may act in atherosclerosis, apoptotic clearance, and protective immunity. J Clin Invest 105, 1731-1740; Shaw et al. 2001. *Human-derived anti-oxidized LDL autoantibody blocks uptake of oxidized LDL by macrophages and localizes to atherosclerotic lesions in vivo.* Arterioscler Thromb Vasc Biol 21, 1333-1339.

Furthermore, an examination of clinical data has demonstrated that low levels of natural IgM anti-PC antibodies are associated with an increased risk of MACE in ACS patients (Frostegard, J. 2010. *Low level natural antibodies against phosphorylcholine: a novel risk marker and potential mechanism in atherosclerosis and cardiovascular disease*. Clin Immunol 134, 47-54).

Accordingly, there is a need for anti-PC antibody molecules that can be effectively used in therapy, particularly fully human anti-PC antibodies suitable for human therapy. To the applicant's knowledge, to date the art has failed to provide therapeutically efficacious human anti-PC antibodies. The identification of such antibodies has been hampered by the fact that *in vitro* screening methods for human antibodies with anti-PC binding activity are poor predictors of *in vivo* therapeutic activity.

In view of this, there is a need in the art for human anti-PC antibody molecules that provide effective and advantageous properties when used in *in vivo* systems, in particular when administered to humans for therapy.

SUMMARY

In one aspect, there is provided a human antibody or antibody fragment capable of binding to phosphorylcholine and/or a phosphorylcholine conjugate, wherein the antibody or antibody fragment comprises a variable heavy chain (VH) domain and a variable light chain (VL) domain, and wherein -

(a) the VH domain comprises an amino acid sequence that includes:

i) a CDR1 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 17;

a CDR2 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 18; and

a CDR3 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 19;

or

ii) a CDR1 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 17;

a CDR2 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 18; and

a CDR3 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 20;

or

iii) a CDR1 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 17;

a CDR2 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 18; and

a CDR3 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 21; or

or

iv) a CDR1 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 17;

a CDR2 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 18; and

a CDR3 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 22; and

(b) the VL domain comprises an amino acid sequence that includes:

i) a CDR4 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 23;

a CDR5 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 25; and

a CDR6 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 26;

or

ii) a CDR4 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 24;

a CDR5 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 25; and

a CDR6 sequence comprising an amino acid sequence having the sequence of SEQ ID NO: 26,

wherein the antibody or antibody fragment binds to aminophenyl-phosphorylcholine immobilized through coupling to the free amine group, with a Kd of no greater than 500nM, when tested using a surface plasmon resonance sensor.

In one aspect, there is provided a pharmaceutical composition comprising or consisting essentially of an antibody or an antibody fragment as described herein and a pharmaceutically acceptable carrier or excipient, optionally wherein the only antibodies or antibody fragments present in the composition are those as described herein.

In one aspect, there is provided an antibody or antibody fragment as described herein, or a pharmaceutical composition as described herein for use in medicine.

In one aspect, there is provided an antibody or antibody fragment as described herein, or a pharmaceutical composition as described herein for use in the prevention, prophylaxis and/or treatment of mammals, including humans, against atherosclerosis, an atherosclerotic related disease or cardiovascular disease.

In one aspect, there is provided a nucleic acid sequence encoding an antibody or an antibody fragment as described herein.

In one aspect, there is provided a vector or plasmid comprising the nucleic acid sequence as described herein.

In one aspect, there is provided a host cell comprising the nucleic acid sequence of as described herein and/or a vector or plasmid as described herein.

In one aspect, there is provided a method of producing an antibody or an antibody fragment as described herein comprising culturing a host cell as described herein, and recovering therefrom an antibody or an antibody fragment as described herein.

In one aspect, there is provided a method of preparing a variant of the antibody or antibody fragments as described herein, which variant retains the ability to bind to phosphorylcholine and/or a phosphorylcholine conjugate with a Kd of no greater than 500nM, when tested using a surface plasmon resonance sensor, the method comprising –

(i) providing a nucleic acid as described herein encoding a parent antibody or antibody fragment;

(ii) introducing one or more nucleotide mutations into the amino acid coding regions of the nucleic acid sequence, optionally within the regions encoding the VH and/or VL domain(s), such that the mutated nucleic acid encodes a variant antibody or antibody fragment having a different amino acid sequence compared to the parent antibody or antibody fragment;

(iii) expressing the variant antibody or antibody fragment that is encoded by the mutated nucleic acid sequence; and

(iv) comparing the ability of the variant antibody or antibody fragment and the parent antibody or antibody fragment to bind to phosphorylcholine and/or a phosphorylcholine conjugate,

wherein the step of assessing the ability of the variant antibody or antibody fragment to bind to phosphorylcholine and/or a phosphorylcholine conjugate further comprises selecting those variants that have substantially equal or enhanced ability to bind to phosphorylcholine and/or a phosphorylcholine conjugate compared to the parent.

DESCRIPTION OF THE INVENTION

The present application describes the production and testing of new antibodies and antibody fragments comprising novel antigen-binding regions capable of binding to phosphorylcholine and/or phosphorylcholine conjugates.

In a first aspect, the present invention provides an antibody or antibody fragment capable of binding to phosphorylcholine and/or a phosphorylcholine conjugate, wherein the antibody or antibody fragment comprises a variable heavy chain (VH) domain and/or a variable light chain (VL) domain, and wherein -

(a) the VH domain comprises an amino acid sequence that includes one, two or preferably three complementarity determining regions (CDRs) selected from the group consisting of: