

use of antibodies, antibody fragments or other binding domains targeting the PC of OxPL can ameliorate or prevent many diseases that are accentuated, or caused to worsen in progression, by activation of TLR 2 mediated signaling pathways.

In one aspect, the present disclosure provides the use of an antibody, antibody fragment or polypeptide that binds specifically to an oxidative phospholipid (OxPL) in the manufacture of a medicament for treating a subject with Kawasaki disease, wherein the antibody, antibody fragment or polypeptide inhibits a biological activity of the OxPL, and comprises: a variable heavy chain domain (VH) comprising the complementarity determining regions (CDRs) of the VH amino acid sequence set forth in SEQ ID NO: 2; and a variable light chain domain (VL) comprising the CDRs of the VL amino acid sequence set forth in SEQ ID NO: 2 or 4.

In a certain embodimentexample, the disclosure provides a method of treating a subject with a toll-like receptor 2 (TLR2)-mediated disease or disorder comprising, administering a therapeutically effective amount of an antibody, antibody fragment, or polypeptide that binds specifically to an oxidative phospholipid (OxPL), wherein the antibody, antibody fragment or polypeptide inhibits a biological activity of the OxPL. In a further embodimentexample, the method further comprises administering to the subject an additional therapeutic agent that is useful for treating a TLR2-mediated disease or disorder. Examples of TLR2-mediated diseases or disorders, includes but are not limited to, Kawasaki disease, type 2 diabetes, rheumatoid arthritis, dermatologic disease, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, Graves' Disease, Sjögren's syndrome, autoimmune thyroid diseases, or vasculitis. In a particular embodimentexample, the TLR2-mediated disease or disorder is Kawasaki disease. In a further embodimentexample, the method further comprises administering to the subject Intravenous immunoglobulin (IVIG) and/or salicylates. In yet a further embodimentexample, the subject is a human subject that is less than five years old. In another embodimentexample, the biological activity of the OxPL comprises activation of CD36-TLR2 apoptosis pathway. In yet another embodimentexample, the antibody, antibody fragment, or polypeptide is a single-chain variable fragment (ScFv). In a certain embodimentexample, the antibody or antibody fragment recognizes and binds to a phosphocholine headgroup of an oxidized phospholipid, wherein the antibody or antibody fragment comprises a variable heavy chain (V_H) domain and/or a variable light chain (V_L) domain, and wherein (a) the V_H domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:6 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:6; SEQ ID NO:7 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID

NO:7; and SEQ ID NO:8 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:8; and (b) the V_L domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:9 or 12 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:9 or 12; SEQ ID NO:10 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:10; and SEQ ID NO:11 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:11. In a further ~~embodiment~~example, the antibody, antibody fragment or polypeptide is administered intravascularly. In yet a further ~~embodiment~~example, the V_H domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:6, 7 and 8, and/or the V_L domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:9, 10 and 11, or SEQ ID NO:10, 11 and 12. In another ~~embodiment~~example, the antibody or antibody fragment is selected from the group consisting of: (a) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 9, 10 and 11; and (b) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 10, 11 and 12. In another ~~embodiment~~example, the heavy and light chain domains are linked to an Fc or FC2 region. In yet another ~~embodiment~~example, the antibody fragment comprises a single chain variable fragment ("scFv") that recognizes a phosphocholine headgroup of an oxidized phospholipid. In a particular ~~embodiment~~example, the scFv is soluble under physiological conditions. Other OxPL binding agents that inhibit the biological activity of OxPL can be used (see, e.g., International Publ. No. WO/2013/020995, which is incorporated herein by reference for all purposes).

DESCRIPTION OF DRAWINGS

[0010] **Figure 1A-B** provides **(A)** a diagram of the process that can be used to produce a single-chain variable fragment ("scFv"). As indicated, site directed mutagenesis can be employed to mutate the variable domain of the heavy chain ("V_H") of a double chain immunoglobulin antibody to increase the solubility of scFv (left). Linker, leader, and effector regions of the scFv are also indicated

WHAT IS CLAIMED IS:

1. ~~Use~~ A method of treating a subject with a toll-like receptor 2 (TLR2)-mediated disease or disorder comprising, administering a therapeutically effective amount of an antibody, antibody fragment, or polypeptide that binds specifically to an oxidative phospholipid (OxPL) in the manufacture of a medicament for treating a subject with Kawasaki disease, } , wherein the antibody, antibody fragment or polypeptide inhibits a biological activity of the OxPL, and comprises: a variable heavy chain domain (VH) comprising the complementarity determining regions (CDRs) of the VH amino acid sequence set forth in SEQ ID NO: 2; and a variable light chain domain (VL) comprising the CDRs of the VL amino acid sequence set forth in SEQ ID NO: 2 or 4.

2. The ~~use~~method of claim 1, wherein said medicament is to be administered~~the method further comprises administering to the subject in combination with an additional therapeutic agent that is useful for treating a TLR2-mediated disease or disorder.~~

3. The use of claim 1 or 2, wherein said medicament is to be administered to the subject in combination with Intravenous immunoglobulin (IVIG) and/or salicylates.

3. ~~The method of claim 1 or claim 2, wherein the TLR2-mediated disease or disorder is Kawasaki disease, type 2 diabetes, rheumatoid arthritis, dermatologic disease, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, Graves' Disease, Sjögren's syndrome, autoimmune thyroid diseases, or vasculitis.~~

4. ~~The method of claim 3, wherein the TLR2-mediated disease or disorder is Kawasaki disease.~~

~~5. The method of claim 4, wherein the method further comprises administering to the subject Intravenous immunoglobulin (IVIG) and/or salicylates.~~

~~64. The method use of any one of claims 4 or claim 51-3, wherein the subject is a human subject that is less than five years old.~~

~~57. The usemethod of any one of claimsclaim 1 - 4, wherein the biological activity of the OxPL comprises activation of CD36-TLR2 apoptosis pathway.~~

~~68. The usemethod of any one of claims 1 - 5to 7, wherein the antibody, antibody fragment, or polypeptide is a single-chain variable fragment (ScFv).~~

~~7. The use of any one of claims 1 - 6, wherein the antibody, antibody fragment or polypeptide is to be administered intravascularly.~~

~~9. The method of any one of claims 1 to 8, wherein the antibody or antibody fragment recognizes and binds to a phosphocholine headgroup of an oxidized phospholipid, wherein the antibody or antibody fragment comprises a variable heavy chain (V_H) domain and/or a variable light chain (V_L) domain, and wherein (a) the V_H domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:6 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:6; SEQ ID NO:7 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:7; and SEQ ID NO:8 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:8; and (b) the V_L domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:9 or 12 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:9 or 12; SEQ ID NO:10 and sequence that are~~

~~at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:10; and SEQ ID NO:11 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:11.~~

~~10. The method of claim 1, wherein the antibody, antibody fragment or polypeptide is administered intravascularly.~~

~~11. The method of claim 9, wherein the V_H domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:6, 7 and 8, and/or the V_L domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:9, 10 and 11, or SEQ ID NO:10, 11 and 12.~~

~~12. The method of claim 9, wherein the antibody or antibody fragment is selected from the group consisting of: (a) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 9, 10 and 11; and (b) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 10, 11 and 12.~~

~~8. The use 13. The method of any one of claims 1 - 78 to 12,~~
wherein the heavy and light chain domains are linked to an Fc or FC2 region.

~~9-14. The use method of any one of the claims 1 - 8 to 13,~~ wherein the antibody fragment comprises a single chain variable fragment ("scFv") that recognizes a phosphocholine headgroup of an oxidized phospholipid.

~~10-15. The method or use of claim 9-14,~~ wherein the scFv is soluble under physiological conditions.

11. The use of any one of claims 1 - 10, wherein: the V_H comprises the CDR amino acid sequences set forth in SEQ ID NO: 6, 7 and 8; and

the VL comprises the CDR amino acid sequences set forth in SEQ ID NO: 9, 10 and 11.

~~16. A method of inhibiting one or more immunopotentiating agent selected from the group consisting of TNF α , CCL5, CCL2, CXCL1, IL-6 and IL12 comprising, administering a therapeutically effective amount of an antibody, antibody fragment, or polypeptide that binds specifically to an oxidative phospholipid (OxPL), wherein the antibody, antibody fragment or polypeptide inhibits the level of the immunopotentiating agent in the plasma of a subject.~~

~~17. The method of claim 17, wherein the antibody, antibody fragment, or polypeptide is a single-chain variable fragment (ScFv).~~

~~18. The method of claim 16 or 17, wherein the antibody or antibody fragment recognizes and binds to a phosphocholine headgroup of an oxidized phospholipid, wherein the antibody or antibody fragment comprises a variable heavy chain (V_H) domain and/or a variable light chain (V_L) domain, and wherein (a) the V_H domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:6 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:6; SEQ ID NO:7 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:7; and SEQ ID NO:8 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:8; and (b) the V_L domain comprises an amino acid sequence that includes one, two or three complementarity determining regions (CDRs) selected from the group consisting of: SEQ ID NO:9 or 12 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:9 or 12; SEQ ID NO:10 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:10; and SEQ ID NO:11 and sequence that are at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to SEQ ID NO:11.~~

~~19. The method of claim 16, wherein the antibody, antibody fragment or polypeptide is administered intravascularly.~~

~~20. The method of claim 18, wherein the V_H domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:6, 7 and 8, and/or the V_L domain comprises an amino acid sequence that includes CDRs comprising SEQ ID NO:9, 10 and 11, or SEQ ID NO:10, 11 and 12.~~

~~21. The method of claim 18, wherein the antibody or antibody fragment is selected from the group consisting of: (a) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 9, 10 and 11; and (b) an antibody or scFv with heavy and light chain domains comprising the complementarity determining regions of SEQ ID NO:6, 7, 8, 10, 11 and 12.~~

~~22. The method of any one of claims 18-21, wherein the heavy and light chain domains are linked to an Fc or FC2 region.~~

~~23. The method of any one of the claims 18-21, wherein the antibody fragment comprises a single chain variable fragment ("scFv") that recognizes a phosphocholine headgroup of an oxidized phospholipid.~~

~~24. The method or use of claim 23, wherein the scFv is soluble under physiological conditions.~~

12. The use of claim 11, wherein: the VH comprises an amino acid sequence that is at least 95% identical to the VH amino acid sequence set forth in SEQ ID NO: 2; and the VL comprises an amino acid sequence that is at least 95% identical to the VL amino acid sequence set forth in SEQ ID NO: 2.

13. The use of claim 11 or 12, wherein: the VH comprises the VH amino acid set forth in SEQ ID NO: 2; and the VL comprises the VL amino acid sequence set forth in SEQ ID NO: 2.

14. The use of any one of claims 1 -10, wherein: the VH comprises the CDR amino acid sequences set forth in SEQ ID NO: 6, 7 and 8; and the VL comprises the CDR amino acid sequences set forth in SEQ ID NO: 12, 10 and 11.

15. The use of claim 14, wherein: the VH comprises an amino acid sequence that is at least 95% identical to the VH amino acid sequence set forth in SEQ ID NO: 4; and the VL comprises an amino acid sequence that is at least 95% identical to the VL amino acid sequence set forth in SEQ ID NO: 4.

16. The use of claim 14 or 15, wherein: the VH comprises the VH amino acid set forth in SEQ ID NO: 4; and the VL comprises the VL amino acid sequence set forth in SEQ ID NO: 4.