Targeting the C-type Lectins-Mediated Host-Pathogen Interactions with Dextran

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ABSTRACT - Dextran, the α-1,6-linked glucose polymer widely used in biology and medicine, promises new applications. Linear dextran applied as a blood plasma substitute demonstrates a high rate of biocompatibility. Dextran is present in foods, drugs, and vaccines and in most cases is applied as a biologically inert substance. In this review we analyze dextran's cellular uptake principles, receptor specificity and, therefore, its ability to interfere with pathogen–lectin interactions: a promising basis for new antimicrobial strategies. Dextran-binding receptors in humans include the DC-SIGN (dendritic cell–specific intercellular adhesion molecule 3-grabbing nonintegrin) family receptors: DC-SIGN (CD209) and L-SIGN (the liver and lymphatic endothelium homologue of DC-SIGN), the mannose receptor (CD206), and langerin. These receptors take part in the uptake of pathogens by dendritic cells and macrophages and may also participate in the modulation of immune responses, mostly shown to be beneficial for pathogens *per se* rather than host(s). It is logical to predict that owing to receptor-specific interactions, dextran or its derivatives can interfere with these immune responses and improve infection outcome. Recent data support this hypothesis. We consider dextran a promising molecule for the development of lectin–glycan interaction-blocking molecules (such as DC-SIGN inhibitors) that could be applied in the treatment of diseases including tuberculosis, influenza, hepatitis B and C, human immunodeficiency virus infection and AIDS, etc. Dextran derivatives indeed change the pathology of infections dependent on DC-SIGN and mannose receptors. Complete knowledge of specific dextran–lectin interactions may also be important for development of future dextran applications in biological research and medicine.

INTRODUCTION

Dextran is a glucose polymer with a prevalence of α-1,6-linked units and is usually linear (Figure 1). Dextran is a component of vaccines, cosmetics, foods, and drugs. In addition, it is one of the most widely used blood plasma substitutes. Dextran-based molecules (e.g., fluorescent markers) play an important role in biomedical research. Dextran's properties provide various advantages including adjustable molecular size and viscosity; chemical stability and simplicity of modification; ability to target certain cell types and cellular compartments; relative biological inertness. We are the first to highlight that dextran shares specific receptors with many pathogens. According to recent studies, this commonality lends dextran the capability to have antimicrobial properties.

Detailed publications on dextran have been written for medical professionals (1), biochemists, pharmacists, and biotechnology specialists (2-4). However complex work is lacking on dextran's fate at the cellular level. Topics that must be addressed include types of cells that take up dextran, its receptors and interference with infectious processes. Dextran's biological inertness is implied in many of its applications: it is often used as a nonfunctional biocompatible core molecule conjugated with the functional groups (fluorescent dyes, drugs, charged or hydrophobic groups). However, dextran-binding receptors that belong to the family of C-type lectins, namely mannose receptors (MRs), dendritic cell (DCs)-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing nonintegrin (DC-SIGN), L-SIGN (the liver and lymphatic endothelium homologue of DC-SIGN),

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and langerin, are involved in the immune recognition and uptake of numerous pathogens such as human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (5).

In HIV infection, DC-SIGN binding to gp120 is considered to be a critical phase in the entry of HIV-1. DC-SIGN antibodies (6), short hairpin RNAs suppressing DC-SIGN gene expression (7) and carbohydrate-binding agents (8) have been touted to inhibit DC-SIGN binding of the HIV-1 envelope complex to DCs and to prevent viral transmission. We have successfully reported inhibition of DC-SIGN and gp120 interaction by screening known inhibitors and carbohydrate-binding agents by devising a novel target-specific high-throughput screening assay (9). We also found that DC-SIGN plays a critical role in infection through human T-lymphotropic virus-1 (HTLV-1) envelope glycoprotein binding and DCs to T-cell transmission (10, 11). Overall, in these studies blocking of DC-SIGN was shown to prevent the binding and transmission of human retroviruses, indicating the suitability of the dextran-binding receptor, DC-SIGN, as an antiretroviral drug target.

Hepatitis B and C viruses, influenza, and various fungi and protozoa are also associated with uptake via C-type lectins, specifically the dextran-binding receptors. These receptors take part in uptake of the pathogens by DCs and macrophages and also participate in the modulation of intracellular signaling and immune responses. In many cases such modulation is beneficial for pathogens (5). Pathogens' interactions with MR and DC-SIGN suppress T-helper type 1 (Th1) immune responses which are crucial for defense against intracellular pathogens (12). Dextran unlike the surface molecules of pathogens is an inert ligand of mannose receptor and DC-SIGN that does not induce production of cytokines suppressing Th1 response (13). Therefore we suggest that dextran owing to receptor-specific interactions might interfere with an unfavorable immune response and give preference to Th1-inducing pathogen-Toll-like receptor signaling. Moreover dextran could prevent binding and uptake of many viruses via its receptors. To indicate all areas that show potential promise for future applications of dextran as a receptor-specific molecule, we point towards its existing medical and research applications (Figure 2). At last, the paradigm of "biologically inert" dextran can be revised, as this molecule affects the infectious process, most likely owing to the lectin-glycan interaction mechanism.

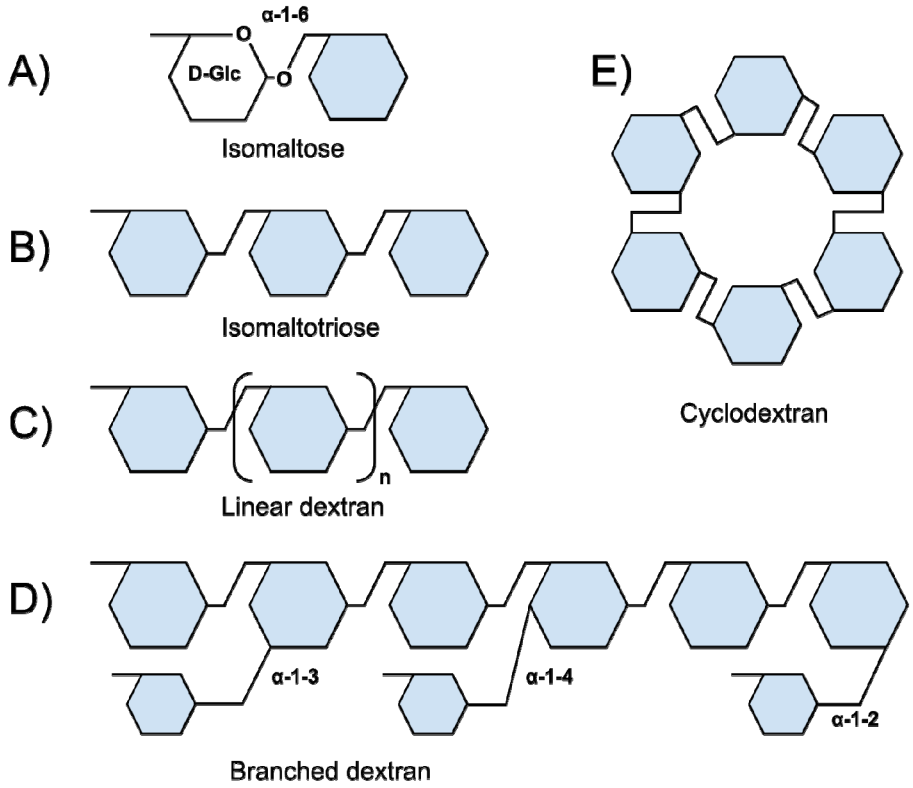

Figure 1. Types of α-1,6 glucosides. A) Isomaltose (two glucose molecules with α-1-6 linkage). B) Isomaltotriose. C) Linear dextrans. D) Branched dextrans (schematically). e) α-Cyclodextran.

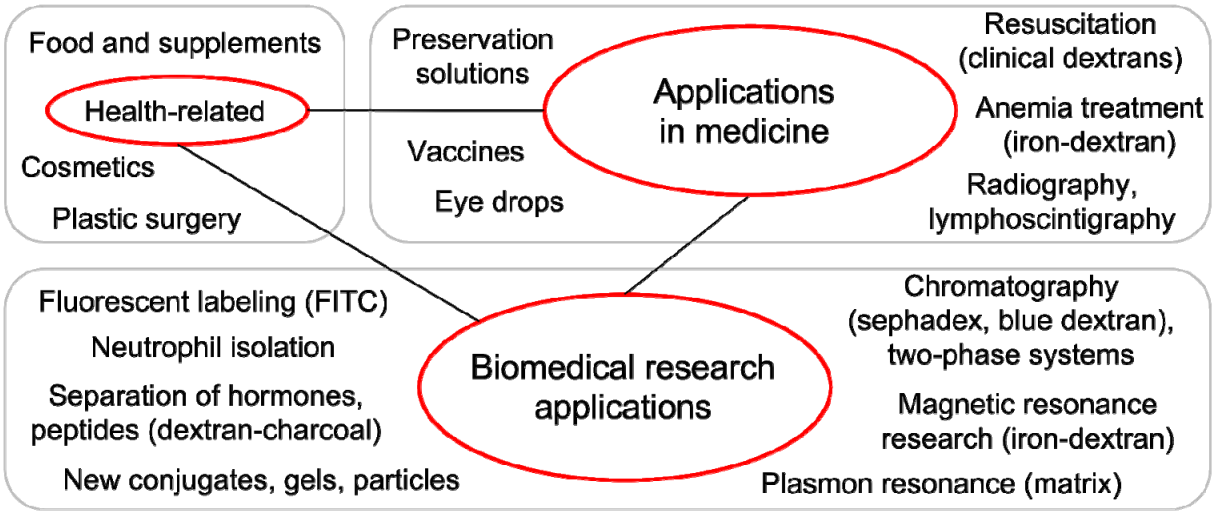

Figure 2. Dextran applications. Many dextran applications, especially medical and biological, can benefit from taking into account the receptor specificity of dextran. FITC = fluorescein isothiocyanate.

DEXTRAN-BINDING RECEPTORS

Mannose receptor: Macrophage mannose receptor (MR, CD206) is a carbohydrate receptor from the superfamily of C-type lectins (14, 15). It is expressed in liver and spleen endothelial cells, in macrophages, and to a lesser extent, in DCs (16). Its main role in mammals is the metabolism of glycoproteins taking place predominantly in the liver (17, 18). MR is also responsible for recognition and phagocytosis of pathogens and allergens, promotion of Th2 immune responses, and antigen presentation (13, 15). Moreover, the uptake of dextran via MR has been proven before (19). A list of all the cell types expressing MR that are able to take up dextran is depicted in Table 1.

DC-SIGN family receptors: DC-SIGN is a receptor expressed by monocyte-derived dendritic cells (MDDCs) *in vitro* and *in vivo* (20), and by dermal/intestinal/genital mucosae dendritic cells *in vivo* (21, 22). It is also expressed on activated B cells (23), wound-healing (IL-4-activated) and alternative (M-CSF-activated) monocyte-derived macrophages, tumor-associated macrophages (24), certain tissue macrophages such as in the alveoli and lung (25). This receptor is responsible for the interactions of DCs with T cells (26), vascular and lymphatic endothelial cells (27), including umbilical vein (28) as well as blood-brain barrier endothelial cells (D. Sagar and P. Jain, unpublished results), and also pathogens (12) and allergens (29) (providing their uptake and/or intracellular signaling). Signaling via DC-SIGN limits Th1 responses influencing Toll-like receptor–dependent pathways through Raf1 kinase (30). DC-SIGN is involved in the reception of pathogens of bacterial, viral, fungal, and protozoan origin, as well as those from multicellular parasites. This group of pathogens recognized by DC-SIGN includes mycobacteria, *Helicobacter pylori*, the worm *Schistosoma mansoni,* HIV-1, Ebola virus, cytomegalovirus, and *Leishmania*. Antigenic interaction with DC-SIGN shifts the T helper type1/T helper type 2 balance, causing a chronic infection (12). DC-SIGN receptor in humans has one homologue, L-SIGN (liver/lymph node-specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin), expressed mainly in the liver (31); there are eight orthologues in mice, including SIGN-R1 to SIGN-R8 (32). Uptake of dextran via DC-SIGN family receptors (DFRs) DC-SIGN, L-SIGN, SIGN-R1, and SIGN-R3 is proven (33-36). Cells that express these receptors are able to take up dextran (Table 1).

Langerin and LSECtin: Langerin is a receptor specific to Langerhans cells of the skin (37) and uptake of dextran via langerin is proven (36). Human and mouse liver and lymph node sinusoidal endothelial C-type lectin receptors (LSECtins) are expressed mainly by liver endothelial sinusoidal cells and lymph endothelium (38). Although these receptors are not proven to bind dextran, it seems probable because of specificity similar to other dextran-binding receptors. Cells expressing these receptors take up dextran (Table 1).

Table 1. Expression of mannose receptor, LSECtin, langerin, and DC-SIGN family receptors correlates with dextran uptake capacity

Organ	Receptor expression	Dextran uptake
Liver	1) MR: Kupffer cells, LSEC (16)	1) Dextran uptake is present in Kupffer cells (39) and in LSEC (40)
	2) L-SIGN, LSECtin: LSEC (31)	2) Dextran uptake is present in LSEC (40); dextran uptake is present in liver DCs (41)
Spleen	1) MR: splenic macrophages, endothelial cells (16)	1) Dextran uptake is present in phagocytes (39) and can be presumed according to dextran uptake along capillaries in endothelial cells (42)
	2) SIGN-R1: spleen macrophages (35) DC-SIGN: spleen DCs (26)	2) SIGN-R1-dependent dextran uptake is present in spleen macrophages (35); dextran uptake is present in spleen phagocytes (39) and in spleen DCs (41)
Lung	1) MR: alveolar macrophages (16) 2) DC-SIGN: alveolar macrophages (25)	1, 2) Dextran uptake is present in alveolar macrophages (43)
Kidney	MR: macrophages, glomerular mesangial cells (16)	Dextran uptake is present in phagocytes (39) and in mesangial cells (44)
Heart muscles	MR: macrophages (16)	Dextran uptake is present in phagocytes (39)
Brain	MR: retinal microglia cells (45)	Dextran uptake is present (45)
Skin	MR: dermal microvascular endothelial cells (46)	Dextran uptake is present (46)
Lymphatic system	1) MR: endothelial cells of the lymph ducts (47)	1) Dextran uptake (or at least binding) seems to be present in lymphatic endothelial cells due to dextran use in visualization of lymph vessels (49-51)
	2) L-SIGN and LSECtin: endothelial cells of the lymph ducts and lymph nodes (31, 48); LSECtin: peripheral blood and thymic DCs (31)	2) Dextran uptake or binding seems to be present in lymphatic endothelial cells due to dextran use in visualization of lymph vessels (49, 51)
APC	1) MR: APCs in skin, muscles, salivary gland, thyroid, pancreas (52) 2) DC-SIGN: human immature MDDCs, mucosal DCs, immature DCs on periphery (skin, tonsils), and mature DCs in lymphoid organs (26); plasmacytoid DC precursors (25); activated B cells (23) 3) Langerin: Langerhans cells	1, 2, 3) Dextran uptake is present in human immature MDDCs and Langerhans cells (53), plasmacytoid DCs (54), activated B cells (55)

APC, antigen-presenting cell; DC-SIGN, dendritic cell–specific intercellular adhesion molecule (ICAM) 3-grabbing nonintegrin; L-SIGN, liver/lymph node-specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin; LSEC, liver sinusoidal endothelial cell; MDDC, monocyte-derived dendritic cell; MR, mannose receptor.

RECEPTOR-DEPENDENT AND INDEPENDENT ENDOCYTOSIS OF DEXTRAN

In the context of possible antimicrobial application of dextran, it is important to note that this molecule can be taken up into the cells. Clinical dextrans (linear molecules with molecular masses 35,000–80,000 that can curculate in the bloodstream from hours to days) are more potent to be taken up into the cells compared to oligodextrans (linear oligomers of α-1,6-linked glucose) (36). The rate of endocytosis is critical for the development of new applications: bigger molecules provide prolonged action and delivery into the cells, while smaller molecules do not provide the receptor clustering and are more potent as the entry inhibitors because they do not induce receptor-dependent endocytosis by themselves.

Dextran is recognized and taken up by macrophages, DCs, LSECs and some other cell types prefferedly via specific receptors (33-36). However dextran can also be taken up via mechanisms of nonspecific fluid-phase endocytosis (FPE). Table 2 specifies the mechanisms of dextran internalization associated with certain cell types and receptors. MR (14) and DC-SIGN (56) participate in the clathrin-mediated endocytosis (CME) mechanism. MRs and DFRs are necessary and sufficient for receptor-mediated dextran uptake in human immature MDDCs (33, 57).

Use of dextran as a marker for different endocytosis processes requires the discrimination between CME, phagocytosis, and FPE. In CME the uptake of dextran can be dependent on receptors including MR, DC-SIGN (human), L-SIGN (human), SIGN-R1 (mouse), SIGN-R3 (mouse), and langerin. CME is available for particles up to 200 nm (72). Uptake of small particles via CME (and other endocytosis mechanisms) is sometimes called *phagocytosis*. This term has specific implications. Phagocytosis indeed uses the machinery of different types of endocytosis at the initial stage. However, owing to the initiation of additional mechanisms, it allows uptake of much bigger particles of 500 to 2000 nm or more in diameter. Phagocytosis of dextran-based or dextran-covered particles can be dependent on the same receptors as CME (MRs, DFRs, langerin). Dextrans dissolved in media can be taken up by FPE mechanisms independent of ligand recognition. In the case of FPE, potential mechanisms include macropinocytosis or cdc42-dependent—so-called CLIC/GEEC—pinocytosis. The main molecules participating in this process are clathrin-independent carriers (CLICs) and glycosylphosphatidylinositol-enriched endocytic compartments (GEECs). Different endocytosis mechanisms may be activated simultaneously.

Fluorescently labeled dextrans became quite popular in endocytosis studies when Schröder et al. first developed fluorescently labeled dextran (fluorescein isothiocyanate, FITC-dextran) in 1976 (73). Ohkuma and Poole published their classical work on lysosomal acidification control using FITC-dextran in 1978 (74). In recent decades the labeled dextrans have been used extensively as lysosomal markers (75). They were used to evaluate FPE (76), endocytic activity in general (77), phagocytosis (78, 79), macropinocytosis (80), and macropinocytosis plus MR-mediated uptake (19). They were also applied as the ligands of MR (81), SIGN-R1 (35), and as the ligand of MR and DC-SIGN simultaneously (57). All the terms *clathrin-mediated endocytosis, phagocytosis*, *fluid-phase endocytosis*, and *macropinocytosis* applied to dextran (or dextran-containing particles) as an endocytotic or lysosomal marker are applicable, but in different cases: dependent on cell types and phenotypes.

When clinical dextran is injected into the bloodstream, one part is taken up by cells, another part is excreted by the kidney and a third part is retained in the bloodstream. Ratio of these parts depends on the molecular weight and the dose (for more specific data see (39, 82, 83)). The main organs of dextran uptake are liver, spleen, lung, and kidney. From the blood, dextran can enter into interstitial fluid, then the lymph, and then back to the bloodstream. Hepatocytes are able to transport small amounts of dextran to the bile (39, 84-87). Kidney filtration of dextran is dependent on the molecular mass/size: molecules smaller than ~50 kDa are excreted quickly, whereas larger ones stay in the blood longer (Figure 3A and B) (85, 88). Cells that take up dextran are able to metabolize it slowly into glucose by acid and neutral α-glucosidases expressed in all cell types (89-92). These glucose molecules participate in glucose metabolism and can yield dextran-derived exhaled carbon dioxide (93, 94).

DEXTRAN DERIVATIVES IN TUBERCULOSIS, CANDIDIASIS, AND INFLUENZA MODELS

Dextran has shown to be inert to DC cytokine reactions while the ligands of pathogens binding to MR and DFRs restrict Th1 response (12, 13).

Table 2. Dextran endocytosis

Endocytosis	Characteristics of dextran uptake
CME, receptor-dependent uptake	1) MR-dependent CME of fluorescent dextran in: ● Human immature MDDCs, simultaneously with macropinocytosis (19) ● Human immature MDDCs, dependent on MR expression (58) ● Human inflammatory dendritic epidermal cells (59) ● Human retinal microglia cells (45) ● Mouse immature spleen and bone marrow DCs, macrophages (fluorescent dextran 3/70/500/2000) (60) ● Mouse liver sinusoidal endothelial cells (61) 2) DFRs-dependent CME of fluorescent dextran in (receptor-positive cells here means transfectants): ● Human embryonic kidney SIGN-R1-positive and SIGN-R3-positive HEK293T cells (36) ● Mouse spleen macrophages *in vivo*, SIGN-R1-dependent uptake (35) ● Mouse leukemic SIGN-R1-positive RAW264.7 transfectants and mouse spleen macrophages, SIGN-R1-dependent uptake (62) ● Mouse spleen marginal zone SIGN-R1 -/- macrophages do not take up fluorescent dextran (63) ● Hamster ovary L-SIGN-positive Cho cells (34) 3) Langerin-dependent CME of fluorescent dextran in langerin-positive HEK293T cells (36)
Macropino-cytosis or FPE	FPE of fluorescent dextran in: ● Human immature DCs, simultaneously with MR-dependent CME (19) ● Human epithelial carcinoma cells (64) ● Mouse synovial fibroblasts (65), embryo fibroblasts NIH3T3 (66) ● Mouse bone marrow–derived macrophages (67) ● Mouse bone marrow–derived immature (not in mature) DCs (68) ● Mouse bone marrow macrophages (macro- and micropinosomes are present) (69) ● Mouse bone marrow macrophages (uptake is accompanied by leaks of fluorescent dextran into cytosol) (70) ● Madin-Darby canine kidney cells (71)
Phagocytosis	Use of this term is misleading for dextran particles <0.5 μm in diameter

CME, clathrin-mediated endocytosis; DFR, DC-SIGN (dendritic cell–specific intercellular adhesion molecule [ICAM]-3-grabbing nonintegrin) family receptors; FPE, fluid-phase endocytosis; L-SIGN, liver/lymph node-specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin; MDDC, monocyte-derived dendritic cell; MR, mannose receptor.

The studies of dextran or dextran-drug conjugates in models of bacterial, fungal, and viral infections that are dependent on dextran-binding receptors (Table 3) are of great interest. In such models, the dextran core is able to interfere with pathogen–macrophage and pathogen-DC interaction. Possible inhibition of pathogen uptake or changes in immune response by dextran should influence infection outcomes and several studies confirm this notion.

Dextran-isoniazid has shown interesting results in a model of tuberculosis-like granulomatosis induced by Bacillus Calmette–Guérin (BCG) injection. The intensity of fibrotic lesions in this model after treatment with dextran conjugate was compared with free isoniazid treatment. Fibrosis of the lung decreased 30%, of the spleen 3.5-fold, and of the liver more than fourfold. Hepatotoxicity decreased 2.2-fold, and the development of necrosis into granulomas decreased 10-fold (159). Decreased lung remodeling may be beneficial for prevention of caviation and subsequent transmission (160) of tuberculosis, and could also help drugs reach the mycobacteria inside granulomas, that is itself an important problem (161).

Dextran influences the phagosomal-lysosomal fusion and the death rate of mycobacteria BCG inside mouse peritoneal macrophages. The control rate of death inside macrophages was 33%, and with dextran (22 μg/ml) it was 39%. Isoniazid treatment (7 μg/ml) yielded a bacterial death rate of 43%, while the conjugate of dextran with isoniazid (25 μg/ml, same isoniazid content) yielded a 53% death rate.

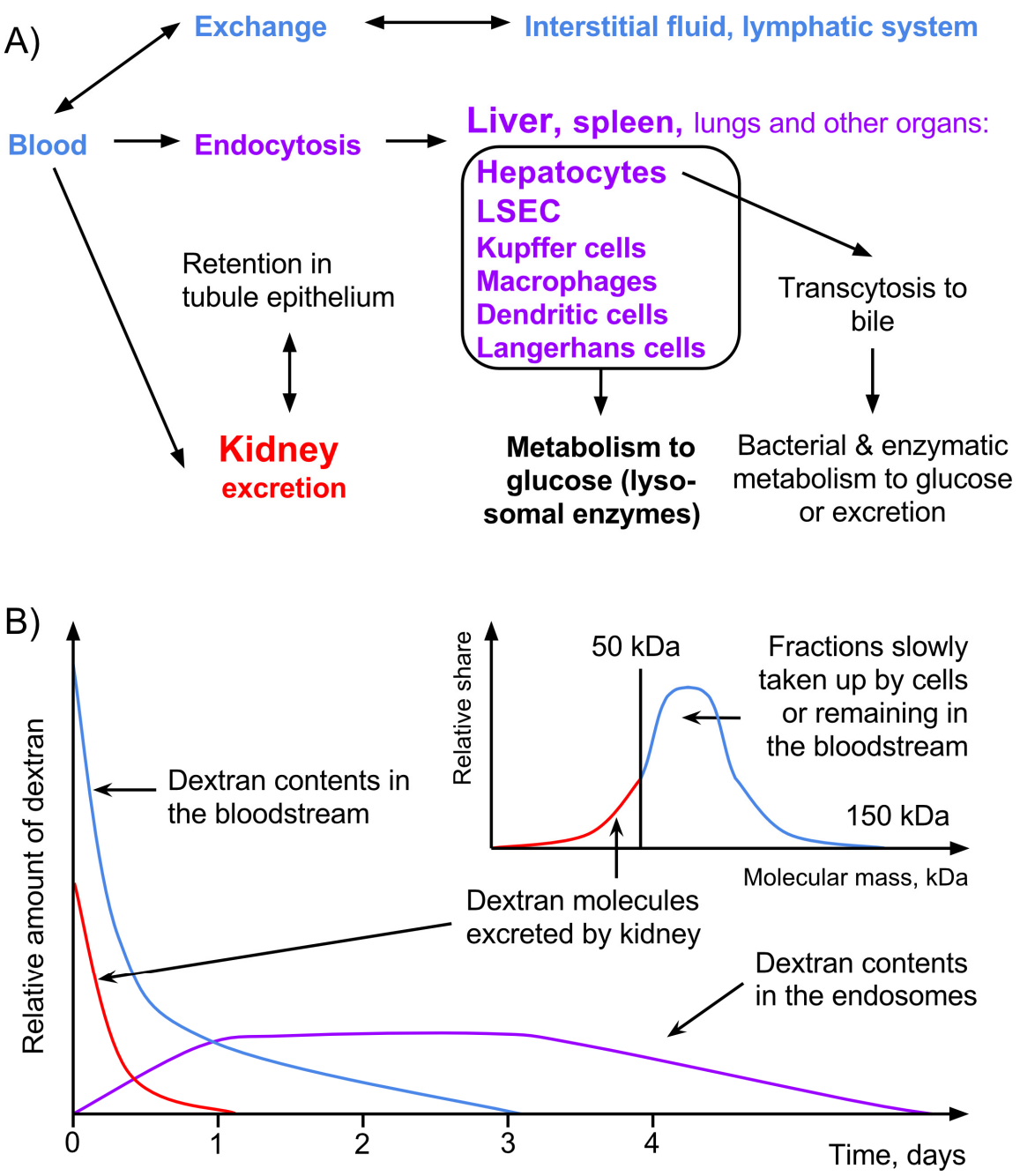

Figure 3. A) Dextran metabolism and excretion pathways. Dextran from the blood circulates in the interstitial fluid and lymph ducts and interacts with most cell types. The main organs of active dextran uptake are the liver, spleen, and lungs. Kidney cells take up dextran via pinocytosis and do not metabolize it, providing only temporarily retention. B) Time dependence of clinical dextran excretion and metabolism. After dextran injection, kidneys excrete the fractions with low molecular mass. Heavier fractions circulate in the body fluids or are taken up into the endosomes. Endosomal compartment volume is limited and some injected dextran may remain in the circulation. In the endosomes, dextrans are metabolized to glucose or excreted by transcytosis. Owing to metabolism, new endosomal volume becomes available and can be filled with dextran molecules from the blood. Thus the dextran endosomal pool depletes when dextran concentration in the blood does not provide its renewal. LSEC, liver sinusoidal endothelial cells.

Table 3. Dextran-binding receptors: roles in infections

Receptor	Pathogens	Receptor role in infection
Mannose receptor	1. *Mycobacterium tuberculosis; M. kansasii, M. phlei, and M. smegmatis*	1. Uptake of bacteria (95), inhibition of phagosomal-lysosomal fusion (96) and restriction of Th1 response (13); uptake (97)
	2. *Retroviridae* (HIV-1; Visna/Maedi virus; lentivirus)	2. Uptake of virus (98), induction of IFN-□ (99), increase of sexual transmission efficiency (100); virus uptake, in sheep (101); increased organ damage (102)
	3. *Candida albicans*	3. Impaired killing (103), uptake (104)
	4. *Orthomyxoviridae* (influenza viruses)	4. Uptake of virus (105)
	5. *Flaviviridae* (Dengue virus)	5. Uptake of virus (106)
	6. *Rhabdoviridae* (vesicular stomatitis virus)	6. Induction of IFN-□ (99)
	7. *Herpetoviridae* (herpes simplex virus)	7. Induction of IFN-□ (99)
	8. *Hepadnaviridae* (hepatitis B virus)	8. Uptake of virus (107)
	9. *Schistosoma mansoni*	9. Induction of Th2 phenotype (108)
	10. *Bunyaviridae* (Rift Valley fever virus, Toscana virus, Uukuniemi virus)	10. Uptake of virus (109)
	11. *Paramyxoviridae* (measles virus)	11. Virus attachment, DCs and T cells infection (110)
	12. *Francisella tularensis*	12. Bacteria uptake (111)
	13. *Yersinia pestis*	13. Bacteria uptake (112)
	14. *Leishmania* spp.	14. Uptake of the pathogen, modulation of immune response (113, 114)
DC-SIGN	1. *M. tuberculosis*	1. Uptake of mycobacteria by DCs (115), restriction of Th1 response (12)
	2. *Retroviridae* (HIV-1; human T-lymphotropic virus 1)	2. Uptake of virus and transinfection of other cells (6); cross-talk with Nef-1 signaling and decrease of IL-6 production (116); binding (11), uptake of virus, infection and transinfection (10)
	3. *Candida albicans*	3. Uptake of fungi (117)
	4. *Orthomyxoviridae* (influenza viruses)	4. Uptake of virus and transinfection of other cells (118); improved viral replication (119)
	5. *Coronaviridae* (SARS; infectious bronchitis virus)	5. Uptake of virus (120); uptake of virus (121)
	6. *Arenaviridae* (Lassa virus, Junin virus)	6. Uptake of virus (122); uptake of virus (123)
	7. *Flaviviridae* (hepatitis C virus; Dengue virus; West Nile virus, Tick-borne encephalitis virus)	7. Uptake of virus (124); uptake of virus (125), platelet activation (126); uptake of virus (127); predisposition to severe forms of encephalitis (128)
	8. *Paramyxoviridae* (human respiratory syncytial virus)	8. Modulation of immune response (129)

	9. *Herpesviridae* (cytomegalovirus, herpesvirus 8)	9. Uptake of virus and transinfection of other cells (130), virus uptake (131, 132)
	10. *Filoviridae* (Ebola virus; Marburg virus)	10. Uptake of virus, transinfection (120, 133)
	11. *Helicobacter pylori*	11. Uptake of bacteria, modulation of immune response (134)
	12. *Leishmania sp.*	12. Uptake of the pathogen, modulation of immune response (114, 134-136)
	13. *S. mansoni*	13. Binding of the surface molecule to the host cells, modulation of immune response (137)
	14. Togaviridae (Sindbis virus)	14. Uptake of virus (138)
	15. *Escherichia coli*	15. Support of phagocytosis (139)
	16. *Klebsiella pneumoniae lipopolysaccharide serotype O3*	16. Binding of bacteria (134)
	17. Bacteroides fragilis	17. Processing and presentation to T cells (140)
SIGN-R1	1. *M. tuberculosis*	1. Binding of bacteria, modulation of immune response (141)
	2. *Candida albicans*	2. Uptake of fungi (142)
	3. *Streptococcus pneumoniae*	3. SIGN-R1 plays a defensive role (143), being important in development of IgM response (144)
SIGN-R3	1. *M. tuberculosis*	1. Binding, modulation of immune response (145)
	2. *Leishmania* spp.	2. Binding and uptake of bacteria, modulation of immune response (136)
L-SIGN	1. *M. tuberculosis*	1. Binding, modulation of immune response (141)
	2. Retroviridae (HIV-1, HIV-2; SIV)	2. Uptake of virus and transinfection of other cells (48, 146)
	3. *Coronaviridae* (infectious bronchitis virus)	3. Uptake of virus (121)
	4. *Arenaviridae* (Lassa virus, Junin virus)	4. Uptake of virus (123)
	5. *Flaviviridae* (hepatitis C virus; West Nile virus)	5. Uptake of virus (124, 147); uptake of virus (127)
	6. S. mansoni	6. Binding of the pathogen (148)
	7. Filoviridae (Ebola virus; Marburg virus)	7. Uptake of virus and transinfection of other cells (133, 149); uptake of virus (120)
	8. *Coronaviridae* (SARS coronavirus)	8. Uptake of virus (120)
	9. Togaviridae (Sindbis virus)	9. Uptake of virus (138)
	10. *Leishmania infantum*	10. Uptake of bacteria (135)
Langerin	1. *Mycobacterium leprae*	1. Uptake and antigen presentation (150)

	2. *Retroviridae* (HIV-1)	2. Uptake of virus and its degradation (151)
	3. Candida spp. (including *C. albicans), Saccharomyces* species, and *Malassezia furfur*	3. Binding and phagocytosis of fungi (152)
	4. *Paramyxoviridae* (measles virus)	4. Uptake of virus (153)
LSECtin (probable dextran-binding receptor)	1. *Hepadnaviridae* (hepatitis B virus)	1. LSECtin downregulates inflammation but prolongs the time of virus liver clearance (154)
	2. *Filoviridae* (Ebola virus)	2. Binding of the virus, infection enchancement (155, 156)
	3. *Coronaviridae* (SARS coronavirus, SARS)	3. Binding, infection enchancement (155)
	4. *Flaviviridae* (hepatitis C virus)	4. Virus binding (157)
	5. *Arenaviridae* (Lassa virus)	5. Virus binding (158)

DC, dendritic cell; DC-SIGN, dendritic cell–specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin; IFN, interferon; L-SIGN, liver/lymph node-specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin; SARS, severe acute respiratory syndrome; SIV, simian immunodeficiency virus.

The latter result may be explained by targeted delivery of dextran into the phagosomes and lysosomes where the pathogen is taken up (162). An increase in phagocytic activity after dextran uptake is probably connected with NADPH oxidase 2 upregulation which is responsible for antimicrobial activity (163). In the systemic candidiasis model the dextran-amphotericin B conjugate given 10 days after infection decreased the number of granulomas in the liver by fourfold (164). In experiments on dextran–rimantadine this conjugate has shown to have a significantly better defencive effect in the chicken embryo and mouse models for influenza A and B virus and in the mouse model of tick-borne encephalitis (165). It remained unclear whether dextran alone could cause similar effects in the treatment of infections.

Regularly infused in mice in a model of BCG-induced granulomatosis, oxidized dextran (OD; in these studies-the molecule of clinical dextran containing less than 3% of glucose units oxidized with formation of aldehyde groups) reduced the number and size of granulomas in the organs; increased numbers of fibroblasts (with reduced activity) in the granulomas; decreased destructive and necrotic changes in the liver; and decreased fibrosis in the liver and lungs (166). In a mouse influenza model, OD decreased fatality by 3.3-fold and significantly decreased lung fibrosis (167). In a model of systemic candidiasis, the number of granulomas in the brain decreased eightfold after OD treatment compared with antifungal amphotericin B. While the control group of mice died, 60% of OD-treated mice survived (168).

The mechanism of OD action is still undiscovered; however, this form of dextran has been shown to increase the degree of adhesion of peritoneal cells, which may indicate increased activity of macrophages (169). OD reduces the viability of these cells, but conversely it stimulates metabolic and oxidative processes (169). *In vitro* dextran, and to a greater extent OD, are able to stimulate macrophage production of granulocyte-macrophage colony-stimulating factor (169), which supports the differentiation and activation of antigen-presenting cells (170). OD causes a shift in the balance of activities between nitric oxide synthase and arginase towards increasing nitric oxide production by macrophages (171). Another effect is increased macrophage ROS production (172).

Chemical differences between dextran and OD are not significant; it is unknown whether oxidation played a role in *in vivo* results. Probably specific binding of MR and DFRs by dextran modulates pathogen-induced T helper responses (Figure 4) (173, 174). Thus antifibrotic action of dextran in BCG model (159, 166) could be linked to restricted Th2 reaction contributing to tissue remodelling. If this hypothesis is true, dextran could also modulate the immune response to Th2

overreaction-inducing allergens dependent on MR (175) and DC-SIGN (176, 177).

Preliminary results are available concerning the *in vivo* action of nonmodified dextran in models of infections dependent on dextran-binding receptors. Dextran introduced intranasally simultaneously with heat-killed *M. tuberculosis* H37Rv decreased lung concentrations of both IFN-γ and IL-10, while the IFN-γ/IL-10 ratio decreased 2.5-fold, a result that rather illustrates suppression of Th1 response (178).

Dextran introduced intranasally simultaneously or a day before infection with 10 LD_{50} of the H5N1 influenza virus saved or prolonged lives of mice (179). These experiments do not provide evidence on dextran's mechanisms of action, a question that will be addressed in future works. They show, however, that dextran may be a promising molecule to add to the long list of treatments against infections dependent on dextran-binding receptors (Table 3).

DEXTRAN IN PREVENTING HIV INFECTION AND TRANSMISSION

Sexual transmission of HIV is the most prevalent route for infection (180, 181). DCs of intestinal and genital mucosae express DC-SIGN (21). They can be productively infected with HIV and have high capacity to trans-infect the T cells—the main HIV targets. DC-SIGN itself is an important player in the formation of DC-T cell infectious synapses (182, 183); signaling via DC-SIGN promotes increased viral uptake (184) and productive infection (185), and also influences DCs regulatory roles (30). HIV entry inhibitors are commonly used antiretrovirals (186), but there are still no inhibitors of HIV-DC-SIGN interaction introduced into the clinics, in spite of proven importance of receptor in myeloid cells infection and trans-infection of T cells.

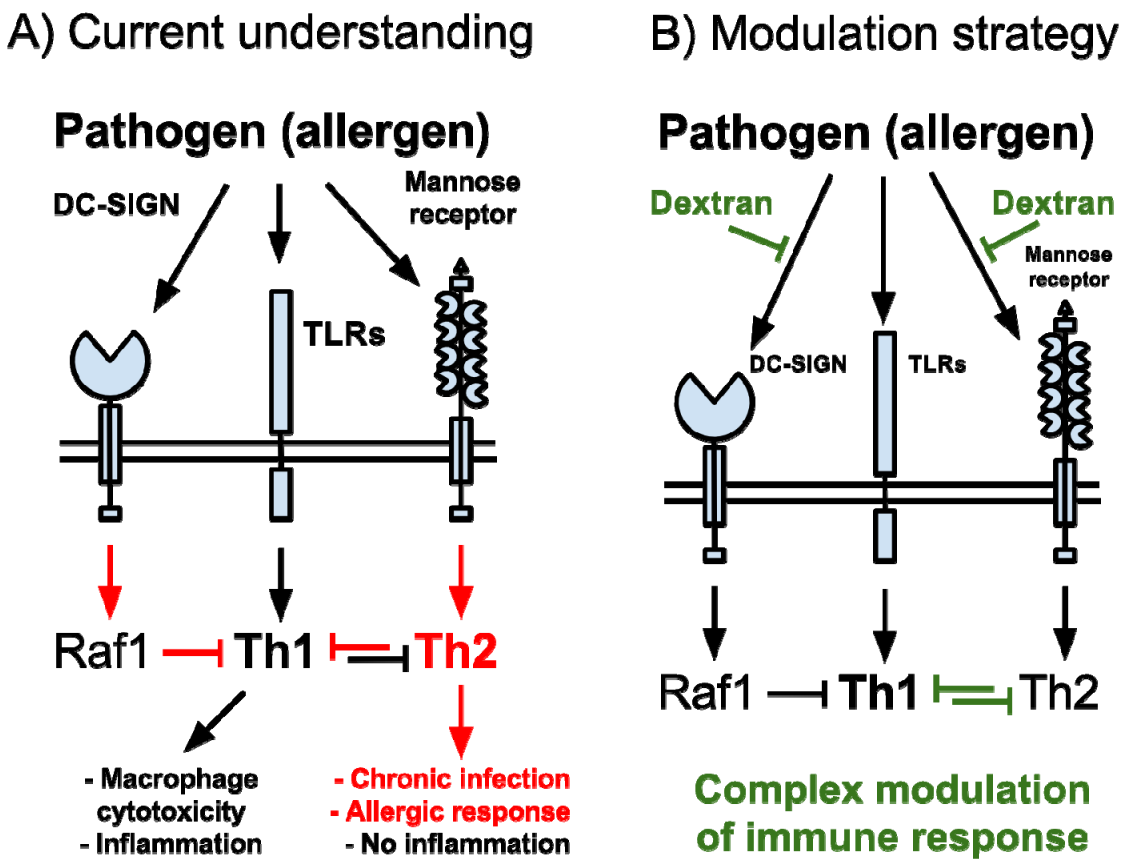

Figure 4. Dextran and glycan-lectin interactions. This simplified scheme shows that if dextran decrease the availability of MR and DC-SIGN for the pathogens, this may influence immune responses. It is known that DC-SIGN ligands prevent binding and entry of pathogens, interfere with trans-infection of T cells by DCs, skew the myeloid cells activation phenotypes and influence immune response.

Dextran 60 given before and after infection provides significant decrease of the HIV-1 viral RNA inside the B-THP-1/DC-SIGN cells. Dextran oligomers also inhibit infection (S. Pustylnikov and P. Jain, unpublished results) and indeed carbohydrate-binding domain of DC-SIGN binds to ~3 carbohydrate units (187). This suggests dextran is an effective inhibitor of HIV-DC-SIGN interaction. It was shown that dextran decreases the mortality rate of HIV-infected human monocyte-derived macrophages from 84% to 48% (188). This could be a result of the inhibition of the minor HIV-DC-SIGN binding (189), as well as a result of the inhibition of HIV-MR interaction shown in macrophage infection and viral transmission (98).

We suggest that dextran as a DC-SIGN and MR ligand could not only decrease the rates of HIV infection and trans-infection in myeloid cells, but could also serve to deliver the antiretrovirals or vaccines to DCs. Anti-HIV gel formulations have proven their efficiency in clinical trials (190); use of viral entry inhibitors in gel formultions can provide full protection *in vivo* (191). If dextran proves to be an HIV entry inhibitor, it could be used as a gel formulation.

CONCLUSIONS

The combination of dextran properties is unique. Dextran is a hydrophilic, nonionic molecule with adjustable molecular mass distribution (Figure 2) and viscosity/density in solutions. Dextran's lack (or near lack) of toxic effects, pyrogenic or allergic reactions and accumulation in the body; its thermal and chemical stability allowing sterilization and obtaining the derivatives; its applicability in mass production at comparably low costs (82, 192): all make dextran an appealing biopolymer for multiple applications.

Antimicrobial strategies that could exploit dextran is a speculative topic due to the lack of data. However currently dextran is already used in a great amount of diverse aplications in fields of research and medicine which can benefit from our analysis of the dextran-binding receptors (Figure 2). Dextran is a popular component of conjugates and nano-particles. Numerous works on drug-dextran conjugates show interesting results *in vitro* and *in vivo* and provide arguments for improved pharmaceutical properties of such compounds (reviewed in (193-198). Our analysis suggests that concept of targeted delivery—the conjugation of dextran with antimicrobials to reach the pathogens inside the specific cells that take up dextran (liver cells, macrophages and DCs)—being itslef not a new idea, can benefit from knowledge of dextran-binding receptors and their roles in a number of infections.

Dextran's influences on infections has not been studied comprehensively to date and only minor influences are known. Dextran-binding MR, DC-SIGN (in human)/SIGN-R1/SIGN-R3 (in mice), L-SIGN, and langerin play large roles in infectious diseases (Table 3). Besides regulation of immune cell interplay, these receptors participate in binding, recognition, and uptake of different pathogens. Targeting of dextran-binding receptors (e.g., MR and DC-SIGN) is a popular concept. In recent years studies devoted to the development of DC-SIGN therapeutic ligands have yielded new data in cell biology (203), immunology (204), and biochemistry (205, 206). The concept of therapeutic DC-SIGN antagonists/inhibitors is promising and in need of further development (9, 207). Targeting the MR is suggested for vaccine development (201), for delivery of cargo into macrophages (202) or liver cells (195). Dextran can play a role in the prevention of pathogen binding, entry and signaling in MR-expressing myeloid cells wich participate in blood-brain barrier disruption in neuroinvasive infections (208): this was probably the case in prevention of *C. albicans* infection in the brain (168). Skewing the T helper responses could be a mechanism that allowed dextran derivatives to decrease tissue remodelling in the BCG infection model (159, 166) (Figure 4). Dextran has been recently used as a backbone for the nucleic acids delivery conjugate and our analysis could help in the development of this field (199). We also note that dextran could be of use in the glycosilation of adenoviruses used for gene transfer (200), possibly improving the biocompatibility and providing predictable uptake by certain cell types and receptors.

Further, the route of delivery of dextran and its derivatives require to be taken into consideration. Infusion will result in primary uptake in the liver, which is not a target of respiratory or mucosal infections. Dextran-based sprays or gels are an option, but they are not helpful in generalized infections. Clinical dextrans with molecular weights in the range 35,000 to 80,000 cannot reach a systemic infection if given orally, but smaller molecules such as dextran with an average molecular weight of 1,000 probably can. Dextrans with high molecular weights induce active endocytosis, while smaller molecules do not (36). They may not only decrease the amount of available

dextran-binding receptors on the cell surface but also prevent endocytosis and following recycling of receptors (shown for both MR (209) and DC-SIGN (210)) and keep the cells' endocytic capacity at its initial level.

Medical and biological applications of dextran can be considered in a new way via the prism of receptor-specific interactions. This can be an instrument to interpret the data on dextran conjugates and derivatives. If antimicrobial properties of dextran can be applied in humans, dextran might become an approved, specific, nontoxic, cheap, and accessible immunomodulatory drug. These qualities are extremely important in the case of deadly infections that affect resource-limited populations. Dextran may possess antimicrobial and antiallergic effects owing to binding to MR, DFRs, and langerin. This review suggests a primary aim for future studies: testing of the ability of dextran to act against a panel of pathogens exploiting dextran-binding receptors to enter the cells and to modulate the immune responses.

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List of abbreviations

APC, antigen-presenting cell; BCG, Bacillus Calmette–Guérin; cdc42, cell division control protein 42 homolog; CLIC, clathrin-independent carriers; CME, clathrin-mediated endocytosis; DC, dendritic cell; DC-SIGN, dendritic cell–specific ICAM-3-grabbing nonintegrin; DFRs, DC-SIGN family receptors; FITC, fluorescein isothiocyanate; FPE, fluid-phase endocytosis; GEEC, glycosylphosphatidylinositol-enriched endocytic compartments; gp120, HIV envelope glycoprotein; HIV, human immunodeficiency virus; HIV-1, HIV type 1; HTLV-1, Human T-lymphotropic virus 1; ICAM-3, intercellular adhesion molecule-3; IFN, interferon; IL-4, interleukin 4; LD_{50}, median lethal dose; LSEC, liver sinusoidal endothelial cells; L-SIGN, liver/lymph node-specific ICAM-3-grabbing nonintegrin; MDDCs, monocyte-derived dendritic cells; MR, mannose receptor; M-CSF, macrophage colony-stimulating factor; NADPH, nicotinamide adenine dinucleotide phosphate; OD, oxidized dextran; Raf1, proto-oncogene serine/threonine-protein kinase; SARS, severe acute respiratory syndrome; SIGN-R1 (-R2, ... -R8), murine homologues of DC-SIGN; SIV, simian immunodeficiency virus; Th1 (2), Type 1 (2) T helper cell; TLRs, toll-like receptors

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