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

[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 that binds an extracellular domain of an ENDO180 polypeptide present on a cell and is internalized into the cell by binding the ENDO180

polypeptide; 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~~bound , wherein the ENDO180 binding moiety comprises an ENDO180 antibody or a functional fragment thereof selected from the group consisting of:

a. an isolated monoclonal antibody produced by the hybridoma cell line E3-8D8 deposited with the BCCM under Accession Number LMBP 7203CB, or an antigen binding fragment thereof;

b. an antibody that binds to the same epitope as the antibody of (a), or an antigen binding fragment thereof;

c. a humanized version of the antibody or antigen-binding fragment thereof of (a), or a humanized version of the antibody or antigen-binding fragment of (b);

d. a chimeric version of the antibody or antigen-binding fragment thereof of (a), or a chimeric version of the antibody or antigen-binding fragment of (b);

e. a recombinant polypeptide comprising the antigen binding domain of the antibody of (a), which is internalized into a cell by binding the ENDO180 polypeptide;

f. an antigen-binding fragment of an antibody comprising a polypeptide substantially similar to SEQ ID NO: 6; and

g. a recombinant polypeptide comprising CDRs having an amino acid sequence substantially similar to amino acid sequences set forth in SEQ ID NO:7 and 8.

[0010] In one 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.

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

[0046] In another aspect, provided herein is a method 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 that binds an extracellular domain of an ENDO180 polypeptide present on a cell and is internalized into the cell by binding the ENDO180 polypeptide; and c) a diagnostic agent; and comparing the level of diagnostic agent in the biological sample with that of a reference sample from a healthy subject or to a known standard, wherein the ENDO180 binding moiety comprises an ENDO180 antibody or a functional fragment thereof selected from the group consisting of:

a. an isolated monoclonal antibody, produced by the hybridoma cell line E3-8D8 deposited with the BCCM under Accession Number LMBP 7203CB, or an antigen-binding fragment thereof;

b. an antibody that binds to the same epitope as the antibody of (a), or an antigen-binding fragment thereof;

c. a humanized version of the antibody or antigen-binding fragment thereof of (a), or a humanized version of the antibody or antigen-binding fragment of (b);

d. a chimeric version of the antibody or antigen-binding fragment thereof of (a), or a chimeric version of the antibody or antigen-binding fragment of (b);

e. a recombinant polypeptide comprising the antigen binding domain of the antibody of (a), which is internalized into a cell by binding the ENDO180 polypeptide;

f. an antigen-binding fragment of an antibody comprising a polypeptide substantially similar to SEQ ID NO: 6; and

g. a recombinant polypeptide comprising CDRs having an amino acid sequence substantially similar to amino acid sequences set forth in SEQ ID NO:7 and 8.

[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 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

CLAIMS

1. A composition comprising a) a lipid-based carrier moiety; b) an ENDO180 targeting moiety that binds an extracellular domain of an ENDO180 polypeptide present on a cell and is internalized into the cell by binding the ENDO180 polypeptide; 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 bound, wherein the ENDO180 binding moiety comprises an ENDO180 antibody or a functional fragment thereof selected from the group consisting of:
   a. an isolated monoclonal antibody produced by the hybridoma cell line E3-8D8 deposited with the BCCM under Accession Number LMBP 7203CB, or an antigen-binding fragment thereof;
   b. an antibody that binds to the same epitope as the antibody of (a), or an antigen-binding fragment thereof;
   c. a humanized version of the antibody or antigen-binding fragment thereof of (a), or a humanized version of the antibody or antigen-binding fragment of (b);
   d. a chimeric version of the antibody or antigen-binding fragment thereof of (a), or a chimeric version of the antibody or antigen-binding fragment of (b);
   e. a recombinant polypeptide comprising the antigen binding domain of the antibody of (a), which is internalized into a cell by binding the ENDO180 polypeptide;
   f. an antigen-binding fragment of an antibody comprising a polypeptide substantially similar to SEQ ID NO: 6; and
   g. a recombinant polypeptide comprising CDRs having an amino acid sequence substantially similar to amino acid sequences set forth in SEQ ID NO:7 and 8.

2. The composition of claim 1, wherein the carrier moiety and the targeting moiety are covalently bound via a surface modification of the carrier moiety with a synthetic polymer, a natural polymer or a semi synthetic polymer.

3. The composition of claim 2, wherein the synthetic polymer comprises a PEG moiety.

4. The composition of claim 3, wherein the PEG moiety comprises NHS-PEG-DSPE [3-(N-succinimidyloxyglutaryl) aminopropyl, polyethyleneglycol-carbamyl distearoylphosphatidyl-ethanolamine].

5. The composition of claim 2, wherein the natural polymer comprises a polysaccharide or a glycosaminoglycan.

6. The composition of claim 5, wherein the glycosaminoglycan comprises hyaluronic acid.

~~7. The composition of any one of claims 1 to 6, wherein the ENDO180 targeting moiety comprises an ENDO180 binding protein that binds an extracellular domain of an ENDO180 polypeptide present on a cell and is internalized into the cell by the ENDO180 polypeptide.~~

~~8~~7. The composition of claim ~~7~~1, wherein the ~~ENDO180 binding protein comprises an~~ ENDO180 antibody or a functional fragment thereof is capable of binding ENDO180.

~~9~~8. The composition of claim ~~8~~7, wherein the ENDO180 antibody or functional fragment thereof capable of binding ENDO180 is selected from the group consisting of a full IgG, a monoclonal antibody, a polyclonal antibody, a human antibody, a humanized antibody, a humanized antigen binding fragment, a Fab fragment, a Fab' fragment, an F(ab')2 fragment, the variable portion of the heavy and/or light chains thereof, a Fab miniantibody, and a scFv, or a combination thereof.

~~10. The composition of claims 8 or 9, wherein the ENDO180 antibody or a functional fragment thereof is selected from the group consisting of:~~

~~a. an isolated monoclonal antibody or an antigen-binding fragment thereof, produced by the hybridoma cell line E3-8D8 deposited with the BCCM under Accession Number LMBP 7203CB;~~

~~b. an antibody or an antigen-binding fragment thereof that binds to the same epitope as the antibody of (a);~~

~~c. a humanized version of the antibody or an antigen-binding fragment thereof of (a), or a humanized version of the antibody or antigen-binding fragment of (b);~~

~~d. a chimeric version of the antibody or an antigen-binding fragment thereof of (a), or a chimeric version of the antibody or antigen-binding fragment of (b);~~

~~e. a recombinant polypeptide or antigen-binding fragment thereof comprising the antigen binding domain of the antibody of (a) which is internalized in to a cell by the ENDO180 receptor;~~

~~f. an antigen-binding fragment of an antibody comprising a polypeptide substantially similar to SEQ ID NO: 6; and~~

~~g. a recombinant polypeptide comprising CDRs having an amino acid sequence substantially similar to amino acid sequences set forth in SEQ ID NO:7 and 8.~~

~~11~~9. The composition of any one of claims ~~8~~7 to ~~10~~8, wherein the ENDO180 antibody or functional fragment thereof comprises an antigen-binding fragment of a humanized version of the isolated monoclonal antibody.

~~12~~10. The composition of any one of claims 1 to ~~11~~9, wherein the lipid-based carrier moiety comprises a lipid particle.

~~13~~11. The composition of claim ~~12~~10, wherein the lipid particle comprises one or more lipid selected from the group consisting of phosphatidylcholine or a derivative thereof, phosphatidylglycerol or derivative thereof, and phosphatidylethanolamine (PE) or a derivative thereof; or a combination thereof.

~~14~~12. The composition of claims ~~12~~10 or ~~13~~11, wherein the lipid particle further comprises one or more cationic lipid.

~~15~~13. The composition of any one of claims ~~12~~10 to ~~14~~12, wherein the lipid particle further comprises cholesterol.

~~16~~14. The composition of claim ~~15~~13, wherein the lipid particle comprises dioleoyl phosphatidylethanolamine (DOPE) and cholesterol.

~~17~~15. The composition of claim ~~16~~14, wherein the lipid particle further comprises hydrogenated soy phosphatidylcholine (HSPC).

~~18~~16. The composition of claim ~~17~~15, wherein the lipid particle comprises DOPE, Hydrogenated soybean phosphatidylcholine (HSPC), cholesterol (Chol) and the PEG moiety NHS-PEG-DSPE at a molar ratio of about 4.5:20:75:0.5 (DOPE:HSPC:Chol:NHS-PEG-DSPE).

~~19~~17. The composition of any of claims ~~16~~14 to ~~18~~16, wherein the lipid particle further comprises DOTMA.

~~20~~18. The composition according to claim ~~19~~17, wherein the lipid particle comprises Dioleoyl Phosphatidylethanolamine (DOPE), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and cholesterol (Chol) at a molar ratio of about 4:2:1 (DOPE:DOTMA:Chol).

~~21~~19. The composition of claim ~~15~~13, wherein the lipid particle comprises DPPE and cholesterol.

~~22~~20. The composition of claim ~~21~~19, wherein the lipid particle further comprises soy PC.

~~23~~21. The composition of claim ~~22~~20, wherein the lipid particle comprises soy PC, DPPE and cholesterol at a molar ratio of about 3:1:1 (soy PC:DPPE:cholesterol).

~~24~~22. The composition of any one of claims 1 to ~~23~~21, wherein the lipid particle is about 85 to about 200 nM in diameter, preferably about 85 to about 130 nm.

~~25~~23. The composition of any one of claims 1-to ~~24~~22, wherein the lipid particle comprises a zeta potential of about (–7) to about (–40).

~~26~~24. The composition of claim 1, wherein the composition comprises a diagnostic agent, which is an imaging agent selected from the group consisting of a radioisotope, a fluorophore, a luminescent agent, a magnetic label, and an enzymatic label.

~~27~~25. The composition of claim 1, wherein the composition comprises at least one therapeutic agent selected from the group consisting of a nucleic acid compound and a non-nucleic acid compound, or a combination thereof.

~~28~~26. The composition of claim ~~27~~25, wherein the non-nucleic acid compound is selected from the group consisting of a small molecule, a peptide, a polypeptide, a peptidomimetic, a glycolipid, and an antibody, or a combination thereof.

~~29~~27. The composition of claim ~~28~~26, wherein the therapeutic agent comprises doxorubicin or mitomycin.

~~30~~28. The composition of claim ~~28~~26, wherein the nucleic acid is selected from the group consisting of an antisense compound, a chemically modified double stranded RNA compound, an unmodified double stranded RNA compound, a chemically modified shRNA compound, an unmodified shRNA compound, a chemically modified miRNA compound, and an unmodified

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

~~31~~29. The composition of claim ~~30~~28, 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~~30. Use of the composition of any one of claims 1 to ~~31~~29 for the manufacture of a medicament for treating a subject afflicted with a proliferative disorder.

~~33~~31. The composition of any of claims 1 to ~~31~~29, for use in therapy.

~~34~~32. The composition of claim ~~33~~31, wherein the therapy comprises treatment of a proliferative disorder.

~~35~~33. The use or composition of any of claims ~~32~~30 to ~~34~~32, wherein the composition is to be administered systemically.

~~36~~34. The use or composition of claims ~~32~~30 or ~~34~~32, 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~~35. The use or composition of claim ~~36~~34, wherein the proliferative disorder is a solid tumor or a hematopoietic tumor.

~~38~~36. The use or composition of claim ~~37~~35, 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~~37. The use or composition of claim ~~36~~34, wherein the macrophage-associated disorder comprises inflammation or atherosclerosis.

~~40~~38. 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 that binds an extracellular domain of an ENDO180 polypeptide present on a cell and is internalized into the cell by binding the ENDO180 polypeptide; 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, wherein the ENDO180 binding moiety

comprises an ENDO180 antibody or a functional fragment thereof selected from the group consisting of:

a. an isolated monoclonal antibody produced by the hybridoma cell line E3-8D8 deposited with the BCCM under Accession Number LMBP 7203CB, or an antigen-binding fragment thereof;

b. an antibody that binds to the same epitope as the antibody of (a), or an antigen-binding fragment thereof;

c. a humanized version of the antibody or antigen-binding fragment thereof of (a), or a humanized version of the antibody or antigen-binding fragment of (b);

d. a chimeric version of the antibody or antigen-binding fragment thereof of (a), or a chimeric version of the antibody or antigen-binding fragment of (b);

e. a recombinant polypeptide comprising the antigen binding domain of the antibody of (a), which is internalized into a cell by binding the ENDO180 polypeptide;

f. an antigen-binding fragment of an antibody comprising a polypeptide substantially similar to SEQ ID NO: 6; and

g. a recombinant polypeptide comprising CDRs having an amino acid sequence substantially similar to amino acid sequences set forth in SEQ ID NO:7 and 8.