2618; Sheikh et al., 2000, J. Cell. Sci. 113: 1021-1032; Behrendt et al., 2000, J. Biol. Chem. 275: 1993-2002). ENDO180 is unusual in the family of mannose receptors in that it is targeted from the plasma membrane to the recycling endosomes rather than to a late endosome/lysosome compartment (Howard and Isacke, 2002. JBC 35:32320-31) and functions in cell motility and remodeling of the extracellular matrix by promoting cell migration and uptake of collagens for intracellular degradation (Behrendt. 2004 Biol Chem. 385(2):103-36; Kjoller et al, 2004 Exp Cell Res. 293(l):106-16; Wienke et al., 2007 Cancer Res. 67(21): 10230-40).

[0006] PCT Patent Application Publication No. WO 2004/100759 relates to methods of diagnosing and treating, respectively, diseases associated with ENDO180. PCT Patent Application Publication No. WO 2010/111198 provides anti-ENDO180 antibodies, compositions comprising same and uses thereof.

Lipid Complexes

[0007] US 2009/0232730 discloses a method for producing immunoliposomes. US 2010/0008937 discloses leukocyte selective delivery agents.

[0008] A targeted system for delivery of therapeutic and diagnostic agents would be of great value.

SUMMARY ~~OF THE INVENTION~~

[0009] Disclosed herein are compositions for selective and targeted delivery of therapeutic and/or diagnostic agents to aberrantly proliferating cells. The compositions comprise ENDO180-targeting moieties and carrier moieties, further comprising a therapeutic and/or diagnostic agent for targeted delivery of the therapeutic or diagnostic agent to a cell expressing an ENDO180 receptor. The composition is useful for targeted delivery of at least one diagnostic agent and/or therapeutic agent including a small molecule, such as an oligonucleotide, an antibody or fragment thereof, a polypeptide or peptide, or a combination thereof, to the intracellular space of a cell expressing the ENDO180 receptor. Without wishing to be bound to theory, the ENDO180 receptor is an endocytic receptor specifically expressed on activated myoblasts in fibrotic tissues and tumors and on subsets of tumor cells, on macrophages and on endothelial cells.

[0009a] In one aspect there is provided, a composition comprising a) a lipid-based carrier moiety; b) an ENDO180 targeting moiety; and c) an effective amount of a therapeutic agent or a diagnostic agent or a combination thereof; wherein the carrier moiety and the targeting moiety are covalently bonded.

[0010] In one ~~aspect~~embodiment disclosed herein is a composition comprising a) a carrier moiety; b) an ENDO180 targeting moiety; and c) an effective amount of a therapeutic agent and/or or a diagnostic agent.

[0033] In some embodiments the therapeutic agent is a nucleic acid selected from an antisense compound, a chemically modified dsRNA compound, an unmodified dsRNA compound, a chemically modified siRNA compound, an unmodified siRNA compound, a chemically modified shRNA compound, an unmodified shRNA compound, a chemically modified miRNA compound, and an unmodified miRNA compound, a ribozyme, or combinations thereof. In various preferred embodiments the therapeutic agent is chemically modified siRNA. In some preferred embodiments, the therapeutic agent is an unmodified siRNA compound.

[0034] In some preferred embodiments the lipid particle comprises Dioleoyl Phosphatidylethanolamine (DOPE), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and cholesterol (Chol), hyaluronic acid, an anti-ENDO180 antibody or an antigen-binding fragment of a humanized or chimeric anti-ENDO180 antibody and a therapeutic agent selected from doxorubicin, mitomycin C and a therapeutic nucleic acid molecule. In some embodiments the Dioleoyl Phosphatidylethanolamine (DOPE), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and cholesterol (Chol) are present at a molar ratio of about 4:2:1 (DOPE:DOTMA:Chol)

[0035] In other preferred embodiments the lipid particle comprises DOPE, Hydrogenated soybean phosphatidylcholine (HSPC), cholesterol and NHS-PEG-DSPE, an anti-ENDO180 antibody or an antigen-binding fragment of a humanized or chimeric anti-ENDO180 antibody and a therapeutic agent selected from doxorubicin, mitomycin C and a therapeutic nucleic acid molecule. In some embodiments, the lipid particle further comprises DOTMA. In some embodiments, the DOPE, Hydrogenated soybean phosphatidylcholine (HSPC), cholesterol and NHS-PEG-DSPE are present at a molar ratio of about 4.5:20: 75:0.5 (DOPE:HSPC:Chol: NHS-PEG-DSPE).

[0036] In other preferred embodiments the lipid particle comprises soy PC, 1,2-Bis(diphenylphosphino)ethane (DPPE) and cholesterol, hyaluronic acid, an anti-ENDO180 antibody or an antigen-binding fragment of a humanized or chimeric anti-ENDO180 antibody and a therapeutic agent selected from doxorubicin, mitomycin C and a therapeutic nucleic acid molecule. In some embodiments the soy PC, 1,2-Bis(diphenylphosphino)ethane (DPPE) and cholesterol are present at a molar ratio of about 3:1:1 (soy PC:DPPE:cholesterol).

[0037] In another ~~aspect~~embodiment, provided herein is a method of treating a subject afflicted with a proliferative disorder comprising administering to the subject a therapeutically effective amount of a composition comprising a) a carrier moiety; b) an ENDO180 targeting moiety and c) a therapeutic agent.

[0037a] In one aspect, there is provided use of the composition as defined herein for the manufacture of a medicament for treating a subject afflicted with a proliferative disorder.

[0037b] In another aspect, there is provided the composition as defined herein, for use in therapy.

[0038] In another ~~aspect~~embodiment, provided herein is a composition comprising a) a carrier moiety; b) an ENDO180 targeting moiety and c) a therapeutic agent, for use in therapy.

[0039] In another ~~aspect~~embodiment provided herein is a composition comprising a) a carrier moiety; b) an ENDO 180 targeting moiety and c) a therapeutic agent, for use in treating a proliferative disorder.

[0040] In some embodiments, the composition is administered systemically.

[0041] In some embodiments the proliferative disorder is selected from a solid tumor, a hematopoietic tumor, metastases, fibrosis and a macrophage associated disorder. In some embodiments, the proliferative disorder is a solid tumor or a hematopoietic tumor.

[0042] In some embodiments the tumor is an ovarian tumor, a breast tumor, osteoblastic/osteocytic cancer, prostate cancer, head and neck cancer, leukemia, renal cell carcinoma, or transitional cell carcinoma.

[0043] In some embodiments the fibrosis is liver fibrosis, myelofibrosis, kidney fibrosis for any reason (CKD including end-stage renal disease, ESRD); lung fibrosis (including interstitial lung fibrosis ILF); abnormal scarring (keloids) associated with all possible types of skin injury accidental and jatrogenic (operations); scleroderma; cardiofibrosis, failure of glaucoma filtering operation; intestinal adhesions.

[0044] In some embodiments the macrophage-associated disorder is inflammation or atherosclerosis.

[0045] Non-limiting examples of diseases and disorders include:

1. soft tissue sarcomas in which ENDO180 is expressed in the tumor and tumor stroma cells (activated myofibroblasts, neovasculature and infiltrating cells of macrophage-monocyte lineage);

2. carcinomas in which ENDO180 is expressed in the tumor stroma cells (activated myofibroblasts, neovasculature and infiltrating cells of macrophage-monocyte lineage);

3. carcinomas that express ENDO180 and have undergone epithelial-mesenchymal transition thus acquiring high metastatic potential;

4. leukemia expressing ENDO180 for example, from macrophage-monocyte lineage;

5. fibrotic diseases, for example of kidney, lung and liver with activated myofibroblasts;

6. diseases and disorders associated with macrophage including atherosclerosis and chronic inflammation.

[0046] In another aspect, provided herein is a method ~~of~~for diagnosing a proliferative disorder in a subject, comprising contacting a biological sample that has been obtained from the subject with a composition comprising a)a carrier moiety; b) an ENDO180 targeting moiety and c) a diagnostic agent; and comparing the level of diagnostic agent in the biological sample with that of a reference sample~~, such as a biological sample from a healthy subject~~ from a healthy subject or to a known standard.

[0047] In some embodiments, the biological sample for diagnosis may be taken from a bodily fluid or from a tissue. In some embodiments, the bodily fluid is selected from the group of fluids consisting of blood, lymph fluid, ascites, serous fluid, pleural effusion, sputum, cerebrospinal fluid, lacrimal fluid, synovial fluid, saliva, stool, sperm, blood and urine.

[0048] The present ~~invention~~disclosure is explained in greater detail in the figures, description and claims hereinbelow.

BRIEF DESCRIPTION OF THE FIGURES

[0049] Figure 1 provides a schematic illustration of the process of generating targeted nanoparticles for nucleic acid (NA) molecule delivery.

[0050] Figures 2A and 2B show flow cytometry analysis with NRK-ENDO180 (2A), A549 (2B) cell lines incubated with 1 μg/ml Anti ENDO180 mAbs; Clone 8D8, clone 10C12, Minibody and a secondary Ab FITC goat anti-mouse (1.5 μg/ml). The peaks showing cells bound to anti-ENDO180 are labeled for clarity.

[0051] Figures 3A and 3B show flow cytometry analysis with LLC ENDO180 (3A), DU145 ENDO180 (3B) cell lines incubated with 1 μg/ml Anti ENDO180 mAbs; Clone 8D8, clone 10C12 and Minibody and a secondary Ab FITC goat anti-mouse (1.5 μg/ml). The peaks showing cells bound to anti-ENDO180 are labeled for clarity.

[0052] Figures 4A-4D show flow cytometry analysis with DU145 ENDO180 (4A), DU145 naive (4B), NRK ENDO180 (stably transfected) (4C) and A549 (4D) cell lines incubated with 1 μg/ml Anti ENDO180 mAb; Clone 8D8 (orange line, right most peak in all graphs) and Minibody (new batch, blue line, center peak in all graphs) both were labeled with Alexa fluor-647, in a comparison with control unstained cells (red line, left most peak in all graphs).

[0053] Figures 5A-5D shows cells which have internalized ENDO180 mAbs: 8D8 mAb into NRK-ENDO180 (5A) Minibody new batch into A549 cell line (5B) and 8D8 mAb into A549

miRNA compound, a chemically modified siRNA, a chemically unmodified siRNA, and ribozyme, or a combination thereof

31. The composition of claim 30, wherein the therapeutic agent is a dsRNA molecule selected from the group consisting of a chemically modified siRNA compound and an unmodified siRNA compound.

32. ~~A method of treating a subject afflicted with a proliferative disorder comprising administering to the subject a therapeutically effective amount of~~ Use of the composition of any one of claims 1 to 31 for the manufacture of a medicament for treating a subject afflicted with a proliferative disorder.

33. The composition of any of claims 1 to 31, for use in therapy.

34. The composition of claim 33, wherein the therapy comprises treatment of a proliferative disorder.

35. The ~~method~~ use or composition of any of claims 32 to 34, wherein the composition is to be administered systemically.

36. The ~~method~~use or composition of claims 32 or 34, wherein the proliferative disorder is selected from the group consisting of a solid tumor, a hematopoietic tumor, metastases, fibrosis and a macrophage associated disorder.

37. The ~~method~~use or composition of claim 36, wherein the proliferative disorder is a solid tumor or a hematopoietic tumor.

38. The ~~method~~use or composition of claim 37, wherein the tumor is selected from the group consisting of an ovarian tumor, a breast tumor, osteoblastic/osteocytic cancer, prostate cancer, head and neck cancer, leukemia, renal cell carcinoma, and transitional cell carcinoma.

39. The ~~method~~use or composition of claim 36, wherein the macrophage-associated disorder comprises inflammation or atherosclerosis.

40. A method for diagnosing a proliferative disorder in a subject comprising contacting a bodily sample that has been obtained from the subject with a composition comprising a) a carrier moiety; b) an ENDO180 targeting moiety and c) a diagnostic agent; and comparing the level of the diagnostic agent in the biological sample with that of a reference sample from a healthy subject or to a known standard.