of antigens and delivery of cargo to T cells whereas Endo180 is an endocytic receptor involved in remodeling of cellular membranes.

A comprehensive overview of the four mannose receptor family members is provided in Table 15.1.

4 Pathophysiological Features

The expression of mannose receptor is regulated by macrophage differentiation pattern. Consequently, differentiated macrophages reveal abundant receptor expression whereas circulating monocytes do not express mannose receptor [31]. The physiological status also affects the expression pattern. Anti-inflammatory molecules (corticosteroids, IL-10) [32, 33], Vitamin D3 [34], prostaglandin E [35], and Th2 cytokines (IL-4, IL-13) upregulate the mannose receptor expression by promoting synthesis whereas interferon ɣ (IFN ɣ) [32], lipopolysaccharide (LPS) [36], and immune complexes [37] downregulate the expression by restricting the synthesis.

Binding of pathogenic mannosylated ligands to mannose receptor may induce interleukin (IL)-10 and curb IL-12, thereby inhibiting pathways that could enable protective immune responses [30]. Mannose receptor recognizes the mannosylated

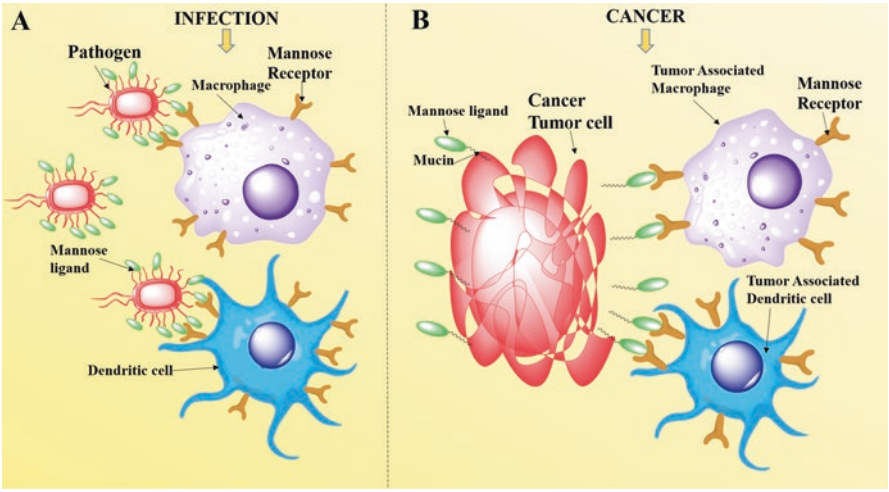

Fig. 15.2 Recognition of (**a**) mannosylated pathogenic cell walls by the mannose receptor present on macrophages and dendritic cells in infections and (**b**) mannose ligands of tumoral mucins by the mannose receptor present on tumor-associated macrophages (TAMs) and dendritic cells in cancers

cell walls of bacteria, fungi, viruses, or parasites, enabling their internalization in the cells (Fig. 15.2a). Pathogens entering the cellular environment using the mannose receptor portal do not evoke an immune reaction.

Although mainly associated with infections, mannose receptor also shows a peculiar expression pattern in cancers. The tumor site shows the presence of mannose receptor expressing macrophages accompanied by ligands for mannose receptor like tumoral mucins [38, 39]. Tumoral mucin MUC1, a ligand of mannose receptor positive cancer cells, comprises of mannose and galactose residues. The tumor cells express abnormal quantities or irregular forms of mucins compared to the healthy cells [40]. The tumoral mucins can invade the immune responses occurring in the tumor microenvironment by binding to mannose receptor on the DCs and tumor-associated macrophages (TAMs) (Fig. 15.2b) and lead to upregulation of IL-10 and suppression of IL-12, thus suppressing Th1-polarized responses, similar to that in infections.

5 Ligands

Mannose receptor binds to various endogenous ligands and acts as a homeostasis regulator by clearing the unwanted molecules from circulation [30, 41]. As discussed earlier, the cysteine region of mannose receptor binds to sulfated moieties whereas the CTLDs bind to glycoproteins rich in mannose oligosaccharides. The fibronectin type II domain shows collagen-specific binding. Classification of ligands

Table 15.2 Ligands for mannose receptor based on domain structure

Domain	Ligands	References
Cysteine-rich domain	Anterior pituitary hormone lutropin	[42]
	CD45	[11]
	Chondroitin sulfate A and chondroitin sulfate B	[10]
	Lewis antigen^{A}, Lewis antigen^{X}	[10]
	Sialoadhesin	[11]
	Sulfated D-galactose	[2]
	Sulfated N-acetyl-D-galactosamine	[43]
	Sulfated N-acetyl-D-glucosamine	[2]
Fibronectin type II domain	Collagen	[16]
CTLDs	Fucose	[2]
	Mannose	[2]
	N-acetyl-D-glucosamine	[2]

based on binding domains is presented in Table 15.2. Utilization of mannose, the most popular ligand, and other ligands like sulfated residues of N-acetyl-D-galactosamine and mannans, etc., for targeted intracellular delivery of therapeutics/antigens is discussed in Sect. 6.

The mannose receptor also binds to exogenous ligands from several microbes and enables their entry into the cell. Microbes may target the mannose receptor to provoke an anti-inflammatory/immune-suppressive response and cause a resistant infection. Mannose receptor lacks the ability to distinguish between pathogenic and nonpathogenic strains, thus internalizing both, unlike the Toll-like receptors [28]. Pathogens, such as *Mycobacterium tuberculosis* [44], *Leishmania donovani* [45], *Trypanosoma cruzi* [46], *Trichinella spiralis* [47], *Streptococcus pneumoniae* [48], HIV virus [49], and influenza virus [50], enter the intracellular environment aided by the carbohydrate ligands on their cell membranes. In the case of *Mycobacterium tuberculosis,* lipoarabinomannan (LAM), a glycolipid present in the mycobacterial cell wall, contains terminal mannose residues that can interact with the mannose receptors. The internalization of LAM-anchored polystyrene beads by mannose receptor mediated phagocytosis is reported. However, mannose receptors bind to virulent H_{37}Rv and Erdman strains but do not bind to the avirulent H_{37}Ra strain of *Mycobacterium tuberculosis* [44]. The biological responses attributed to LAM may be a result of interaction with mannose receptors or other receptors that recognize LAM-like CD14 receptors. In addition to bacterial and viral sugar residues, mannose receptor also recognizes several fungal ligands including glycoprotein A of *Pneumocystis carinii* [51] and mannan from *Candida albicans* [52].

The ligands for other mannose receptor family members are relatively few. Pancreatic $sPLA_2$IB is reported as the only ligand of PLA_2R; however, an interspecies variation in binding affinity was observed [53, 54]. Other potential ligands include $sPLA_2$-V, $sPLA_2$-IID, and $sPLA_2$-X [55, 56]. Specific ligands for DEC-205 are not reported. DEC-205 cysteine-rich domain does not interact with sulfated sugars

and also lacks the C-type lectin activity. Like the mannose receptor, Endo180 is also multifunctional and exhibits binding to a distinct set of ligands. Ca^{2+} - dependent binding of Endo180 to mannose, fucose, and N-acetylglucosamine is evident. Endo180 does not bind to galactose and sulfated sugars [57]. It exhibits binding to components of the extracellular protease systems (MMP13 and uPAR). An interaction of Endo180 with collagen via the fibronectin type II domain is reported.

6 Receptor Targeting Strategies

Among the family of mannose receptors, the most extensively exploited and studied receptor for targeted drug delivery is the mannose receptor. Hence, this section focuses mainly on mannose receptor enabled intracellular delivery. The endocytosis and phagocytosis of microbes in the macrophages occur by interaction of glycoproteins in the cell walls with the mannose receptor. Mannose conjugates and mannosylated nanocarriers target these intracellular pathogens by promoting uptake of the drug-loaded mannosylated constructs in the infected cells via mannose receptor. Nanocarrier-based strategies to target mannose receptor overexpression in tumor microenvironment are reported. Moreover, interaction of mannose ligands with mannose receptor expressed on macrophages/dendritic cells can lead to induction of immune signaling pathways, an approach of great importance in vaccine delivery [58]. Targeting desired cells via ligand-mediated approach can minimize systemic distribution and off-site toxicity. Decoration of surface of nanocarriers with ligands with high affinity to the mannose receptor is the strategy employed for targeting.

6.1 Mannose Conjugates

Mannose conjugates can be prepared by reaction between mannose derivatives and proteins or therapeutic agents like antigens. The stability of the conjugate within the body and release of the therapeutic agent at the site of action depend on the bond between the mannose derivative and the system. Most of the strategies studied involve use of endogenous mannose receptor ligands. Recent studies report utilization of synthetic ligands specific to mannose receptor expressed on macrophages or DCs. Polysaccharide from Bletilla striata (a glucomannan) having high affinity to mannose receptor expressing cells was conjugated to alendronate, a bisphosphonate. The conjugate revealed inhibition of angiogenesis and elimination of TAMs leading to suppressed tumor progression [59]. In some instances, mannose ligand has been employed to act as antigen and potentiate the immunogenicity of the conjugated protein/peptide molecule. A mannosylated vaccine formed by conjugation of glucuronoxylomannan, a polysaccharide found in *Cryptococcus neoformans* capsule and tetanus toxoid, elicited high levels of capsular antibodies [60]. Another study

reports coupling of heptasaccharide oligosaccharide, the immunodeterminant of glucuronoxylomannan with human serum albumin which resulted in induction of immunogenic responses [61].

6.2 *Mannosylated Nanocarriers*

Mannosylated nanocarriers can be prepared by coating/conjugation of mannose ligands to the surface of nanocarriers like liposomes or nanoparticles. Such mannosylated systems enable targeting to the mannose receptor and permit the delivery of cargo (antigen/drug) at the site of interest. Furthermore, particulate nature of the nanocarriers accompanied by mannose association significantly improves uptake by the endocytic and phagocytic pathways.

6.2.1 Mannosylated Liposomes

Liposomes have been extensively studied in the literature as carriers for drugs, proteins, and even fluorescent markers. Mannosylation of liposomes enables their application in treatment of intracellular infections like tuberculosis (TB) and leishmaniasis or as vaccine candidates in cancers or infections. Mannosylated liposomes can be prepared by using mannose lipid conjugates, covalently attaching mannose derivatives to liposomes, or by adsorbing the ligand on liposomal surface [3]. The click reaction was used for the preparation of cytotoxic mannose click conjugates by reaction with aminobenzoic acid derivatives [62]. In one study, mannose-cholesterol conjugates were synthesized by click reaction for liposomal drug delivery systems [63]. Wang et al. studied the effect of varying the chain length of the polyethylene glycol (PEG) linker and the optimal mannose-cholesterol conjugates were used for liposomal messenger RNA (mRNA) delivery [64].

Drug-related issues like toxicity and resistance in leishmaniasis have been tackled by treatment with mannosylated liposomes. Amphotericin B liposomes coated with palmitoyl mannose (Man-Lip) or 4-sulfated N-acetyl galactosamine (sulf-Lip) revealed rapid intracellular uptake of Sulf-Lip and higher liver and spleen Amphotericin B levels indicating specificity of 4-sulfated N-acetyl galactosamine to resident macrophages [65]. In a similar study, mannosylated Amphotericin B loaded liposomes demonstrated maximum reduction in parasite load (78.8 ± 3.9%) compared to Amphotericin B solution (42.5 ± 1.8%) and cationic Amphotericin B loaded liposomes (61.2 ± 3.2%) in *Leishmania donovani*-infected golden hamster model [66]. Among three sugar grafted liposomes (mannose, glucose, and galactose), mannose liposomes loaded with pentamidine isethionate revealed superior reduction in parasite loads [67]. Sinha et al. reported reduced spleen parasitic burden with mannosylated andrographolide loaded liposomes when tested in experimental hamster leishmaniasis model [68]. A succinct summary of other liposome-based mannose receptor targeting for intracellular infections and cancer is provided in Table 15.3.

Table 15.3 Mannosylated liposomes for targeted delivery

Disease	Active	Ligand/nanosystem	Study outcome	Reference
Infections				
Aspergillosis	Hamycin	Mannose	Reduced fungal load in infected organs	[69]
HIV	Stavudine	O-palmitoylmannose-coated liposomes	High uptake in reticuloendothelial system (RES) organs such as lung, liver, and spleen and high systemic clearance	[70]
Leishmaniasis	Benzyl derivative of *Penicillium nigricans* derived compound MT81 (Bz_2MT81)	p-aminophenyl-α-D-mannoside coupled liposomes	Lowering of splenic parasitic burden and reduction in effective dose to kill the splenic parasite	[71]
	CpG-containing oligodeoxynucleotide	p-aminophenyl-α-D-mannopyranoside coupled to liposomes	Inhibition of amastigote multiplication in macrophages and elimination of splenic parasite load in visceral leishmaniasis mouse model	[72]
	Doxorubicin and IFN ɣ	p-aminophenyl-α-D-mannopyranoside coupled to liposomes	Complete elimination of splenic parasites	[73]
Parasitic infection	Ciprofloxacin	Mannose	High uptake and antibacterial efficacy in vitro	[74]
Pneumococcal meningitis	Dichloromethylene diphosphonate	Mannose	Reduced migration of white blood cells into cerebrospinal fluid in experimental infection models	[75]
Cancer				
Drug-resistant colon cancer	Dihydroartemisinin and doxorubicin	Mannose was conjugated to the DSPE-PEG2000-NH2	Improved tumor inhibition and tackling of drug resistance	[76]

Mannosylated liposomes have been reported for vaccination against infections and cancers. Garcon et al. covalently coupled mannosylated albumin to the surface of dehydration–rehydration vesicles (DRVs). These mannosylated DRVs containing tetanus toxoid revealed selective binding to mouse peritoneal macrophages compared to nonmannosylated DRVs with an augmented immunoadjuvant activity in Balb/c mice [77]. In another study, liposomes coated with neoglycolipids (mannopentose or mannotriose) revealed high serum levels of soluble leishmanial antigen (SLA)-specific IgG2a antibody titer and low level of IgG1 antibody titers in comparison to uncoated liposomes along with a delayed footpad swelling progression [78]. In contrast to uncoated liposomes, subcutaneous immunization with oligomannose residue coated liposomes encapsulating peptides representing epitopes of gp120 (a HIV1 envelope glycoprotein) induced MHC class I-restricted CD8+ cytotoxic T-lymphocyte response [79].

A protective immune response against cancer can be elicited by association of immunostimulants or immunomodulators with mannosylated antigen loaded liposomes. Mannosylated liposome–plasmid DNA complex (Man-lipoplex), prepared as a potential DNA vaccine for melanoma, revealed greater pUb-M gene transfection into antigen-presenting cells than uncoated liposomes and demonstrated prolonged survival coupled with melanoma inhibition in mice model [80]. A similar study performed by White et al. revealed mannosylated liposomes of lipid core peptide with Quil A adjuvant acted as prophylactic anticancer vaccines and protected mice against tumors [81].

6.2.2 Mannosylated Nanoparticles (NPs)

Mannosylated NPs are widely investigated in infections and cancers akin to the mannosylated liposomes. Mannosylation of polyanhydride NPs can be performed by techniques such as desolvation or direct coating. Iron oxide NPs may be coated by precipitation of iron salts by incubation with D-mannose solution or by oxidation of NPs followed by addition of D-mannose solution. Chemical modification of polymers with mannosylated ligands is also reported [3].

The mannose receptor is profusely overexpressed on the macrophages, DCs, and foamy cells which constitute the TB granuloma. This permits utilization of mannosylated NPs for targeted intracellular delivery in TB. A multilayer mannosylated drug delivery system for intracellular delivery of first-line antibiotics Rifampicin and Isoniazid has been developed [82]. Isoniazid loaded mannosylated gelatin NPs reduced drug hepatotoxicity and significantly decreased bacterial burden in lungs and spleen of infected Balb/c mice [83]. In an analogous study, licorice loaded mannosylated gelatin NPs revealed enhanced uptake in RAW 264.7 cells and reduced spleen and lung bacterial loads in *Mycobacterium tuberculosis* H_{37}Rv-infected mice compared to untreated animals [84]. Other strategies employing mannosylated NPs for drug delivery in infections and cancer are enlisted in Table 15.4. A summary of mannosylated NPs employed as vaccine carriers is presented in Table 15.5.

Table 15.4 Mannosylated NPs in infections and cancer

Disease	Active	Ligand/nanosystem	Study outcome	Reference
Infections				
Helicobacter pylori infection	Acetohydroxamic acid	Fucose-specific (UEA-I) and mannose-specific (Conconavalin A) lectins conjugated to gliadin NPs	NPs inhibited binding of *Helicobacter pylori* to human stomach cells	[85]
HIV	Didanosine	Mannose conjugated to gelatin NPs	High macrophage uptake and RES localization	[86]
	Didanosine	Mannan conjugated to gelatin NPs	Fivefold higher intracellular uptake and greater localization in spleen, lymph nodes, and brain	[87]
	Stavudine	Mannose conjugated to gelatin NPs	High macrophage uptake and RES localization	[88]
Leishmaniasis	Amphotericin B	Gelatin conjugated to mannose via direct coupling or via PEG spacer	5.4-fold reduction in IC_{50} compared to free Amphotericin B solution in intracellular amastigote model	[89]
	Amphotericin B	4-sulfated Sulfated N-acetyl galactosamine-coated NPs	High RES localization and reduced splenic parasite burden	[90]
	Curcumin	D-mannose conjugated to chitosan NPs	Low in vitro cytotoxicity and reduced parasite loads in spleen	[91]
	Doxorubicin	4-sulfated Sulfated N-acetyl galactosamine-coated NPs	Enhanced intracellular uptake and high RES localization	[92]
	Rifampicin	D-mannose Mannose conjugated to chitosan NPs	High ex vivo uptake and high RES localization	[93]
TB	Isoniazid	Mannose-conjugated solid lipid NPs	High uptake and reduced cytotoxicity in vitro	[94]
	Rifabutin	Mannose-coated solid lipid NPs	Sixfold higher uptake ex vivo and low immunogenicity compared to uncoated formulation. Prolonged circulation and targeted delivery to alveolar tissues	[95]

(continued)

Table 15.4 (continued)

Disease	Active	Ligand/nanosystem	Study outcome	Reference
Cancers				
Lung adenocarcinoma	Gemcitabine	D-Mannose-conjugated solid lipid NPs	Improved uptake and high cytotoxicity in A549 cells with preferential lung accumulation	[96]
Lung cancer	DNA	Mannan-modified solid lipid NPs	Higher gene expressions compared to unmodified DNA loaded NPs suggesting applicability for nonviral vector gene delivery	[97]
Tumor	Doxorubicin	4-Aminophenyl α-D-mannopyranoside modified albumin NPs	Improved localization in brain glioma cells and reduction in tumor size	[98]
	Doxorubicin	Self-assembly of heptamannosylated β-cyclodextrin into NPs	Slow tumor growth in murine xenograft tumor models	[99]

Table 15.5 Mannosylated NPs-based vaccines

Antigen	Ligand/nanosystem	Study outcome	Reference
Ag85A	Mannose moiety of guar gum NPs	Strong systemic and mucosal immune response following oral administration, protecting the antigen from harsh gastric environment.	[100]
Nil	Mannan-coated PLGA NPs	Improved dendritic cells' maturation and stimulatory function.	[101]
Nil	Dimannose and lactose decorated polyanhydride NPs	Surface functionalized pathogen like NPs revealed enhanced expression of MHC II, CD86 and CD40, CIRE, and mannose receptor on the cell surface.	[102]
Ovalbumin	Mannan decorated polylactide-co-glycolide (PLGA) NPs	Enhanced CD4+ and CD8+ T-cell responses in comparison to nonconjugated NPs	[103]
Ovalbumin	Mannosamine-coated polyanhydride NPs	Single subcutaneous or oral dose demonstrated higher and balanced IgG1 and IgG2a antibody responses compared to uncoated NPs. Oral immunization elicited higher levels of intestinal secretory IgA levels than subcutaneous immunization.	[104]
Toll-like receptor 7 agonist, imiquimod (R837)	PLGA NPs coated with mannosylated cancer cell membrane	Enhanced uptake by DCs and delayed tumor development	[105]

6.3 Miscellaneous Applications

6.3.1 Mannosylated SPIONs as MRI Contrast Agents

Superparamagnetic iron oxide nanoparticles (SPIONs) are reported as promising magnetic resonance imaging (MRI) contrast agents. Surface modification of SPIONs becomes essential owing to their drawbacks such as aggregation in water, chemical instability, and nonspecific targeting. To overcome these issues, SPIONs were coated with mannan to enable recognition by mannose receptor present on macrophages [106]. Mannan-coated SPIONs of 28.4 ± 7.2 nm size demonstrated low cytotoxicity in RAW 264.7 cells. Surface coating with mannan prevented aggregation of SPIONs enabling selective delivery into antigen-presenting cells, suggesting applicability as macrophage-targeted MRI contrasting agent.

6.3.2 Two-Photon Photodynamic Therapy

Photodynamic therapy combined with two-photon excitation offers a noninvasive alternative approach to chemo- and radiotherapy to reduce small solid tumors. The photosensitizer was covalently attached to mesoporous silica NPs followed by mannose coating. A single injection aided targeting to tumor site by mannose receptor and two-photon photodynamic therapy led to reduction in tumor size [107].

6.3.3 Biomarker for Pulmonary TB Patients

The serum and pleural concentrations of mannose receptor (CD206) were monitored in pulmonary TB subjects. An increased CD206 level was observed in sera but not in pleura with a sensitivity of 77.3% and specificity of 86.5%. This presents a new application of mannose receptor as a biomarker of pulmonary TB [108].

6.3.4 Lysosomal Targeting in Storage Diseases

Therapeutic enzymes were conjugated to yeast cell wall, a natural source of mannose-6-phosphate (M6P) glycan for utilization in glycogen storage diseases like Pompe disease. Recombinant acid α-glucosidase, a therapeutic in Pompe disease when conjugated to M6P glycans from cell wall of glyco-engineered yeast, revealed efficient intracellular localization and improved accumulated glycogen digestion [109].

7 Clinical Studies

Although targeting to the mannose receptor has been widely investigated, very few mannosylated candidates have entered the clinical trials. Herein, we discuss a promising mannose-based targeted strategy DermaVir, a topical preparation for the treatment of HIV/AIDS and FDA-approved radiopharmaceutical ^{99m}Tc-tilmanocept for sentinel lymph node mapping.

DermaVir (Genetic Immunity) is currently enrolled for Phase III clinical trials, set to begin in 2019. It represents topical immunotherapy for the treatment of HIV/AIDS comprising of plasmid DNA-based mannosylated particles [110, 111]. The mannosylated particles are formed by complexation of DNA with a cationic polymer (PEIm) while glucose present in the formulation acts as an aggregation inhibitor and stabilizer. The formulation when applied on the epidermal layer penetrates the skin surface and triggers immune responses.

Staging of cancer progression relies on the mapping of lymph node metastases. Mapping of the sentinel lymph node requires an agent that quickly clears the injection site, rapidly enters, and retains in the sentinel lymph node, without entering the distal lymph nodes. FDA-approved ^{99m}Tc-tilmanocept by Navidea Biopharmaceuticals is a mannose-targeted radiopharmaceutical for the detection of sentinel lymph node and lymphatic mapping in tumors [112, 113]. The radiopharmaceutical has crossed several clinical trials [114–116] and is now employed for stage determination of cancers under the trade name "Lymphoseek."

Chemically, it is ^{99m}Tc-diethylenetriaminepentaacetic acid–mannosyl–dextran comprising of diethylenetriaminepentaacetic acid and mannose units covalently linked to a 10-kDa dextran backbone. The binding occurs via the mannose residues to the receptors expressed by the myeloid cells. Following injection, ^{99m}Tc-tilmanocept enters the lymphatic channels and localizes in the sentinel lymph node by binding to the mannose receptor, thus enabling the mapping of lymph.

8 Advantages and Limitations Related to Specific Targeting through Through Mannose Receptor

As mannose receptor is predominantly located on macrophages, the abode of intracellular infections, specific targeting via mannosylated conjugates and mannose decorated nanocarriers can improve the efficacy of therapeutics and vaccine candidates. Additionally, mannose receptor mediated targeting could provide a practical approach for development of intracellular vaccines. Nevertheless, mannose-targeted vaccines would need to be coupled with other agents to enhance immune response. Interestingly, vaccines based on mannose receptor endocytosis may not only enhance immune responses against cancer and infectious diseases but could also find application in autoimmune disease therapeutics [58]. Surface-modified

mannosylated constructs could provide the additional advantage of both phagocytic and endocytic uptake to augment intracellular drug concentrations. However, the ubiquitous presence of macrophages all over the body could provide challenges in targeting specific macrophages through mannosylated carriers.

9 Conclusion

Targeting the mannose receptors represents an exciting therapeutic strategy for infections and cancers overexpressing the receptors. Extrapolating this strategy to vaccines provides exciting opportunities in the design of targeted therapeutics.

References

1. Zelensky AN, Gready JE. The C-type lectin-like domain superfamily. FEBS J. 2005;272(24):6179–217.
2. East L, Isacke CM. The mannose receptor family. Biochimica et Biophysica Acta (BBA)-General Subjects. 2002;1572(2–3):364–86.
3. Irache JM, Salman HH, Gamazo C, Espuelas S. Mannose-targeted systems for the delivery of therapeutics. Expert Opin Drug Deliv. 2008;5(6):703–24.
4. Azad AK, Rajaram MVS, Schlesinger S. Exploitation of the macrophage mannose receptor (CD206) in infectious disease diagnostics and therapeutics. J Cytol Mol Biol. 2007;137(12):2696–700.
5. Ancian P, Lambeau G, Mattéi MG, Lzadunski M. The human 180-kDa receptor for secretory phospholipases A2. J Biol Chem. 1995;270(15):8963–70.
6. Behrendt N, Jensen ON, Engelholm LH, Mørtz E, Mann M, Danø K. A urokinase receptor-associated protein with specific collagen binding properties. J Biol Chem. 2002;275(3):1993–2002.
7. Sheikh H, Yarwood H, Ashworth A, Isacke CM. Endo180, an endocytic recycling glycoprotein related to the macrophage mannose receptor is expressed on fibroblasts, endothelial cells and macrophages and functions as a lectin receptor. J Cell Sci. 2000;113:1021–32.
8. Jiang W, Swiggard WJ, Heufler C, Peng M, Mirza A, Nussenzweig M, Steinman RM. The receptor DEC-205 expressed by dendritic cells and thymic epithelial cells is involved in antigen processing. Nature. 1995;375:151–5.
9. Simpson DZ, Hitchen PG, Elmhirst EL, Taylor ME. Multiple interactions between pituitary hormones and the mannose receptor. Biochem J. 1999;343(2):403–11.
10. Leteux BC, Chai W, Loveless RW, Yuen C, Uhlin-hansen L, Combarnous Y, et al. The cysteine-rich domain of the macrophage mannose receptor is a multispecific lectin that recognizes chondroitin sulfates A and B and sulfated oligosaccharides of blood group Lewis a and Lewis x types in addition to the sulfated n-glycans of lutropin. J Exp Med. 2000;191(7):1117–26.
11. Crocker PR, Da Silva R, Holmes N, Colominas C, Rudd P, Dwek R, et al. Cell-specific glycoforms of sialoadhesin and CD45 are counter-receptors for the cysteine-rich domain of the mannose receptor. J Biol Chem. 1999;274(49):35211–8.
12. Liu BY, Chirino AJ, Misulovin Z, Leteux C, Feizi T, Nussenzweig MC, et al. Crystal structure of the cysteine-rich domain of mannose receptor complexed with a sulfated carbohydrate ligand. J Exp Med. 2000;191(7):1105–15.
13. Morgunova E, Tuuttila A, Bergmann U, Isupov M, Lindqvist Y, Schneider G, Tryggvason K. Structure of human pro-matrix metalloproteinase-2: activation mechanism revealed. Science. 1999;284:1667–70.

14. Pickford AR, Potts JR, Bright JR, Phan I, Campbell ID. Solution structure of a type 2 module from fibronectin : implications for the structure and function of the gelatin-binding domain. Structure. 1997;5(3):359–70.
15. Hu Z, Shi X, Yu B, Li N, Huang Y, He Y. Structural insights into the pH-dependent conformational change and collagen recognition of the human mannose receptor. Structure. 2018;26:60–71.
16. Napper CE, Drickamer K, Taylor ME. Collagen binding by the mannose receptor mediated through the fibronectin type II domain. Biochem J. 2006;395:579–86.
17. Napper CE, Dyson MH, Taylor ME. An extended conformation of the macrophage mannose receptor. J Biol Chem. 2001;276(18):14759–66.
18. Stahl PD. The macrophage mannose receptor: current status. Am J Respir Cell Mol Biol. 1990;2(4):317–8.
19. Howard MJ, Isacke CM. The C-type lectin receptor Endo180 displays internalization and recycling properties distinct from other members of the mannose receptor family. J Biol Chem. 2002;277(35):32320–31.
20. Mahnke K, Guo M, Lee S, Sepulveda H, Swain SL, Nussenzweig M, et al. The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. J Cell Biol. 2000;151(3):673–83.
21. Aderem A, Underhill DM. Mechanisms of phagocytosis in macrophages. Annu Rev Immunol. 1999;17(1):593–623.
22. Wileman TE, Lennartz MR, Stahl PD. Identification of the macrophage mannose receptor as a 175-kDa membrane protein. Proc Natl Acad Sci. 1986;83(8):2501–5.
23. Linehan SA, Weber R, McKercher S, Ripley RM, Gordon S, Martin P. Enhanced expression of the mannose receptor by endothelial cells of the liver and spleen microvascular beds in the macrophage-deficient PU.1 null mouse. Histochem Cell Biol. 2005;123(4–5):365–76.
24. Groger M, Holnthoner W, Maurer D, Lechleitner S, Wolff K, Mayr BB, et al. Dermal microvascular endothelial cells express the 180-kDa macrophage mannose receptor in situ and in vitro. J Immunol. 2000;165(10):5428–34.
25. Mulay SR, Desai J, Kumar SV, Eberhard JN, Thomasova D, Romoli S, et al. Kaposi's sarcoma cells express the macrophage-associated antigen mannose receptor and develop in peripheral blood cultures of Kaposi's sarcoma patients. Am J Pathol. 1997;150(3):929–38.
26. Szolnoky G, Bata-Csörgö Z, Kenderessy AS, Kiss M, Pivarcsi A, Novák Z, et al. A mannose-binding receptor is expressed on human keratinocytes and mediates killing of Candida albicans. J Investig Dermatol. 2001;117(2):205–13.
27. Wilt ST, Greaton CJ, Lutz DA, McLaughin B. Mannose receptor is expressed in normal and dystrophic retinal pigment epithelium. Exp Eye Res. 1999;69(4):405–11.
28. Astarie-Dequeker C, N'Diaye EN, Le Cabec V, Rittig MG, Prandi J, Maridonneau-Parini I. The mannose receptor mediates uptake of pathogenic and nonpathogenic mycobacteria and bypasses bactericidal responses in human macrophages. Infect Immun. 1999;67(2):469–77.
29. Stahl PD, Ezekowitz RAB. The mannose receptor is a pattern recognition receptor involved in host defense. Curr Opin Immunol. 1998;10(1):50–5.
30. Ailavena P, Chieppa MMP, Piemonti L. From pattern recognition receptor to regulator of homeostasis: the double-faced macrophage mannose receptor. Crit Rev Immunol. 2004;24(3):179–92.
31. Stahl PD. The mannose receptor and other macrophage lectins. Curr Opin Immunol. 1992;4(1):49–52.
32. Mokoena T, Gordon S. Modulation of mannosyl, fucosyl receptor activity in vitro by lymphokines, gamma and alpha interferons, and dexamethasone. J Clin Invest. 1985;75(2):624–31.
33. Shepherds VL, Konish G, Stahl P. Dexamethasone increases expression of mannose receptors and decreases extracellular lysosomal enzyme accumulation in macrophages. J Biol Chem. 1985;260(1):160–4.
34. Clohisy DR, Bar-shavitsb Z, Chappel JC, Teitelbaum LI. 1,25-dihydroxyvitamin D3 modulates bone marrow macrophage precursor proliferation and differentiation. J Biol Chem. 1987;262(33):15922–9.

35. Schreiber S, Blumt JS, Chappel JC, Stenson WF, Stahlt PD, Teitelbaum SL, et al. Prostaglandin E specifically upregulates the expression of the mannose-receptor on mouse. Cell Regul. 1990;1(5):403–13.
36. Shepherd VL, Abdolrasulnia RA, Garrett M, Cowan HB. Down-regulation of mannose receptor activity in macrophages after treatment with lipopolysaccharide and phorbol esters. J Immunol. 1990;145(5):1530–6.
37. Schreiber S, Stenson WF, MacDermott RP, Chappel JC, Teitelbaum SL, Perkins SL. Aggregated bovine IgG inhibits mannose receptor expression of murine bone marrow-derived macrophages via activation. J Immunol. 1991;147(4):1377–82.
38. Taylor-Papadimitriou J, Burchell J, Miles DW, Dalziel M. MUC1 and cancer. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 1999;1455(2–3):301–13.
39. Nath S, Mukherjee P. MUC1: a multifaceted oncoprotein with a key role in cancer progression. Trends Mol Medicine. 2017;20(6):332–42.
40. Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. Am J Clin Pathol. 2004;122(1):61–9.
41. Taylor PR, Gordon S, Martinez-Pomares L. The mannose receptor: linking homeostasis and immunity through sugar recognition. Trends Immunol. 2005;26(2):104–10.
42. Roseman DS, Baenziger JU. Molecular basis of lutropin recognition by the mannose/GalNAc-4-SO4 receptor. Proc Natl Acad Sci. 2000;97(18):9949–54.
43. Fiete DJ, Beranek MC, Baenziger JU. A cysteine-rich domain of the "mannose" receptor mediates GalNAc-4-SO4 binding. Proc Natl Acad Sci. 1998;95(5):2089–93.
44. Schlesinger LS, Hull SR, Kaufman TM. Binding of the terminal mannosyl units of lipoarabinomannan from a virulent strain of Mycobacterium tuberculosis to human macrophages. J Immunol. 1994;152(8):4070–9.
45. Wilson ME, Pearson RD. Evidence that Leishmania donovani utilizes a mannose receptor on human mononuclear phagocytes to establish intracellular parasitism. J Immunol. 1986;136(12):4681–8.
46. Kahn S, Wleklinski M, Aruffo A, Farr A, Coder D, Kahn M. Trypanosoma cruzi amastigote adhesion to macrophages is facilitated by the mannose receptor. J Exp Med. 2004;182(5):1243–58.
47. Gruden-Movsesijan A, Milosavljevic LS. The involvement of the macrophage mannose receptor in the innate immune response to infection with parasite Trichinella spiralis. Vet Immunol Immunopathol. 2006;109(1–2):57–67.
48. Macedo-Ramos H, Campos FSO, Carvalho LA, Ramos IB, Teixeira LM, De Souza W, et al. Olfactory ensheathing cells as putative host cells for Streptococcus pneumoniae: evidence of bacterial invasion via mannose receptor-mediated endocytosis. Neurosci Res. 2011;69(4):308–13.
49. Nguyen DG, Hildreth JE. Involvement of macrophage mannose receptor in the binding and transmission of HIV by macrophage. Eur J Immunol. 2003;33(2):483–93.
50. Reading PC, Miller JL, Anders EM. Involvement of the mannose receptor in infection of macrophages by influenza virus. J Virol. 2000;74(11):5190–7.
51. O'Riordan DM, Standing JE, Limper AH. Pneumocystis carinii glycoprotein A binds macrophage mannose receptors. Infect Immun. 1995;63(3):779–84.
52. van de Veerdonk FL, Marijnissen RJ, Kullberg BJ, Koenen HJ, Cheng SC, Joosten I, et al. The macrophage mannose receptor induces IL-17 in response to Candida albicans. Cell Host Microbe. 2009;5(4):329–40.
53. Lambeau G, Lazdunski M. Receptors for a growing family of secreted phospholipases A2. Trends Pharmacol Sci. 1999;20:162–70.
54. Cupillard L, Mulherkar R, Gomez N, Kadam S, Valentin E, Lazdunski E, Lambeau G. Both group IB and group IIA secreted phospholipases A2 are natural ligands of the mouse 180-kDa M-type receptor. J Biol Chem. 1999;274(11):7043–51
55. Hanasaki K, Ono T, Saiga A, Morioka Y, Ikeda M, Kawamoto K, Higashino KI, Nakano K, Yamada K, Ishizaki J, Arita H. Purified group X secretory phospholipase A2 induced prominent release of arachidonic acid from human myeloid leukemia cells. J Biol Chem. 1999;274(48):34203–11.

56. Hanasaki K, Arita H. Biological and pathological functions of phospholipase A2 receptor. Arch Biochem Biophys. 1999;372(2):215–23.
57. East L, Rushton S, Taylor ME, Isacke CM. Characterization of sugar binding by the mannose receptor family member, Endo180. J Biol Chem. 2002;277(52):50469–75.
58. Keler T, Ramakrishna V, Fanger MW. Mannose receptor-targeted vaccines. Expert Opin Biol Ther. 2004;4(12):1953–62.
59. Zhan X, Jia L, Niu Y, Qi H, Chen X, Zhang Q, et al. Targeted depletion of tumour-associated macrophages by an alendronate glucomannan conjugate for cancer immunotherapy. Biomaterials. 2014;35(38):10046–57.
60. Devi SJ. Preclinical efficacy of a glucuronoxylomannan-tetanus toxoid conjugate vaccine of Cryptococcus neoformans in a murine model. Vaccine. 1996;14(9):841–4.
61. Oscarson S, Alpe M, Svahnberg P, Nakouzi A, Casadevall A. Synthesis and immunological studies of glycoconjugates of Cryptococcus neoformans capsular glucuronoxylomannan oligosaccharide structures. Vaccine. 2005;23(30):3961–72.
62. Hradilová L, Poláková M, Dvořáková B, Hajdúch M, Petruš L. Synthesis and cytotoxicity of some D-mannose click conjugates with aminobenzoic acid derivatives. Carbohydr Res. 2012;361:1–6.
63. Nguyen H, Katavic P, Bashah NA, Ferro V. Synthesis of mannose-cholesterol conjugates for targeted liposomal drug delivery. ChemistrySelect. 2016;1(1):31–4.
64. Wang F, Xiao W, Elbahnasawy MA, Bao X, Zheng Q, Gong L, Zhou Y, Yang S, Fang A, Farag MM, Wu J. Optimization of the linker length of mannose-cholesterol conjugates for enhanced mRNA delivery to dendritic cells by liposomes. Front Pharmacol. 2018;9:1–14.
65. Singodia D, Verma A, Verma RK, Mishra PR. Investigations into an alternate approach to target mannose receptors on macrophages using 4-sulfated N-acetyl galactosamine more efficiently in comparison with mannose-decorated liposomes: an application in drug delivery. Nanomedicine. 2012;8(4):468–77.
66. Rathore A, Jain A, Gulbake A, Shilpi S, Khare P, Jain A, et al. Mannosylated liposomes bearing Amphotericin B for effective management of visceral Leishmaniasis. J Liposome Res. 2011;21(4):333–40.
67. Banerjee G, Nandi G, Mahato SB, Pakrashi A, Basu MK. Drug delivery system: targeting of pentamidines to specific sites using sugar grafted liposomes. J Antimicrobial Chemother. 1996;38(1):145–50.
68. Sinha J, Mukhopadhyay S, Das N, Basu MK. Targeting of liposomal andrographolide to L. donovani-infected macrophages in vivo. Drug Deliv. 2000;7(4):209–13.
69. Moonis M, Ahmad I, Bachhawat B, Moonis M, Ahmad I, Bachhawat BK. Mannosylated liposomes as carriers for hamycin in the treatment of experimental aspergillosis in Balb/C mice. J Drug Target. 1993;1(2):147–55.
70. Garg M, Asthana A, Agashe HB, Agrawal GP, Jain NK. Stavudine-loaded mannosylated liposomes: in-vitro anti-HIV-I activity, tissue distribution and pharmacokinetics. J Pharm Pharmacol. 2006;58(5):605–16.
71. Mitra M, Mandal AK, Chatterjee TK, Das N. Targeting of mannosylated liposome incorporated Benzyl derivative of Penicillium nigricans derived compound MT81 to reticuloendothelial systems for the treatment of visceral leishmaniasis. J Drug Target. 2005;13(5):285–93.
72. Datta N, Mukherjee S, Das L, Das PK. Targeting of immunostimulatory DNA cures experimental visceral leishmaniasis through nitric oxide up-regulation and T cell activation. Eur J Immunol. 2003;33(6):1508–18.
73. Kole L, Das L, Das PK. Synergistic effect of interferon-gamma and mannosylated liposome-incorporated doxorubicin in the therapy of experimental visceral leishmaniasis. J Infect Dis. 1999;180(3):811–20.
74. Chono S, Tanino T, Seki T, Morimoto K. Efficient drug targeting to rat alveolar macrophages by pulmonary administration of ciprofloxacin incorporated into mannosylated liposomes for treatment of respiratory intracellular parasitic infections. J Control Release. 2008;127(1):50–8.
75. Zysk G, Brück W, Huitinga I, Fischer FR, Flachsbarth F, Van Rooijen N, et al. Elimination of blood-derived macrophages inhibits the release of interleukin-1 and the entry of leukocytes

into the cerebrospinal fluid in experimental pneumococcal meningitis. J Neuroimmunol. 1997;73(1–2):77–80.
76. Kang XJ, Wang HY, Peng HG, Chen BF, Zhang WY, Wu AH, Xu Q, Huang YZ. Codelivery of dihydroartemisinin and doxorubicin in mannosylated liposomes for drug-resistant colon cancer therapy. Acta Pharmacol Sin. 2017;38(6):885–96.
77. Garcon N, Gregoriadis G, Taylor M, Summerfield J. Mannose-mediated targeted immunoadjuvant action of liposomes. Immunology. 1988;64:743–5.
78. Shimizu Y, Takagi H, Nakayama T, Yamakami K, Tadakuma T, Yokoyama N, Kojima N. Intraperitoneal immunization with oligomannose-coated liposome-entrapped soluble leishmanial antigen induces antigen-specific T-helper type immune response in BALB/c mice through uptake by peritoneal macrophages. Parasite Immunol. 2007;29(5):229–39.
79. Fukasawa M, Shimizu Y, Shikata K, Nakata M, Sakakibara R, Yamamoto N, Hatanaka M, Mizouchi T. Liposome oligomannose-coated with neoglycolipid, a new candidate for a safe adjuvant for induction of CD8+ cytotoxic T lymphocytes. FEBS Lett. 1998;441(3):353–6.
80. Lu Y, Kawakami S, Yamashita F, Hashida M. Development of an antigen-presenting cell-targeted DNA vaccine against melanoma by mannosylated liposomes. Biomaterials. 2007;28(21):3255–62.
81. White K, Rades T, Kearns P, Toth I, Hook S. Immunogenicity of liposomes containing lipid core peptides and the adjuvant Quil A. Pharm Res. 2006;23(7):1473–81.
82. Praphakar RA, Shakila H, Dusthackeer VN, Munusamy MA, Kumar S, Rajan M. A mannose-conjugated multi-layered polymeric nanocarrier system for controlled and targeted release on alveolar macrophages. Polym Chem. 2018;9(5):656–67.
83. Saraogi GK, Sharma B, Joshi B, Gupta P, Gupta UD, Jain NK, et al. Mannosylated gelatin nanoparticles bearing isoniazid for effective management of tuberculosis. J Drug Target. 2011;19(3):219–27.
84. Viswanathan V, Mehta H, Pharande R, Bannalikar A, Gupta P, Gupta U, Mukne A. Mannosylated gelatin nanoparticles of licorice for use in tuberculosis: formulation, in vitro evaluation, in vitro cell uptake, in vivo pharmacokinetics and in vivo anti-tubercular efficacy. J Drug Delivery Sci Technol. 2018;45:255–63.
85. Umamaheshwari RB, Jain NK. Receptor mediated targeting of lectin conjugated gliadin nanoparticles in the treatment of Helicobacter pylori. J Drug Target. 2003;11(7):415–24.
86. Jain SK, Gupta Y, Jain A, Saxena AR, Khare P, Jain A. Mannosylated gelatin nanoparticles bearing an anti-HIV drug didanosine for site-specific delivery. Nanomedicine. 2008;4(1):41–8.
87. Kaur A, Jain S, Tiwary AK. Mannan-coated gelatin nanoparticles for sustained and targeted delivery of didanosine: in vitro and in vivo evaluation. Acta Pharma. 2008;58(1):61–74.
88. Mahajan S, Prashant CK, Koul V, Choudhary V, Dinda AK. Receptor specific macrophage targeting by mannose-conjugated gelatin nanoparticles- an in vitro and in vivo study. Curr Nanosci. 2010;6(4):413–21.
89. Nahar M, Dubey V, Mishra D, Mishra PK, Dube A, Jain NK. In vitro evaluation of surface functionalized gelatin nanoparticles for macrophage targeting in the therapy of visceral leishmaniasis. J Drug Target. 2010;18(2):93–105.
90. Tripathi P, Dwivedi P, Khatik R, Jaiswal AK, Dube A, Shukla P, Mishra PR. Development of 4-sulfated N-acetyl galactosamine anchored chitosan nanoparticles: a dual strategy for effective management of Leishmaniasis. Colloids Surf B: Biointerfaces. 2015;136:150–9.
91. Chaubey P, Mishra B, Mudavath SL, Patel RR, Chaurasia S, Sundar S, Suvarna V, Monteiro M. Mannose-conjugated curcumin-chitosan nanoparticles: efficacy and toxicity assessments against Leishmania donovani. Int J Biol Macromol. 2018;111:109–20.
92. Dwivedi P, Kansal S, Sharma M, Shukla R, Verma A, Shukla P, Tripathi P, Gupta P, Saini D, Khandelwal K, Verma R. Exploiting 4-sulphate N-acetyl galactosamine decorated gelatin nanoparticles for effective targeting to professional phagocytes in vitro and in vivo. J Drug Target. 2012;20(10):883–96.
93. Chaubey P, Mishra B. Mannose-conjugated chitosan nanoparticles loaded with rifampicin for the treatment of visceral leishmaniasis. Carbohydr Polym. 2014;101(1):1101–8.

94. Costa A, Sarmento B, Seabra V. Mannose-functionalized solid lipid nanoparticles are effective in targeting alveolar macrophages. Eur J Pharm Sci. 2018;114:103–13.
95. Nimje N, Agarwal A, Saraogi GK, Lariya N, Rai G, Agrawal H, et al. Mannosylated nanoparticulate carriers of rifabutin for alveolar targeting. J Drug Target. 2009;17(10):777–87.
96. Soni N, Soni N, Pandey H, Maheshwari R, Kesharwani P, Tekade RK. Augmented delivery of gemcitabine in lung cancer cells exploring mannose anchored solid lipid nanoparticles. J Colloid Interface Sci. 2016;481:107–16.
97. Yu W, Liu C, Liu Y, Zhang N, Xu W. Mannan-modified solid lipid nanoparticles for targeted gene delivery to alveolar macrophages. Pharm Res. 2010;27(8):1584–96.
98. Byeon HJ, Thao LQ, Lee S, Min SY, Lee ES, Shin BS, et al. Doxorubicin-loaded nanoparticles consisted of cationic- and mannose-modified-albumins for dual-targeting in brain tumors. J Control Release. 2016;225:301–13.
99. Ye Z, Zhang Q, Wang S, Bharate P, Varela-Aramburu S, Lu M, et al. Tumour-targeted drug delivery with mannose-functionalized nanoparticles self-assembled from amphiphilic β-cyclodextrins. Chem Eur J. 2016;22(43):15216–21.
100. Kaur M, Malik B, Garg T, Rath G, Goyal AK. Development and characterization of guar gum nanoparticles for oral immunization against tuberculosis. Drug Delivery. 2015;22(3):328–34.
101. Haddadi A, Hamdy S, Ghotbi Z, Samuel J, Lavasanifar A. Immunoadjuvant activity of the nanoparticles' surface modified with mannan. Nanotechnology. 2014 Aug 13;25(35):355101.
102. Carrillo-Conde B, Song EH, Chavez-Santoscoy A, Phanse Y, Ramer-Tait AE, Pohl NLB, et al. Mannose-functionalized "pathogen-like" polyanhydride nanoparticles target C-type lectin receptors on dendritic cells. Mol Pharm. 2011;8(5):1877–86.
103. Hamdy S, Haddadi A, Shayeganpour A, Samuel J, Lavasanifar A. Activation of antigen-specific T cell-responses by mannan-decorated PLGA nanoparticles. Pharm Res. 2011;28(9):2288–301.
104. Salman HH, Irache JM, Gamazo C. Immunoadjuvant capacity of flagellin and mannosamine-coated poly(anhydride) nanoparticles in oral vaccination. Vaccine. 2009;27(35):4784–90.
105. Yang R, Xu J, Xu L, Sun X, Chen Q, Zhao Y, et al. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. ACS Nano. 2018;12(6):5121–9.
106. Yoo MK, Kim IY, Kim EM, Jeong HJ, Lee CM, Jeong YY, et al. Superparamagnetic iron oxide nanoparticles coated with galactose-carrying polymer for hepatocyte targeting. Biomed Res Int. 2008;8:5196–202.
107. Gary-Bobo M, Mir Y, Rouxel C, Brevet D, Basile I, Maynadier M, et al. Mannose-functionalized mesoporous silica nanoparticles for efficient two-photon photodynamic therapy of solid tumors. Angew Chem Int Ed. 2011;50(48):11425–9.
108. Suzuki Y, Shirai M, Asada K, Yasui H, Karayama M, Hozumi H, et al. Macrophage mannose receptor, CD206, predict prognosis in patients with pulmonary tuberculosis. Sci Rep. 2018;8(1):1–9.
109. Kang JY, Shin KK, Kim HH, Min JK, Ji ES, Kim JY, Kwon O, Oh DB. Lysosomal targeting enhancement by conjugation of glycopeptides containing mannose-6-phosphate glycans derived from glyco-engineered yeast. Sci Rep. 2018;8(1):1–14.
110. Lisziewicz J, Trocio J, Whitman L, Varga G, Xu J, Bakare N, Erbacher P, Fox C, Woodward R, Markham P, Arya S. DermaVir: a novel topical vaccine for HIV/AIDS. J Investig Dermatol. 2005;124(1):160–9.
111. Lori F. DermaVir: a plasmid DNA-based nanomedicine therapeutic vaccine for the treatment of HIV/AIDS. Expert Rev Vaccines. 2011;10(10):1371–84.
112. Vera DR, Wallace AM, Hoh CK, Mattrey RF. A synthetic macromolecule for sentinel node detection: (99m)Tc-DTPA-mannosyl-dextran. J Nucl Med. 2001;42(6):951–9.
113. Surasi DS, O'Malley J, Bhambhvani P. 99mTc-Tilmanocept: a novel molecular agent for lymphatic mapping and sentinel lymph node localization. J Nucl Med Technol. 2015;43(2):87–92.
114. Leong SP, Kim J, Ross M, Faries M, Scoggins CR, Metz WL, Cope FO, Orahood RC. A phase 2 study of 99mTc-tilmanocept in the detection of sentinel lymph nodes in melanoma and breast cancer. Ann Surg Oncol. 2011;18(4):961–9.

115. Wallace AM, Han LK, Povoski SP, Deck K, Schneebaum S, Hall NC, Hoh CK, Limmer KK, Krontiras H, Frazier TG, Cox C. Comparative evaluation of [99m Tc]tilmanocept for sentinel lymph node mapping in breast cancer patients: results of two phase 3 trials. Ann Surg Oncol. 2013;20(8):2590–9.
116. Sondak VK, King DW, Zager JS, Schneebaum S, Kim J, Leong SP, Faries MB, Averbook BJ, Martinez SR, Puleo CA, Messina JL. Combined analysis of phase III trials evaluating [99mTc] tilmanocept and vital blue dye for identification of sentinel lymph nodes in clinically node-negative cutaneous melanoma. Ann Surg Oncol. 2013;20(2):680–8.