SPECIFICATION

Humanized monoclonal antibody for inhibiting vascular endothelial lipase enzyme activity

Technical field

[0001] The present invention relates to a humanized monoclonal antibody that inhibits the enzymatic activity of vascular endothelial lipase (hereinafter, referred to also EL) and pharmaceutical compositions containing the same. More specifically, the present invention relates to a humanized monoclonal antibody that selectively inhibits the enzymatic activity of EL, or an antibody fragment thereof, and a pharmaceutical composition containing the same.

Background art

[0002] EL is a phospholipase that belongs to triglyceride lipase (hereinafter, referred to TG) family (non-patent literature: 1). Human EL consists of 500 amino acids (NCBI Accession number NP_006024.1, SEQ ID NO: 1). ELs of non-human mammal include rabbit EL (NCBI Accession number NO_001182567, SEQ ID NO: 2), cynomolgus EL (NCBI Accession No . EHH61805.1), baboon EL (NCBI Accession No . XP_003914420.1) and mouse EL (NCBI Accession No. NP_034850.3). Lipoprotein lipase (hereinafter, referred to LPL) and hepatic lipase (hereinafter, referred to HL) is contained by TG family.

[0003] The analysis of EL knockout mouse and EL transgenic mouse revealed that EL relates to HDL cholesterol (hereinafter, referred to HDL-c) metabolism by its strong phospholipase activity, and have been a focus as a factor which controls HDL-c level in blood (non-patent literature: 2). It has been well-known that there is a negative correlation between coronary artery disease (hereinafter, referred to CAD) and HDL-c level in blood. HDL-c shows anti-artherogenic effect through antioxidant effect, anti-inflammatory effect and reverse cholesterol transport and so on, low HDL-c emia is recognized as one of the risk factor of CAD. Therefore, EL inhibitor could be a therapeutic agent for CAD through increasing HDL-c in blood. In fact, it was reported that lesion mouse of EL knockout increased HDL-c and decreased atherosclerotic lesions (non-patent literature: 3).

These findings indicate that a selective EL inhibitor is useful as therapeutic agent for abnormality of lipid metabolism and arteriosclerosis.

[0004] A selective inhibition of EL is useful as therapeutic agent for abnormality of lipid metabolism and arteriosclerosis, so a production of EL antibodies which inhibit EL activity is one of the important approaches. So far, it has been reported that a rabbit polyclonal antibody which inhibits EL activity was prepared, HDL-c level in mouse blood increased after administrating of the antibody (non-patent literature: 4).

[0005] Polyclonal antibodies recognize various regions of EL and do not have a high selectivity against EL. Also, it is impossible to use rabbit anti-EL polyclonal antibodies having high immunogenicity to human as therapeutic agent for chronic diseases because therapeutic agents for chronic diseases such as the abnormality of lipid metabolism and arteriosclerosis related to EL have to be administrated for a long term. Moreover, it is difficult to manipulate immunogenicity of polyclonal antibodies.

By these circumstances, a monoclonal antibody inhibiting selectively the enzymatic activity of EL is awaited.

[0006]

Non-patent document 1: Nature Genetics., 1999, vol. 21, p. 424

Non-patent document 2: TCM., 2004, vol. 14(5), p. 202-206

Non-patent document 3: The Journal of Biological Chemistry., 2004, vol. 279, No.43, 22 p.45085-45092

Non-patent document 4: J clin Invest., 2003, Vol. 111(3), p. 357

Summary of the invention

Problem to be solved by the invention

[0007] An objective of the present invention is to provide a humanized monoclonal antibody that selectively inhibits enzyme activity of EL, or an antibody fragment thereof, and a pharmaceutical composition containing the same.

Means for solving the problem

[0008] As a result of diligent efforts, the present inventors have succeeded in finding a humanized monoclonal antibody that selectively inhibits the enzymatic activity of EL.

To be more specific, the present invention relates to:

(1) A humanized monoclonal antibody that inhibits the enzymatic activity of vascular endothelial lipase or an antibody fragment thereof, wherein it recognizes amino acid residues at positions of 1 to 157 in the amino acid sequence of SEQ ID NO: 1.

(2) The humanized monoclonal antibody or the antibody fragment thereof of (1), wherein it recognizes amino acid residues at positions of 50 to 100 in the amino acid sequence of SEQ ID NO: 1.

(3) The humanized monoclonal antibody or the antibody fragment thereof of (1) or (2), wherein it recognizes arginine at position 50, asparagine at position 52, arginine at position 54, aspartic acid at position 58, glutamic acid at position 60, histidine at position 61, glycine at position 63, tyrosine at position 65 or asparagine at position 100 in the amino acid sequence of SEQ ID NO: 1.

(4) The humanized monoclonal antibody or the antibody fragment thereof of (1) or (2), wherein it recognizes arginine at position 50, glutamic acid at position 60, histidine at position 61, tyrosine at position 65 or asparagine at position 100 in the amino acid sequence of SEQ ID NO: 1.

(5) The humanized monoclonal antibody or the antibody fragment thereof of (1) or (2), wherein it recognizes tyrosine at position 65 in the amino acid sequence of SEQ ID NO: 1.

(6) A humanized monoclonal antibody that inhibits the enzymatic activity of vascular endothelial lipase or an antibody fragment thereof, wherein it recognizes amino acid residues at positions of 202 to 305 in the amino acid sequence of SEQ ID NO: 1.

(7) The humanized monoclonal antibody or the antibody fragment thereof of (6), wherein it recognizes amino acid residues at positions of 220 to 273 in the amino acid sequence of SEQ ID NO: 1.

(8) The humanized monoclonal antibody or the antibody fragment thereof of (6) or (7), wherein it recognizes histidine at position 220, threonine at position 221, tyrosine at position 222, threonine at position 223, arginine at position 224, phenylalanine at position 226, glycine at position 227, glycine at position 231, isoleucine at position 232, glutamine at position 233, methionine at position 234, aspartic acid at position 240, tyrosine at position 242, proline at position 243, asparagine at position 244, glycine at position 246, glutamine at position 249, proline at position 250, glycine at position 251, leucine at position 254, leucine at position 258, tyrosine at position 263, valine at position 269 or glutamic acid at position 273 in the amino acid sequence of SEQ ID NO: 1.

(9) The humanized monoclonal antibody or the antibody fragment thereof of (6) or (7), wherein it recognizes histidine at position 220, threonine at position 221, aspartic acid at position 240, tyrosine at position 242, proline at position 243, asparagine at position 244, glycine at position 246, glutamine at position 249, proline at position 250 or glycine at position 251 in the amino acid sequence of SEQ ID NO: 1.

(10) The humanized monoclonal antibody or the antibody fragment thereof of (6) or (7), wherein it recognizes histidine at position 220, threonine at position 221, aspartic acid at position 240, tyrosine at position 242, proline at position 243, asparagine at position 244, glycine at position 246, glutamine at position 249, proline at position 250 and glycine at position 251 in the amino acid sequence of SEQ ID NO: 1.

(11) The humanized monoclonal antibody or the antibody fragment thereof of any one of (1) to (10), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC50 of 10 nM or less.

(12) The humanized monoclonal antibody or the antibody fragment thereof of (11), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC50 of 5 nM or less.

(13) The humanized monoclonal antibody or the antibody fragment thereof of (11), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC50 of 2 nM or less.

(14) A humanized monoclonal antibody or an antibody fragment thereof,
selected from the group of
1) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 4, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7.
2) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 4, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 4, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, and

inhibiting the enzymatic activity of vascular endothelial lipase.

4) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 4, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7.

6) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and
inhibiting the enzymatic activity of vascular endothelial lipase.

7) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, and
inhibiting the enzymatic activity of vascular endothelial lipase.

8) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

9) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9.

10) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

11) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, and

inhibiting the enzymatic activity of vascular endothelial lipase.

12) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 8, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

13) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7.

14) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9.

18) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2, the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7.

22) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 7, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9.

26) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, and

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11, the amino acid sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 10, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5, the amino acid sequence of SEQ ID NO: 6 and the amino acid sequence of SEQ ID NO: 9, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 13, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 15, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18.

30) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 13, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 15, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 13, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 15,

wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, and

inhibiting the enzymatic activity of vascular endothelial lipase.

32) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 13, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 15, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18.

34) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, and

inhibiting the enzymatic activity of vascular endothelial lipase.

36) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of

the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21.

38) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino

acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 19, the amino acid sequence of SEQ ID NO: 14 and the amino acid sequence of SEQ ID NO: 20, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18.

42) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21.

46) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22, the amino acid sequence of SEQ ID NO: 23 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

49) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18.

50) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

51) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, and

inhibiting the enzymatic activity of vascular endothelial lipase.

52) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 18, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

53) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21.

54) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

55) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, and

inhibiting the enzymatic activity of vascular endothelial lipase.

56) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25, the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of SEQ ID NO: 24,

wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16, the amino acid sequence of SEQ ID NO: 17 and the amino acid sequence of SEQ ID NO: 21, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

57) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 26, the amino acid sequence of SEQ ID NO: 27 and the amino acid sequence of SEQ ID NO: 28, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 29, the amino acid sequence of SEQ ID NO: 30 and the amino acid sequence of SEQ ID NO: 31.

58) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 26, the amino acid sequence of SEQ ID NO: 27 and the amino acid sequence of SEQ ID NO: 28, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 29, the amino acid sequence of SEQ ID NO: 30 and the amino acid sequence of SEQ ID NO: 31, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

59) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 26, the amino

acid sequence of SEQ ID NO: 27 and the amino acid sequence of SEQ ID NO: 28, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 29, the amino acid sequence of SEQ ID NO: 30 and the amino acid sequence of SEQ ID NO: 31, and

inhibiting the enzymatic activity of vascular endothelial lipase.

60) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 26, the amino acid sequence of SEQ ID NO: 27 and the amino acid sequence of SEQ ID NO: 28, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 29, the amino acid sequence of SEQ ID NO: 30 and the amino acid sequence of SEQ ID NO: 31, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

61) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 32, the amino acid sequence of SEQ ID NO: 33 and the amino acid sequence of SEQ ID NO: 34, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 35, the amino acid sequence of SEQ ID NO: 36 and the amino acid sequence of SEQ ID NO: 37.

62) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 32, the amino acid sequence of SEQ ID NO: 33 and the amino acid sequence of SEQ ID NO: 34, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 35, the amino acid sequence of SEQ ID NO: 36 and the amino acid sequence of SEQ ID NO: 37, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

63) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 32, the amino acid sequence of SEQ ID NO: 33 and the amino acid sequence of SEQ ID NO: 34, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 35, the amino acid sequence of SEQ ID NO: 36 and the amino acid sequence of SEQ ID NO: 37, and

inhibiting the enzymatic activity of vascular endothelial lipase.

64) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 32, the amino acid sequence of SEQ ID NO: 33 and the amino acid sequence of SEQ ID NO: 34, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 35, the amino acid sequence of SEQ ID NO: 36 and the amino acid sequence of SEQ ID NO: 37,

wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

65) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 38, the amino acid sequence of SEQ ID NO: 39 and the amino acid sequence of SEQ ID NO: 40, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 41, the amino acid sequence of SEQ ID NO: 42 and the amino acid sequence of SEQ ID NO: 43.

66) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 38, the amino acid sequence of SEQ ID NO: 39 and the amino acid sequence of SEQ ID NO: 40, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 41, the amino acid sequence of SEQ ID NO: 42 and the amino acid sequence of SEQ ID NO: 43, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

67) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 38, the amino acid sequence of SEQ ID NO: 39 and the amino acid sequence of SEQ ID NO: 40, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 41, the amino acid sequence of SEQ ID NO: 42 and the amino acid sequence of SEQ ID NO: 43, and

inhibiting the enzymatic activity of vascular endothelial lipase.

68) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 38, the amino acid sequence of SEQ ID NO: 39 and the amino acid sequence of SEQ ID NO: 40, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 41, the amino acid sequence of SEQ ID NO: 42 and the amino acid sequence of SEQ ID NO: 43, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

69) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 46, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49.

70) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 46, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

71) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 46, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, and

inhibiting the enzymatic activity of vascular endothelial lipase.

72) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 46, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

73) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 50, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49.

74) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 50, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

75) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 50, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, and

inhibiting the enzymatic activity of vascular endothelial lipase.

76) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 50, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and
inhibiting the enzymatic activity of vascular endothelial lipase.
77) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 51, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49.
78) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 51, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of

the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

79) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 51, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, and

inhibiting the enzymatic activity of vascular endothelial lipase.

80) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 51, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

81) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 52, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 53,

and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49.

82) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 52, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 53, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

83) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 52, the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 53, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, and

inhibiting the enzymatic activity of vascular endothelial lipase.

84) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 52, the amino

acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 53, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47, the amino acid sequence of SEQ ID NO: 48 and the amino acid sequence of SEQ ID NO: 49, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

85) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 54, the amino acid sequence of SEQ ID NO: 55 and the amino acid sequence of SEQ ID NO: 56, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 57, the amino acid sequence of SEQ ID NO: 58 and the amino acid sequence of SEQ ID NO: 59.

86) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 54, the amino acid sequence of SEQ ID NO: 55 and the amino acid sequence of SEQ ID NO: 56, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 57, the amino acid sequence of SEQ ID NO: 58 and the amino acid sequence of SEQ ID NO: 59, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

87) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 54, the amino acid sequence of SEQ ID NO: 55 and the amino acid sequence of SEQ ID NO: 56, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 57, the amino acid sequence of SEQ ID NO: 58 and the amino acid sequence of SEQ ID NO: 59, and

inhibiting the enzymatic activity of vascular endothelial lipase.

88) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 54, the amino acid sequence of SEQ ID NO: 55 and the amino acid sequence of SEQ ID NO: 56, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 57, the amino acid sequence of SEQ ID NO: 58 and the amino acid sequence of SEQ ID NO: 59, wherein one or several amino acids are deleted, substituted or added in at least one of the three CDRs, and

inhibiting the enzymatic activity of vascular endothelial lipase.

(15) A humanized monoclonal antibody or an antibody fragment thereof,

selected from the group of

1) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61.

2) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61 and

inhibiting the enzymatic activity of vascular endothelial lipase.

4) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61.

6) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

7) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61 and

inhibiting the enzymatic activity of vascular endothelial lipase.

8) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
9) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61.
10) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
11) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61, and
inhibiting the enzymatic activity of vascular endothelial lipase.
12) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
13) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64.

14) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61.

18) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64.

22) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61.

26) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, and

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64.

30) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

32) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67.

34) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67, and

inhibiting the enzymatic activity of vascular endothelial lipase.

36) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68.

38) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68, and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69.

42) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69, and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

46) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

49) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

50) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

51) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72 in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, and

inhibiting the enzymatic activity of vascular endothelial lipase.

52) A humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, in

which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

53) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73.

54) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

55) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, and

inhibiting the enzymatic activity of vascular endothelial lipase.

56) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

57) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

58) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

59) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, and

inhibiting the enzymatic activity of vascular endothelial lipase.

60) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

61) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73.

62) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

63) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, and inhibiting the enzymatic activity of vascular endothelial lipase.

64) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

65) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

66) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

67) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, and

inhibiting the enzymatic activity of vascular endothelial lipase.

68) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

69) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 73.
70) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
71) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 73, and
inhibiting the enzymatic activity of vascular endothelial lipase.
72) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 73, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
73) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 76.
74) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 76, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

75) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76, and

inhibiting the enzymatic activity of vascular endothelial lipase.

76) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

77) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

78) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

79) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, and

inhibiting the enzymatic activity of vascular endothelial lipase.

80) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

81) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79.

82) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

83) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79, and

inhibiting the enzymatic activity of vascular endothelial lipase.

84) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

85) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

86) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 80, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
87) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 80, and
inhibiting the enzymatic activity of vascular endothelial lipase.
88) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 80, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
89) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 79.
90) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 79, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
91) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, in

which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79, and

inhibiting the enzymatic activity of vascular endothelial lipase.

92) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

93) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

94) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

95) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, and

inhibiting the enzymatic activity of vascular endothelial lipase.

96) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

97) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83.

98) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

99) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83, and

inhibiting the enzymatic activity of vascular endothelial lipase.

100) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

101) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84.

102) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84, in

which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

103) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84, and

inhibiting the enzymatic activity of vascular endothelial lipase.

104) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

105) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85.

106) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

107) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, and

inhibiting the enzymatic activity of vascular endothelial lipase.

108) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

109) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85.

110) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

111) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, and

inhibiting the enzymatic activity of vascular endothelial lipase.

112) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

113) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 88.

114) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 88, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

115) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

116) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 88, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

117) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 89.

118) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 89 in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

119) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 89, and

inhibiting the enzymatic activity of vascular endothelial lipase.

120) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 89, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

121) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 90.

122) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 90 in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

123) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 90, and

inhibiting the enzymatic activity of vascular endothelial lipase.

124) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 90, in

which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

125) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92.

126) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

127) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, and

inhibiting the enzymatic activity of vascular endothelial lipase.

128) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

129) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92.

130) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

131) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, and

inhibiting the enzymatic activity of vascular endothelial lipase.

132) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

133) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94.

134) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

135) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, and

inhibiting the enzymatic activity of vascular endothelial lipase.

136) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

137) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94.

138) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

139) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, and

inhibiting the enzymatic activity of vascular endothelial lipase.

140) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

141) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 95, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96.

142) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 95, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

143) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 95, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

144) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 95, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

145) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 97, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96.

146) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 97, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

147) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 97, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

148) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 97, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

149) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 98, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96.

150) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 98, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

151) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 98, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

152) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 98, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

153) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96.

154) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

155) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

156) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

157) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 101.

158) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 101, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

159) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 101, and

inhibiting the enzymatic activity of vascular endothelial lipase.

160) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 101, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

161) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 102.

162) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 102 in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

163) A humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 102, and

inhibiting the enzymatic activity of vascular endothelial lipase.

164) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 102, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

165) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 103.

166) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 103, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

167) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 103, and

inhibiting the enzymatic activity of vascular endothelial lipase.

168) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 103, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

169) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 104.

170) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 104, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

171) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 104, and

inhibiting the enzymatic activity of vascular endothelial lipase.

172) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 104, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

173) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 105.

174) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 105, in which one or several amino acids are deleted, substituted or added, and

inhibiting the enzymatic activity of vascular endothelial lipase.

175) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 105, and
inhibiting the enzymatic activity of vascular endothelial lipase.
176) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, in which one or several amino acids are deleted, substituted or added, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 105, in which one or several amino acids are deleted, substituted or added, and
inhibiting the enzymatic activity of vascular endothelial lipase.
(16) A humanized monoclonal antibody or an antibody fragment thereof,
selected from the group of
1) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 64.
2) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 67.
3) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 68.
4) A humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 69.
5) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64.

6) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67.

7) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68.

8) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69.

9) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67.

10) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68.

11) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69.

12) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67.

13) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68.

14) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69.

15) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73.

16) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

17) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79.

18) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

19) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

20) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

21) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79.

22) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

23) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

24) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

25) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79.

26) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

27) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

28) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78.

29) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79.

30) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

31) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

32) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73.

33) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

34) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71.

35) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73.

36) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

37) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80.

38) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83.

39) A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84.

(17) The pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody fragment thereof of any one of (1) to (16).

(18) The pharmaceutical composition of (17), wherein the disease related to vascular endothelial lipase is dyslipidemia.

(19) The humanized monoclonal antibody or the antibody fragment thereof of any one of (1) to (16) for the treatment or prevention of a disease related to vascular endothelial lipase.

(20) The humanized monoclonal antibody or the antibody fragment thereof of (19), wherein the disease related to vascular endothelial lipase is dyslipidemia.

(21) A method for the treatment or prevention of a disease related to vascular endothelial lipase characterized by administering to a humanized monoclonal antibody or the antibody fragment thereof of any one of (1) to (16).

(21) The method of (21), wherein the disease related to vascular endothelial lipase is dyslipidemia.

Effect of the invention

[0009] As a humanized monoclonal antibody of the present invention has the activity for selectively inhibiting enzymatic activity of EL, pharmaceutical compositions containing the humanized monoclonal antibody of the present invention is very useful as a drug, especially a drug for prevention and/or treatment of dyslipidemia, hyperlipidemia,

arteriosclerosis, atherosclerosis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity and/or syndrome X.

Brief explanation of drawings

[0010] [Fig. 1A] Fig. 1A shows measurement results of inhibition of enzymatic activity of 55A1 antibody against cynomolgus EL, baboon EL and human (1-157) mouse chimera EL.

[Fig. 1B] Fig. 1B shows measurement results of inhibition of enzymatic activity of 7D4 antibody against cynomolgus EL, baboon EL and human (1-157) mouse chimera EL.

[Fig. 1C] Fig. 1C shows measurement results of inhibition of enzymatic activity of 14A1 antibody against cynomolgus EL, baboon EL and human (1-157) mouse chimera EL.

[Fig. 1D] Fig. 1D shows measurement results of inhibition of enzymatic activity of 2D5 antibody against cynomolgus EL, baboon EL and human (1-157) mouse chimera EL.

[Fig. 1E] Fig. 1E shows measurement results of inhibition of enzymatic activity of 53A11 antibody against cynomolgus EL, baboon EL and human (1-157) mouse chimera EL.

[Fig. 1F] Fig. 1F shows measurement results of inhibition of enzymatic activity of 13B3 antibody against cynomolgus EL, baboon EL, rabbit EL and human (1-157) mouse chimera EL.

[Fig. 1G] Fig. 1G shows measurement results of inhibition of enzymatic activity of 23H8 antibody against cynomolgus EL, baboon EL, rabbit EL and human (1-157) mouse chimera EL.

[Fig. 1H] Fig. 1H shows measurement results of inhibition of enzymatic activity of 16B3 antibody against cynomolgus EL, baboon EL, rabbit EL, human (1-157) mouse chimera EL and human (1-305) mouse chimera EL.

[Fig. 1I] Fig. 1I shows measurement results of inhibition of enzymatic activity of 16E7 antibody against cynomolgus EL, baboon EL, rabbit EL, human (1-157) mouse chimera EL and human (1-305) mouse chimera EL.

[Fig. 1J] Fig. 1J shows measurement results of inhibition of enzymatic activity of

14E1 antibody against cynomolgus EL, baboon EL, rabbit EL, human (1-157) mouse chimera EL and human (1-305) mouse chimera EL

[Fig. 1K] Fig. 1K shows measurement results of inhibition of enzymatic activity of 19E7 antibody against cynomolgus EL, baboon EL, rabbit EL, human (1-157) mouse chimera EL and human (1-305) mouse chimera EL

[Fig. 2A] Fig. 2A shows measurement results of inhibition of enzymatic activity of 55A1 antibody against human HL and human LPL.

[Fig. 2B] Fig. 2B shows measurement results of inhibition of enzymatic activity of 7D4 antibody against human HL and human LPL.

[Fig. 2C] Fig. 2C shows measurement results of inhibition of enzymatic activity of 14A1 antibody against human HL and human LPL.

[Fig. 2D] Fig. 2D shows measurement results of inhibition of enzymatic activity of 2D5 antibody against human HL and human LPL.

[Fig. 2E] Fig. 2E shows measurement results of inhibition of enzymatic activity of 53A11 antibody against human HL and human LPL.

[Fig. 2F] Fig. 2F shows measurement results of inhibition of enzymatic activity of 13B3 antibody against human HL and human LPL.

[Fig. 2G] Fig. 2G shows measurement results of inhibition of enzymatic activity of 23H8 antibody against human HL and human LPL.

[Fig. 2H] Fig. 2H shows measurement results of inhibition of enzymatic activity of 16B3 antibody against human HL and human LPL.

[Fig. 2I] Fig. 2I shows measurement results of inhibition of enzymatic activity of 16E7 antibody against human HL and human LPL.

[Fig. 2J] Fig. 2J shows measurement results of inhibition of enzymatic activity of 14E1 antibody against human HL and human LPL.

[Fig. 2K] Fig. 2K shows measurement results of inhibition of enzymatic activity of 19E7 antibody human HL and human LPL.

[Fig. 2L] Fig. 2L shows measurement results of inhibition of enzymatic activity of 16F6 antibody human HL and human LPL.

[Fig. 3A] Fig. 3A shows measurement results of binding activity of 55A1 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3B] Fig. 3B shows measurement results of inhibition of enzymatic activity of 7D4 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3C] Fig. 3C shows measurement results of inhibition of enzymatic activity of 14A1 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3D] Fig. 3D shows measurement results of inhibition of enzymatic activity of 2D5 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3E] Fig. 3E shows measurement results of inhibition of enzymatic activity of 53A11 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3F] Fig. 3F shows measurement results of inhibition of enzymatic activity of 13B3 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3G] Fig. 3G shows measurement results of inhibition of enzymatic activity of 23H8 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL and human (1-157) mouse chimera EL.

[Fig. 3H] Fig. 3H shows measurement results of inhibition of enzymatic activity of 16B3 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL, human (1-157) mouse chimera EL, human (1-305) mouse chimera EL and human (202-500) mouse chimera EL.

[Fig. 3I] Fig. 3I shows measurement results of inhibition of enzymatic activity of 16E7 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL, human (1-157) mouse chimera EL, human (1-305) mouse chimera EL and human (202-500) mouse chimera EL.

[Fig. 3J] Fig. 3J shows measurement results of inhibition of enzymatic activity of 14E1 antibody against cynomolgus EL, baboon EL, rabbit EL, mouse EL, human (1-157) mouse chimera EL, human (1-305) mouse chimera EL and human (202-500) mouse chimera EL.

[Fig. 3K] Fig. 3K shows measurement results of inhibition of enzymatic activity of 19E7 antibody against cynomolgus EL, baboon EL, rabbit EL, human (1-157) mouse

chimera EL and human (1-305) mouse chimera EL.

[Fig. 3L] Fig. 3L shows measurement results of inhibition of enzymatic activity of 16F6 antibody against cynomolgus EL, human (1-305) mouse chimera EL and human (187-500) mouse chimera EL.

[Fig. 4A] Fig. 4A shows the amino acid sequences of the variable regions of 55A1 antibody.

[Fig. 4B] Fig. 4B shows the amino acid sequences of the variable regions of 7D4 antibody.

[Fig. 4C] Fig. 4C shows the amino acid sequences of the variable regions of 14A1 antibody.

[Fig. 4D] Fig. 4D shows the amino acid sequences of the variable regions of 2D5 antibody.

[Fig. 4E] Fig. 4E shows the amino acid sequences of the variable regions of 53A11 antibody.

[Fig. 4F] Fig. 4F shows the amino acid sequences of the variable regions of 13B3 antibody.

[Fig. 4G] Fig. 4G shows the amino acid sequences of the variable regions of 23H8 antibody.

[Fig. 4H] Fig. 4H shows the amino acid sequences of the variable regions of 16B3 antibody.

[Fig. 4I] Fig. 4I shows the amino acid sequences of the variable regions of 16E7 antibody.

[Fig. 4J] Fig. 4J shows the amino acid sequences of the variable regions of 14E1 antibody.

[Fig. 4K] Fig. 4K shows the amino acid sequences of the variable regions of 19E7 antibody.

[Fig. 4L] Fig. 4L shows the amino acid sequences of the variable regions of 16F6 antibody.

[Fig. 5A] Fig. 5A shows an alignment of the amino acid sequences of heavy chain variable region of 55A1 antibody, 7D4 antibody, 14A1 antibody and 2D5 antibody.

[Fig. 5B] Fig. 5B shows an alignment of the amino acid sequences of light chain variable region of 55A1 antibody, 7D4 antibody, 14A1 antibody and 2D5 antibody.

[Fig. 5C] Fig. 5C shows an alignment of the amino acid sequences of heavy chain variable region of 53A11 antibody, 13B3 antibody and 23H8 antibody.

[Fig. 5D] Fig. 5D shows an alignment of the amino acid sequences of light chain variable region of 53A11 antibody, 13B3 antibody and 23H8 antibody.

[Fig. 6A] Fig. 6A shows an alignment of the amino acid sequences of heavy chain variable region of 16B3 antibody and 16E7 antibody.

[Fig. 6B] Fig. 6B shows an alignment of the amino acid sequences of light chain variable region of 16B3 antibody and 16E7 antibody.

[Fig. 6C] Fig. 6C shows an alignment of the amino acid sequences of heavy chain variable region of 14E1 antibody and 19E1 antibody.

[Fig. 6D] Fig. 6D shows an alignment of the amino acid sequences of light chain variable region of 14E1 antibody and 19E1 antibody.

[Fig. 7A] Fig. 7A shows binding activity of 55A1 antibody against baboon EL that was introduced mutation.

[Fig. 7B] Fig. 7B shows binding activity of 7D4 antibody against baboon EL that was introduced mutation.

[Fig. 7C] Fig. 7C shows binding activity of 14A1 antibody against baboon EL that was introduced mutation.

[Fig. 7D] Fig. 7D shows binding activity of 2D5 antibody against baboon EL that was introduced mutation.

[Fig. 7E] Fig. 7E shows binding activity of 53A11 antibody against baboon EL that was introduced mutation.

[Fig. 7F] Fig. 7F shows binding activity of 13B3 antibody against baboon EL that was introduced mutation.

[Fig. 7G] Fig. 7G shows binding activity of 23H8 antibody against baboon EL that was introduced mutation.

[Fig. 7H] Fig. 7H shows binding activity of 16B3 antibody against baboon EL that was introduced mutation.

[Fig. 7I] Fig. 7I shows binding activity of 16E7 antibody against baboon EL that was introduced mutation.

[Fig. 7J] Fig. 7J shows binding activity of 14E1 antibody against baboon EL that was introduced mutation.

[Fig. 7K] Fig. 7K shows binding activity of 19E7 antibody against baboon EL that was introduced mutation.

[Fig. 7L] Fig. 7L shows binding activity of 16F6 antibody against baboon EL that was introduced mutation.

[Fig. 8A] Fig. 8A shows an alignment of the amino acid sequences of heavy chain variable region of h16B3-S1 –S7 antibody.

[Fig. 8B] Fig. 8B shows an alignment of the amino acid sequences of light chain variable region of h16B3-S1 –S7 antibody.

[Fig. 8C] Fig. 8C shows an alignment of the amino acid sequences of heavy chain variable region of h16B3-F1 –F3 antibody.

[Fig. 8D] Fig. 8D shows an alignment of the amino acid sequences of light chain variable region of h16B3-F1 –F3 antibody.

[Fig. 9A] Fig. 9A shows an alignment of the amino acid sequences of heavy chain variable region of h55A1-S1 –S7 antibody.

[Fig. 9B] Fig. 9B shows an alignment of the amino acid sequences of light chain variable region of h55A1-S1 –S7 antibody.

[Fig. 9C] Fig. 9C shows an alignment of the amino acid sequences of heavy chain variable region of h55A1-F1 –F6 antibody.

[Fig. 9D] Fig. 9D shows an alignment of the amino acid sequences of light chain variable region of h55A1-F1 –F6 antibody.

[Fig. 10A] Fig. 10A shows an alignment of the amino acid sequences of heavy chain variable region of h53A11-S1 –S4 antibody.

[Fig. 10B] Fig. 10B shows an alignment of the amino acid sequences of light chain variable region of h53A11-S1 –S4 antibody.

[Fig. 11A] Fig. 11A shows an alignment of the amino acid sequences of heavy chain variable region of h23H8-S1 –S3 antibody.

[Fig. 11B] Fig. 11B shows an alignment of the amino acid sequences of light chain variable region of h23H8-S1 –S3 antibody.

[Fig. 12A] Fig. 12A shows an alignment of the amino acid sequences of heavy chain variable region of h13B3-S1 –S4 antibody.

[Fig. 12B] Fig. 12B shows an alignment of the amino acid sequences of light chain variable region of h13B3-S1 –S4 antibody.

[Fig. 13A] Fig. 13A shows an alignment of the amino acid sequences of heavy chain variable region of h12B10-S1 –S4 antibody.

[Fig. 13B] Fig. 13B shows an alignment of the amino acid sequences of light chain variable region of h12B10-S1 –S4 antibody.

[Fig. 14A] Fig. 14A shows an alignment of the amino acid sequences of heavy chain variable region of h16F6-S1 –S5 antibody.

[Fig. 14B] Fig. 14B shows an alignment of the amino acid sequences of light chain variable region of h16F6-S1 –S5 antibody.

[Fig. 15A] Fig. 15A shows the amino acid sequences of the variable regions of h16b3-S1 antibody.

[Fig. 15B] Fig. 15B shows the amino acid sequences of the variable regions of h16b3-S2 antibody.

[Fig. 15C] Fig. 15C shows the amino acid sequences of the variable regions of h16b3-S3 antibody.

[Fig. 15D] Fig. 15D shows the amino acid sequences of the variable regions of h16b3-S4 antibody.

[Fig. 15E] Fig. 15E shows the amino acid sequences of the variable regions of h16b3-S5 antibody.

[Fig. 15F] Fig. 15F shows the amino acid sequences of the variable regions of h16b3-S6 antibody.

[Fig. 15G] Fig. 15G shows the amino acid sequences of the variable regions of h16b3-S7 antibody.

[Fig. 15H] Fig. 15H shows the amino acid sequences of the variable regions of h16b3-S8 antibody.

[Fig. 15I] Fig. 15I shows the amino acid sequences of the variable regions of h16b3-F1 antibody.

[Fig. 15J] Fig. 15J shows the amino acid sequences of the variable regions of h16b3-F2 antibody.

[Fig. 15K] Fig. 15K shows the amino acid sequences of the variable regions of h16b3-F3 antibody.

[Fig. 15F] Fig. 15F shows the amino acid sequences of the variable regions of h16b3-S6 antibody.

[Fig. 15G] Fig. 15G shows the amino acid sequences of the variable regions of h16b3-S7 antibody.

[Fig. 16A] Fig. 16A shows the amino acid sequences of the variable regions of h55A1-S1 antibody.

[Fig. 16B] Fig. 16B shows the amino acid sequences of the variable regions of h55A1-S2 antibody.

[Fig. 16C] Fig. 16C shows the amino acid sequences of the variable regions of h55A1-S3 antibody.

[Fig. 16D] Fig. 16D shows the amino acid sequences of the variable regions of h55A1-S4 antibody.

[Fig. 16E] Fig. 16E shows the amino acid sequences of the variable regions of h55A1-S5 antibody.

[Fig. 16F] Fig. 16F shows the amino acid sequences of the variable regions of h55A1-S6 antibody.

[Fig. 16G] Fig. 16G shows the amino acid sequences of the variable regions of h55A1-S7 antibody.

[Fig. 16H] Fig. 16H shows the amino acid sequences of the variable regions of h55A1-F1 antibody.

[Fig. 16I] Fig. 16I shows the amino acid sequences of the variable regions of h55A1-F2 antibody.

[Fig. 16J] Fig. 16J shows the amino acid sequences of the variable regions of h55A1-F3 antibody.

[Fig. 16K] Fig. 16K shows the amino acid sequences of the variable regions of h55A1-F4 antibody.

[Fig. 16L] Fig. 16L shows the amino acid sequences of the variable regions of h55A1-F5 antibody.

[Fig. 16M] Fig. 16M shows the amino acid sequences of the variable regions of h55A1-F6 antibody.

[Fig. 17A] Fig. 17A shows the amino acid sequences of the variable regions of h53A11-S1 antibody.

[Fig. 17B] Fig. 17B shows the amino acid sequences of the variable regions of h53A11-S2 antibody.

[Fig. 17C] Fig. 17C shows the amino acid sequences of the variable regions of h53A11-S3 antibody.

[Fig. 17D] Fig. 17D shows the amino acid sequences of the variable regions of h53A11-S4 antibody.

[Fig. 18A] Fig. 18A shows the amino acid sequences of the variable regions of h23H8-S1 antibody.

[Fig. 18B] Fig. 18B shows the amino acid sequences of the variable regions of h23H8-S2 antibody.

[Fig. 18C] Fig. 18C shows the amino acid sequences of the variable regions of h23h8-S3 antibody.

[Fig. 19A] Fig. 19A shows the amino acid sequences of the variable regions of h13B3-S1 antibody.

[Fig. 19B] Fig. 19B shows the amino acid sequences of the variable regions of h13B3-S2 antibody.

[Fig. 19C] Fig. 19C shows the amino acid sequences of the variable regions of h13B3-S3 antibody.

[Fig. 19D] Fig. 19D shows the amino acid sequences of the variable regions of h13B3-S4 antibody.

[Fig. 20A] Fig. 20A shows the amino acid sequences of the variable regions of h12B10-S1 antibody.

[Fig. 20B] Fig. 20B shows the amino acid sequences of the variable regions of h12B10-S2 antibody.

[Fig. 20C] Fig. 20C shows the amino acid sequences of the variable regions of h12B10-S3 antibody.

[Fig. 20D] Fig. 20D shows the amino acid sequences of the variable regions of h12B10-S4 antibody.

[Fig. 21A] Fig. 21A shows the amino acid sequences of the variable regions of h16F6-S1 antibody.

[Fig. 21B] Fig. 21B shows the amino acid sequences of the variable regions of h16F6-S2 antibody.

[Fig. 21C] Fig. 21C shows the amino acid sequences of the variable regions of h16F6-S3 antibody.

[Fig. 21D] Fig. 21D shows the amino acid sequences of the variable regions of h16F6-S4 antibody.

[Fig. 21E] Fig. 21E shows the amino acid sequences of the variable regions of h16F6-S5 antibody.

Mode for carrying out the invention

[0011] The present invention provides a humanized monoclonal antibody characterized by selectively inhibiting the enzymatic activity of vascular endothelial lipase. As the monoclonal antibody of the present invention has the activity for selectively inhibiting enzymatic activity of vascular endothelial lipase, it is very useful as a drug for prevention or treatment of arteriosclerosis or metabolic syndrome.

[0012] It is important to use peptide having consecutive amino acid residues containing the amino acid sequence at positions of 1 to 157 or 202 to 305 region in the amino acid sequence of SEQ ID NO: 1 as antigen to produce a monoclonal antibody of the present invention. The length is not particularly limited, but six or more residues which have immunogenicity are desired. We can use naturally or artificially highly expressed cell lines, these membrane fractions, these purified products, fusion proteins with other proteins or peptides (for examples, tag proteins such as FLAG-tag, HIS-tag, GST-tag or C2tag etc. or fluorescent proteins such as GFP or EGFP etc.) , or chemically synthesized peptides as specific examples of these antibodies. In addition, preparation methods of these immunogens are known to those skilled in the art.

[0013] The monoclonal antibody of the present invention may be prepared by an known commonly used production method. Concretely, a mammal, preferably, mouse, rat, hamster, guinea pig, rabbit, cat, dog, pig, goat, sheep, donkey, horse or bovine, more preferably mouse, rat, hamster, guinea pig or rabbit is immunized with an immunogen of the present invention, together with Freund's adjuvant as necessary, by one or several times of subcutaneous, intramuscular, intravenous, intrafootpad or intraperitoneal injection. Usually, immunization is conducted once to four times every about 1 to 21 days after primary immunization, and antibody producing cells may be acquired from the immunized mammal after about 1 to 10 days from the final immunization. The number of times and time interval of immunization may be appropriately changed depending on the property of the immunogen being used.

[0014] Hybridoma that secrets monoclonal antibody may be prepared according to the Kohler and Milstein's method (Nature, 1975, vol. 256, p. 495-497) and a corresponding method. That is, hybridoma may be prepared by cell fusion between an antibody producing cell contained in spleen, lymph node, bone marrow, tonsil or the like, preferably in spleen acquired from a mammal immunized as described above, and a myeloma cell lacking autoantibody producing ability derived, preferably from a mammal such as mouse, rat, guinea pig, hamster, rabbit or human, more preferably from mouse, rat or human.

As a myeloma cell used in cell fusion, generally, cell lines obtained from mouse, for example, P3-U1, NS-1, SP-2, 653, X63, AP-1 and the like may be used.

[0015] Hybridoma that produces monoclonal antibody is screened by culturing a hybridoma, for example, in a microtiter plate, measuring reactivity to an immunogen used in mouse immunization as described above in culture supernatant in the well where proliferation is observed, by a measuring method such as RIA, ELISA or FACS and selecting a clone that produces a monoclonal antibody exhibiting specific affinity with the immunogen or hapten. When measuring the said reactivity, an immunogen is usually solid-phased, and an antibody in culture supernatant that binds to the solid-phased immunogen is detected by an anti-mouse secondary antibody labeled with a radioactive substance, a fluorescent substance or an enzyme. Further in the case of using the cells expressing the immunogen, we add the hybridoma culture supernatant to the cells, then after reacting with secondary antibodies labeled with a fluorescent, we can detect a monoclonal antibody of the present invention that binds to the immunogen on the cell membrane by measuring fluorescence intensity of the cells with fluorescence detection apparatus such as flow cytometry or the like.

[0016] Production of monoclonal antibody from selected hybridoma may be achieved by culturing hybridoma *in vitro* or in ascites of mouse, rat, guinea pig, hamster or rabbit, preferably of mouse or rat, or more preferably of mouse, followed by isolation from the obtained culture supernatant or ascites of mammal. In the case of *in vitro* culture, the hybridoma may be cultured in a known nutrient medium or in any nutrient cultures derived and prepared from a known base medium used for proliferating, maintaining and storing hybridoma and for producing monoclonal antibody in culture supernatant, depending on various conditions such as property of cultured cell species, object of the test research and culturing method.

[0017] As a base medium, for example, low-calcium media such as Ham'F12 medium, MCDB153 medium or low-calcium MEM culture, and high-calcium media such as MCDB104 medium, MEM medium, D-MEM medium, RPMI1640 medium, AF104 medium, or RD medium can be recited, and such a base medium may contain, for example, serum, hormone, cytokine and/or various inorganic or organic substances depending on the object.

[0018] Isolation and purification of monoclonal antibody may be achieved by subjecting the culture supernatant or ascites as described above to saturated ammonium sulfate, ion exchange chromatography (e.g., DEAE or DE52), affinity column chromatography such as anti-immunoglobulin column or protein A column or the like.

[0019] As a monoclonal antibody of the present invention, a recombinant antibody that is produced using gene recombination technique in such a manner that an antibody gene is cloned from antibody producing cell, for example, hybridoma, and incorporated into an appropriate vector, and the vector is introduced into a host may be used (for example, Carl et al., THERAPEUTIC MONOCLONAL ANTIBODIES, published in 1990).

[0020] Concretely, from a hybridoma that produces an objective antibody, or from an immune cell that produces an antibody, for example, from a cell obtained by immortalizing sensitized lymphocyte or the like by cancer gene or the like, mRNA encoding a variable region (V region) of antibody is isolated. In isolation of mRNA, whole RNA is prepared by a known method, for example, by guanidine ultracentrifugation (Chirgwin, J. M. et al., Biochemistry (1979) 18, 5294-5299) or the like, and mRNA is prepared by using mRNA Purification Kit (available from Pharmacia) or the like.

[0021] From the obtained mRNA, cDNA of antibody V region is synthesized using a reverse transcriptase. Synthesis of cDNA may be conducted using AMV Reverse Transcriptase First-strand cDNA Synthesis Kit or the like. Further, for synthesis and amplification of cDNA, 5'-Ampli FINDER RACEKit (available from Clonetech) and 5'-RACE method using PCR (Frohman, M. A. et al, Proc. Natl. Acad. Sci. USA 1988, vol. 85, p. 8998) may be used. An objective DNA fragment is purified from the obtained PCR product, and connected with vector DNA. A recombinant vector is thus created and introduced into E. coli or the like, and a colony is selected and a desired recombinant vector is prepared. DNA base sequence of objective DNA is verified by a known method, for example, by deoxy method.

[0022] If DNA encoding V region of objective antibody is obtained, the DNA is connected with DNA encoding a desired antibody constant region (C region), and incorporated into an expression vector. Alternatively, DNA encoding V region of antibody may be incorporated into an expression vector containing DNA of antibody C region. For production of antibody used in the present invention, antibody gene is incorporated into an expression vector in such a manner that it is expressed under control of an expression control region, for example, enhancer/promoter. Next, a host cell can be transformed with this expression vector to cause expression of antibody.

[0023] For expression of antibody gene, heavy chain (H chain) or light chain (L chain) of antibody may be separately incorporated into expression vectors, or a host may be co-transformed with these expression vectors, or DNA encoding H chain and L chain may be incorporated into a single expression vector to transform a host with the resultant expression vector (see WO94/11523).

[0024] Preparation method of a monoclonal antibody of the present invention other than the above can be also used so called phage display technology. Concretely, for example antibody gene library prepared as a material human or animal (for example, rabbit, mouse, rat, hamster or the like) B lymphosate by known method or completely synthesized antibody gene library prepared from selected and modified human or animal germ line sequence is presented to the cell surface, on the ribosome or the like of bacteriophage, Escherichia coli, yeast, animal cells or the like. In this case, the forms of the antibody to be presented on the cell surface are listed IgG molecules, IgM molecules, Fab fragments, single chain Fv (scFv) fragments, *etc.*

[0025] We can obtain antibody genes by rearranging thus obtained monoclonal antibody fragment to the corresponding region of the IgG antibody gene by a known method. And we incorporate thus genes obtained in this manner into a suitable vector, introduce the vector into the host, we can prepare the antibody with recombinant DNA techniques (for examples, see Carl *et.al.* THERAPEUTIC MONOCLONAL ANTIBODIES, 1990 issue).

[0026] The monoclonal antibody of the present invention is characterized in being selective for the inhibition of the enzymatic activity of vascular endothelial lipase. Below, we show an example of a procedure for measuring ability of inhibiting the enzymatic activity of EL.

[0027] The DNA encoding EL is cloned into pcDNA3.1 expression vector (Invitrogen).

The expression vector is transfected into HEK293F cells and culture at 37°C、8% CO2 for 2days. The cell cultures are centrifuged, the cells are collected, and the cells are suspended with PBS containing 20U/mL of Heparin. The cell suspension is incubated at 37°C for 45 min. The supernatant obtained by removing cells with centrifugation is used as human EL enzyme solution to measure inhibitory activity.

After adding a monoclonal antibody to the solution containing 20 mM Tris-HCl Buffer (pH 7.5), 0.5% bovine serum albumin, 4mM CaCl2, 150mM NaCl and 2mg/mL human HDL (Athens Research&Techonology), EL enzyme solution is added . After reaction at 37°C for 2hr, free fatty acid (NEFA) made from HDL by EL enzyme is determined using NEFA C-test Wako (Wakojyunyakukougyo), the NFFA amount is used as enzyme activity index. Enzyme activity in the case of adding no antibody was determined as control value and the specific activity is calculated against the control value at each concentration of the antibody. The concentration where 50% of the antibody is inhibited can be calculated from the inhibition curve.

[0028] Effective concentration (IC50) of antibody which shows 50% inhibition of EL enzyme activity is often used as an indicator of EL inhibitory activity.

[0029] In the present invention, a monoclonal antibody or an antibody fragment thereof inhibiting the enzymatic activity of vascular endothelial lipase with an IC50 of 10 nM or less means a monoclonal antibody or a fragment thereof showing IC50 of 10 nM or less measured by method of said [0028]. Any species EL may be used for the measurement if the EL is derived from a mammal. If a monoclonal antibody or an antibody fragment thereof inhibits the enzymatic activity of EL of any kind of mammal species with an IC50 of 10 nM or less, the monoclonal antibody or an antibody fragment thereof is a monoclonal antibody or an antibody fragment thereof showing IC50 of 10 nM or less.

[0030] And the monoclonal antibody of the present invention is characterized in being selective for the inhibition of the enzymatic activity of EL. Below, we show an example of a confirmation procedure for measuring ability of selectively inhibiting the enzymatic activity of EL, in other words, not inhibiting the enzymatic activity of LPL or HL.

[0031] The DNA encoding HL is cloned into pcDNA3.1 expression vector (Invitrogen). The expression vector is transfected into HEK293F cells and culture at 37 °C、8 % CO2 for 2 days. The cell cultures are centrifuged, the cells are collected, and the cells are suspended with PBS containing 20 U/mL of Heparin. The cell suspension is incubated at

37 °C for 45 min. The supernatant obtained by removing cells with centrifugation is used as human HL enzyme solution. LPL enzyme solution is prepared by using the same procedures. After adding a monoclonal antibody to the solution containing 20 mM Tris-HCl Buffer (pH 7.5), 0.5 % bovine serum albumin, 4 mM CaCl2, 150 mM NaCl and 0.5mg/mL human VLDL (INTRACEL), HL or LPL enzyme solution is added. After reaction at 37 °C for 2 hr, free fatty acid (NEFA) made from VLDL by HL or LPL enzyme is determined using NEFA C-test Wako (Wakojyunyakukougyo), the NFFA amount is used as enzyme activity index. Enzyme activity in the case of adding no antibody was determined as control value and the specific activity is calculated against the control value at each concentration of antibody.

[0032] Being selective for the inhibition of the enzymatic activity of EL means inhibiting not more than 3 % LPL or HL enzymatic activities, when the monoclonal antibody are added at a concentration equal to IC50 against EL. An epitope region of a monoclonal antibody of the present invention is preferably the region of EL that has not homology with LPL or HL because a monoclonal antibody of the present invention is characterized by not inhibiting enzyme activity of LPL and HL, and is characterized in being selective for the inhibition of enzyme activity of EL.

[0033] The humanized monoclonal antibody of the present invention is a humanized version of monoclonal antibody having above described feature. A humanized monoclonal antibody is obtained by transplanting a complementarity determining region (CDR) of antibody of a mammal other than human, for example, of a mouse, into CDR of human antibody. Therefore, framework region derives from human antibody. Suitable framework can be selected according to documents of Kabat E.A. et al. FR can be selected in such a manner that CDR can form appropriate antigen-binding site. If necessary, amino acid of FR of variable region may be substituted in such a manner that CDR of reconstructed humanized antibody can form appropriate antigen-binding site (Sato, K. et al., Cancer Res. 1993, vol.53. p851). The proportion of substituted amino acids of the FR is 0 to 15 % of all FR region, preferably 0 to 5 % of all FR region.

[0034] General production method for humanized monoclonal antibody is also known (for example, WO95/14041 and WO96/02576 etc.). Concretely, DNA sequence, encoding variable region designed to connect CDR of mouse antibody with FR of human antibody, is synthesized by PCR method from several oligonucleotides

prepared to have overlapping parts in their terminals (refer to WO98/13388). Obtained DNA is connected to DNA encoding constant region of human antibody and the resultant DNA is incorporated into expression vector. Alternatively, DNA encoding variable region of antibody may be incorporated into expression vector comprising DNA encoding constant region of antibody. To prepare for antibody of the present invention, antibody gene may be incorporated into an expression vector to express under control of an expression control region, for example enhancer/promoter. Further, the host cells are transformed with this expression vector and could thus produce antibody. As host cell, vertebrate cell such as COS cells or CHO cells, procaryotic cell or yeast can be recited.

[0035] For expression of antibody gene, genes of heavy chain (H chain) and light chain (L chain) of antibody may be separately incorporated into expression vectors, and a host may be transformed simultaneously with these expression vectors, or DNA encoding H chain and L chain may be incorporated into a single expression vector to transform a host with the resultant expression vector (see WO94/11523).

[0036] Desirable transformants, obtained by methods previously described, can be cultured by the methods known for the skilled person. By this culture, humanized monoclonal antibody against PcrV is produced in the transformants or outside the cells. Medium for the culture can be selected from conventional mediums appropriately depending on the host cell. In the case of above described COS cells, medium such as RPMI-1640, Dulbecco's Modified Eagle Minimum Essential Medium (DMEM), are available and if necessary, the serum ingredients likewise Fetal Bovine Serum (FBS) can be added. The temperature for cultivating the transformants is not restricted, as far as not lowering the ability for producing protein in the cell seriously. Preferably temperatures of 32 to 42 °C are recited. Most preferably, temperature of 37 °C is recited. As necessary, cultivating can be performed in the atmosphere containing carbon dioxide of 1 to 10% (v/v).

[0037] Fractions containing humanized antibody against PcrV of the present invention, produced in the transformants or outside cells by the methods previously described, can be refined by the heretofore known separation methods. These methods are based on physical property or chemical property of the target protein. Concretely, for example, treatment with protein precipitant, chromatography such as ultrafiltration chromatography, size separation chromatography, adsorption filtration chromatography, ion exchange chromatography, affinity chromatography, or high

performance liquid chromatography, dialysis, and combination thereof are available.

[0038] According to methods previously described, desirable humanized monoclonal antibody against EL can be produced easily in good yield and good purity. The amino acid sequences of the variable regions of the optimized antibodies are shown as Fig.15 to 21. These antibodies were constructed by grafting amino acid of whole CDR sequences and partial FR sequences, which are determined for humanization of mouse monoclonal antibody (16B3, 55A1, 53A11, 23H8, 13B3, 12B10 or 16F6), into human antibody.

[0039] Compared to mouse antibody (16B3, 55A1, 53A11, 23H8, 13B3, 12B10 or 16F6) produced by hybridoma cells, these humanized antibodies had equivalent the enzymatic inhibitory activity of EL. Though humanization of antibody with maintaining activity of the original antibody is usually difficult, the inventors of the present invention were successful to obtain humanized antibody having equivalent activity of the original mouse antibody. Humanized antibody is useful for the purpose for treatment because of its lower antigenicity in human body.

[0040] As a constant region the humanized antibody of the present invention, human antibody constant region is available. As a preferred human antibody constant region, Cγ can be recited for heavy chain, and for example, Cγ1, Cγ2, Cγ3 and Cγ4 may be used and Cκ or Cλ can be recited for light chain. Further, human antibody C region may be modified to improve its stability of antibody or its productivity. In humanization, available human antibody may be any isotype such as IgG, IgM, IgA, IgE and IgD. In the present invention, IgG is preferable and IgG1 or IgG4 are more preferable.

[0041] Humanized monoclonal antibody of the present invention may be conjugated antibody, which is made by conjugating with some molecule such as polyethylene glycol (PEG), radioactive substance, or toxin. These conjugated monoclonal antibodies are obtained by modifying the antibody chemically. Methods for modifying antibody have established in this technical field. Humanized monoclonal antibody of the present invention embraces these conjugated monoclonal antibodies.

[0042] Humanized monoclonal antibody of the present invention may be fused with other proteins at its N terminal site or C terminal site (Clinical Cancer Research, 2004, 10, 1274-1281. The skilled person can select proteins for fusion appropriately.

[0043] In the present invention, "a monoclonal antibody fragment" means a part of the above-mentioned monoclonal antibody of the present invention and has the specific

binding ability to vascular endothelial lipase as with the monoclonal antibody, or means a fragment that has the specific binding ability to vascular endothelial lipase as with the monoclonal antibody and has the effect of the inhibiting enzymatic activity of vascular endothelial lipase as with the monoclonal antibody.

[0044] Concretely, fragments that have specific associativity against EL are listed Fab, $F(ab')_2$, Fab', single chain antibody (scFv), disulfide stabilized antibody (dsFv), dimerized V region fragment (Diabody), peptide containing CDR, *etc.* (Expert opinion on therapeutic patents, vol. 6, No. 5, p. 441-456, 1996).

[0045] Fab is an antibody fragment having a molecular weight of about 50,000 with antigen binding activity, made up of about a half of N-terminal side of H chain and whole L chain, obtained by degrading with an enzyme papain a peptide part above two disulfide bonds (S-S bond) cross-linking two H chains in hinge region of IgG. Fab used in the present invention may be obtained by treating the monoclonal antibody of the present invention with papain. Alternatively, Fab may be produced by inserting DNA encoding Fab of monoclonal antibody of the present invention into an expression vector for cell and by introducing the vector into a cell to cause expression.

[0046] $F(ab')_2$ is an antibody fragment having a molecular weight of about 100,000 with antigen binding activity, formed by binding two Fab' regions in a hinge part. These Fab' regions are obtained by pepsin degradation below two S-S bonds of hinge region of IgG. The $F(ab')_2$ used in the present invention may be obtained by treating the monoclonal antibody of the present invention with pepsin. Alternatively, $F(ab')_2$ may be produced by inserting DNA encoding $F(ab')_2$ of the monoclonal antibody into an expression vector for cell and by introducing the vector into E. coli, yeast or animal cell to cause expression.

[0047] Fab' is an antibody fragment having a molecular weight of about 50,000 with antigen binding activity, obtained by cutting S-S bond between hinges of the aforementioned $F(ab')_2$. Fab' used in the present invention may be obtained by treating $F(ab')_2$ of monoclonal antibody of the present invention with a reducing agent, dithiothreitol. Alternatively, Fab' may be produced by inserting DNA encoding Fab' of the monoclonal antibody into an expression vector for cell and by introducing the vector into E. coli, yeast or animal cell to cause expression.

[0048] scFv is VH-P-VL or VL-P-VH peptide in which one VH chain and one VL chain are connected using an appropriate peptide linker (hereinafter, denoted by P),

and is an antibody fragment having antigen activity. VH and VL contained in scFv used in the present invention may be derived from the monoclonal antibody of the present invention. scFv used in the present invention may be produced by acquiring cDNA encoding VH and VL from hybridoma producing a monoclonal antibody of the present invention, constructing a scFv expression vector, and causing expression by introducing the expression vector into E. coli, yeast or animal cell.

[0049] dsFv refers to one obtained by binding polypeptides, in which each one amino acid residue is substituted with a cysteine residue in VH and VL, via S-S bond. The amino acid to be substituted with cysteine residue may be selected based on tertiary structure prediction of antibody according to the method indicated by Reiter et al. (Protein Engineering, 7, 697 (1994)). VH or VL contained in dsFv used in the present invention may be derived from the monoclonal antibody of the present invention. dsFv used in the present invention may be produced by acquiring cDNA encoding VH and VL from hybridoma producing a monoclonal antibody of the present invention, constructing a dsFv expression vector by inserting it into an appropriate expression vector, and causing expression by introducing the expression vector into E. coli, yeast or animal cell.

[0050] Diabody is an antibody fragment where a dimer of scFvs having the same or different antigen binding specificity is formed, and is an antibody fragment having bivalent antigen binding activity for the same antigen or two antigen binding activities specific for different antigens. For example, bivalent Diabody that specifically reacts with the monoclonal antibody of the present invention may be produced by acquiring cDNA encoding VH and VL of a monoclonal antibody of the present invention, constructing DNA encoding scFv having a peptide linker of 3 to 10 residues, inserting the DNA into an expression vector for cell, and causing expression of Diabody by introducing the resultant expression vector into E. coli, yeast or animal cell.

[0051] Peptide containing CDR includes at least one region of CDR of VH or VL. Plural CDRs may be combined directly or via an appropriate peptide linker. Peptide containing CDR used in the present invention may be produced by acquiring cDNA encoding VH and VL of a monoclonal antibody of the present invention, constructing DNA encoding CDR, inserting the DNA into an expression vector for animal cell, and causing expression by introducing the resultant expression vector into E. coli, yeast or animal cell. Peptide containing CDR may also be produced by chemical synthesis

method such as Fmoc method (fluorenyl methyloxycarbonyl method) or tBoc method (t-butyloxycarbonyl method).

[0052] A monoclonal antibody or a part thereof of the present invention may be modified insofar as it is suitably used in the present invention. As a modified substance, antibodies bound to various molecules including polyethylene glycol (PEG) or the like may be used. Modification made on antibody may be modification by introduction of chemical bond, or may be modification made on the amino acid sequence of the antibody. A monoclonal antibody or a part thereof of the present invention also embraces these antibody modified substances. For obtaining such antibody modified substances, the obtained antibody may be modified. These techniques have been already established in the art.

[0053] In another aspect, the present invention provides polynucleotide encoding heavy variable region or light variable region of humanized monoclonal antibody of the present invention. The present invention also embraces polynucleotide, which can hybridize with the said polynucleotide in a stringent condition and encodes antibody having equivalent activity with antibody of the present invention.

[0054] The polynucleotide of the present invention is polymer consisting of nucleotide such as several deoxyribonucletic acid (DNA) or ribonucletic acid (RNA), so far as encoding antibody of the present invention. These may include bases other than natural products. The polynucleotide of the invention can be available for producing antibodies in a manner of genetic technology. The polynucleotide of the invention can be also useful as probe for the screening of antibodies having equivalent activity with the antibody of the present invention. So, by using as probe polynucleotide encoding antibody of the present invention or a part thereof, applying technique such as hybridization or gene amplification technique, for example, PCR, DNA which can hybridize with said polynucleotide in the stringent condition and encodes antibody having equivalence activity with antibody of the present invention, is obtainable. Such these DNA are also embraced in the polynucleotide of the present invention.

[0055] Hybridization tequnique (Sambrook, J et al., Molecular Cloning 2nd ed., 9.47-9.58, Cold Spring Harbor Lab. press, 1989) is the well-known art for the skilled person. The condition for hybridization is for example, low-stringent condition. The low-stringent condition means washing step after hybridization is carried on under, for example, 0.1×SSC containing 0.1%SDS at 42°C, preferably 0.1×SSC containing

0.1 % SDS at 50°C. More preferable hybridization condition is high-stringent. High-stringent condition means for example , under 5×SSC containing 0.1%SDS at 65°C. Under these conditions, with higher temperature, higher similarity polynucleotide is expected to be obtained efficiently. As a factor affecting stringency for hybridization, several factors such as temperature, or salt concentration, are recited. The skilled person could select these factors appropriately and could have a similar stringency.

[0056] Antibodies, functionally equivalent to antibody of the present invention, have generally high similarity in the amino acid sequence. These antibodies are encoded by polynucleotide, which are obtained with above described hybridization or gene amplification techniques. The antibodies, which are functionally equivalent to the antibody of the present invention and have high similarity in the amino acid sequence of the antibodies, are embraced in the present invention. High similarity means the similarity of at least more than 50% in the amino acid sequence, preferably the similarity of 75%, and more preferably the similarity of 85% and 95%. To determine the similarity of the polypeptide, algorithm described in the document (Wilbur, W. J. and Lipman, D. J. Proc. Natl. Acad. Sci. USA (1983) 80, 726-730) is available.

[0057] A humanized monoclonal antibody or an antibody fragment thereof of the present invention is characterized of recognizing amino acid residues at positions of 1 to 157 in the amino acid sequence of SEQ ID NO: 1 or recognizing amino acid residues at positions of 202 to 305 in the amino acid sequence of SEQ ID NO: 1. Recognizing amino acid residues at positions of 1 to 157 in the amino acid sequence of SEQ ID NO: 1 means that a monoclonal antibody recognizes an amino acid residue or amino acid residues in this region.

[0058] A humanized monoclonal antibody or an antibody fragment thereof of the present invention is useful as a pharmaceutical composition. Therefore, a pharmaceutical composition containing a humanized monoclonal antibody or an antibody fragment thereof of the present invention may be administered systemically or topically by oral or parenteral route. For parenteral administration, for example, intravenous injection such as drip infusion, intramuscular injection, intraperitoneal injection, subcutaneous injection, intranasal administration, inhalation and the like can be selected.

Also, a humanized monoclonal antibody of the present invention is applicable to the diagnostic for dyslipidemia, hyperlipidemia, arteriosclerosis, atherosclerosis,

hypercholesterolemia, hypertriglyceridemia, diabetes, obesity and/or syndrome X because a humanized monoclonal antibody of the invention has the specific binding ability to against vascular endothelial lipase.

[0059] An patient of the pharmaceutical composition of the present invention is assumed arteriosclerosis and metabolic syndrome. Effective dose is selected in the range of 0.01 mg to 100 mg per 1 kg of body weight per one time. Alternatively, a dose of 5 to 5000 mg, preferably a dose of 10 to 500 mg per a patient may be selected. However, a dose of the pharmaceutical composition containing the monoclonal antibody or an antibody fragment thereof of the present invention is not limited to these doses. Administering duration may be also appropriately selected depending on the age, symptom and the like of the patient. The pharmaceutical composition of the present invention may also include a pharmaceutically acceptable carrier or additive as well depending on the route of administration. Examples of such carrier and additive include water, pharmaceutically acceptable organic solvent, collagen, polyvinyl alcohol, polyvinylpyrrolidone, sodium alginate, water-soluble dextran, pectin, methyl cellulose, ethyl cellulose, casein, diglycerin, propylene glycol, polyethylene glycol, Vaseline, human serum albumin (HSA), mannitol, sorbitol, lactose, and surfactants permitted as a pharmaceutical additive. An additive for use is appropriately selected or combined from the above depending on the dose form, but, it is not limited thereto.

Reference example 1

[0060] Preparation of recombinant adenovirus to express baboon EL

The cDNA of baboon EL with C2 tag was cloned into pShuttle vector (Clontech). This sub-cloned vector and the vector carrying adenoviral backbone gene was digested by PI-SceI and I-CeuI enzyme (Adeno-x Accessory Kit, Clontech). The ligation reaction of the digested fragments was conducted at 16°C for 3hrs (Ligation high, TOYOBO) and the ligation products were transformed to E. coli (OneShot stbl3 Chemically Competent, Invitrogen). After selection of Ampicillin, plasmid DNA was purified from obtained clone (QIAprep spin Miniprep Kit, QIAGEN) and was digested by PacI enzyme to cut E. coli growth area (New England Biolabs). With the above, plasmid DNA was acquired to generate adenovirus vector. Acquired plasmid DNA was transfected to HEK293 cells (American Type Culture Collection) using Lipofectamine 2000 (Invitrogen) and cultured

in DMEM containing 10% FBS at 37 °C. After transfection, we changed culture medium every 5 days and we continued to culture cells until confirming cytopathic effect (CPE) .After confirming CPE, the cells and culture supernatant were collected. After the cells were subjected to five rounds of freeze/thaw with dry ice-methanol bath and warm bath, supernatant which was obtained by 15min centrifugation was collected as cell extracts. The culture supernatant was mixed with the culture medium and used as a primary virus stock. Amplification of the virus stock was achieved by adding the virus stock to HEK293 cells and repeating same procedures. After amplification of the virus stock, the finally obtained cell extracts was treated with Benzonase (Merck-Novagen) for 30 min at 37°C, then supernatant was used for the purification of viral vector by following density gradient centrifugation. We overlaid PBS containing 1.5, 1.35, 1.25g/cm^3 cesium chloride into the centrifuging tube, then overlaid the supernatant. We centrifuged this at 35,000 rpm for 1hr at 16 °C, and collected obtained virus vector by visual. Collected viral vector was dialyzed against PBS containing 10% glycerol, and then used as purified adenoviral vectors. A part of viral vector was used for titration (Adeno-X rapid titer kit, Clontech) and self-proliferative potential gain-of-emergence decision, and only used to immunize the following only those without abnormal.

Reference example 2

[0061] Immunization of baboon EL expression adenoviral vector

6 week-old female mice (A/J Jms Slc spices, obtained from Nihon SLC) were immunized intravenously, subcutaneously or intramuscularly with 2×10^9 i.f.u. adenovirus vector carrying baboon EL gene. Every 7 days after administration, the blood sample was taken from tail vein and the antibody titer was measured. And, additional administration of adenovirus vector carrying baboon EL gene was done intravenously, subcutaneously or intramuscularly. The mice which showed high titer were booster immunized from tail vein as the final administration.

Reference example 3

[0062] Production of hybridoma producing antibodies

The abdominal cavity of mouse which showed high titer was opened and the spleen was isolated three days after final immunization. Spleen cells and mouse myeloma cells

(p3x63-Ag8.U1, Tokyo tumor laboratories) were fused using 50% polyethylene glycol 4000, and hybridoma cells were selected in a culture medium containing hypoxanthine, aminopterin and thymidine.

Reference Example 4

[0063] Screening of a hybridoma cells producing anti-baboon EL antibodies

Ten days after the cell fusion, hybridoma cells which produced anti-baboon EL antibodies were selected. Each well of 384 well microtiter plates (Nunc) was immobilized with 35 μL of Tris/HCl buffer (50 mM Tris/HCl, pH 7.5) containing 0.35μg of anti-mouse IgG-Fc (Jackson Immuno Research). The plates were incubated at 4 °C for 16 hr. After washing the wells one time with 90 μL of washing solution (saline containing 0.01 % Tween20), 100 μL of Block-Ace (Dainihonsumitomo) was added to the wells and incubated at room temperature for 2 hr (immobilized plate of anti-mouse IgG-Fc antibody). After washing the wells three times with 90 μL of washing buffer, 15 μL of assay buffer containing baboon EL heparin extract (50 mM Tris/HCl, PH 7.4 containing 4 % Block-Ace, 0.05 % Tween20, 150 mM NaCl) were added to the wells and incubated at room temperature at 4 °C for 16 hr. After washing the wells three times with 90μL of washing buffer, 15 μL assay buffer containing biotin-labeled anti-C2-tag antibody and HRP-labeled Streptavidin (Thermo scientific) were added to the wells and incubated at room temperature for 1 hr. After washing the wells three times with 90 μL of washing buffer, 15 μL of TMB+—Substrate—Chromogen (DAKO) was added and incubated at room temperature for 30 min. The reaction was stopped with adding 15 μL of 0.05 M H_2SO_4 and then measured absorbance 450nm. From the result of screening, the 11 hybridomas (55A1, 7D4, 14A1, 2D5, 53A11, 13B3, 23H8, 16B3, 16E7, 14E1 and 19E7) which produced anti-baboon EL antibody was selected. The antibody which was produced by hybridoma of 55A1, 7D4, 14A1, 2D5, 53A11, 13B3, 23H8, 16B3, 16E7, 14E1 and 19E7 were named respectively 55A1, 7D4, 14A1, 2D5, 53A11, 13B3, 23H8, 16B3, 16E7, 14E1 and 19E7 antibody. The IgG subclasses were determined using Mouse Immunoglobulin Isotyping Kit (BD Biosciences).

The subclass of 55A1, 2D5, 53A11, 13B3, 23H8, 16B3 and 19E7 was IgG2a. The subclass of 7D4, 14A1, 16E7 and 14E1 was IgG1.

Reference example 5

[0064] Measurement of inhibitory activity of anti-EL antibodies against EL

The inhibitory activity of anti-EL antibodies (55A1, 7D4, 14A1, 2D5, 53A11, 13B3, 23H8, 16B3, 16E7, 14E1 and 19E7) against baboon EL, cynomolgus monkey EL, human (1-157) mouse chimeric EL, human (1-53) mouse chimeric EL, human (61-111) mouse chimeric EL, rabbit EL, mouse EL, human (1-305) mouse chimeric EL and human (202-500) mouse chimeric EL were measured as follows. Anti-EL antibody solution, assay buffer (20 mM Tris/HCl (pH 7.5), 0.5 % BSA, 4 mM $CaCl_2$, 150 mM NaCl) and 2 mg/mL human HDL (Athens Research & Technology) were mixed in a microtiter plate, followed by adding EL heparin extract. After incubation at 37 °C for 90 min, non-esterified Fatty Acid (NEFA) released from HDL was determined using a commercially available kit (NEFA C test-Wako, Wako). The NEFA amount was used as enzyme activity index. Enzyme activity in the case of adding no anti-EL antibody was determined as control value and specific activity was calculated against the control value at each concentration of the anti-EL antibody (Fig. 1A to K). The concentration of anti-EL antibody where 50 % of EL activity was inhibited was calculated from the inhibition curve as IC50 value.

Reference example 6

[0065] Measurement of inhibitory activity of anti-EL antibody against HL and LPL

The DNA encoding human HL was cloned into pcDNA3.1 expression vector (Invitrogen). The expression vector was transfected into HEK293F cells and cultured at 37°C、8% CO2 for 2days. The cells were centrifuged and the cells ware collected, the cells were suspended with PBS containing 20U/mL of Heparin (SIGMA). The cell suspension was incubated at 37°C for 45 min. The supernatant obtained by removing cells with centrifugation was used as human HL enzyme solution. Human LPL enzyme solution was prepared by using the same method. After adding anti-EL antibody to the solution containing 20 mM Tris-HCl Buffer (pH 7.5), 0.5 % bovine serum albumin, 4 mM $CaCl_2$, 150 mM NaCl and 0.5 mg/mL human VLDL (INTRACEL), human HL or human LPL enzyme was added (total volume 10 μl). After reaction at 37 °C for 2 hr, free fatty acid (NEFA) made from VLDL by HL or LPL enzyme was determined using NEFA C-test Wako (Wako), the NFFA amount was used as enzyme activity index. Enzyme activity in the case of adding no anti-EL antibody was determined as control value and the specific

activity was calculated against the control value at each concentration of the antibody (Fig. 2A to K). For comparison, the result was described side by side inhibition curve of cynomolgus monkey EL. As a result, it was shown that 55A1, 7D4, 14A1, 2D5, 53A11, 13B3, 23H8, 16B3, 16E7, 14E1, 19E7 and 16F6 antibodies didn't inhibit neither HL nor LPL enzyme activity.

Reference example 7

[0066] Measurement of binding activity of anti-EL antibody to EL

Assay buffer containing 15 μl of anti-EL antibody was added to anti-mouse IgG-Fc antibody-immobilized microtiter plate, and incubated for 2 hr. After washing the wells three times with 90 μL of washing buffer, 15 μl of cynomolgus monkey EL, baboon EL, rabbit EL, mouse EL, human [1-157]-mouse chimeric EL, human [1-305]-mouse chimeric EL or human [202-500]-mouse chimeric EL heparin extract was added and incubated at 4 °C for 16 hr. After washing the wells three times with 90 μL of washing buffer, 15 μl of assay buffer containing biotin-labeled anti-C2-tag antibody and HRP-labeled Streptavidin were added to the wells and incubated at room temperature for 1 hr. After washing the wells three times with 90 μL of washing buffer, 15μL of TMB+—Substrate—Chromogen (DAKO) was added and incubated at room temperature for 30min and then 15 μL of 0.05 M $H2SO_4$ was added and absorbance at 450nm was measured (Fig. 3A to 3K).

As a result, 55A1, 7D4, 14A1, 2D5, 53A11, 13B3 and 23H8 bound cynomolgus monkey EL, baboon EL and human [1-157]-mouse chimeric EL, but did not bind mouse EL. In addition, 13B3 and 23H8 bound rabbit EL, but 55A1, 7D4, 14A1 2D5 and 53A11 did not. On the other hand, 16B3, 16E7, 14E1 and 19E7 bound cynomolgus monkey EL, baboon EL, human [1-305]-mouse chimeric EL and human [202-500]-mouse chimeric EL, but did not bind mouse El and human [1-157]-mouse chimeric EL. In addition, 16B3, 14E1 and 19E7 bound rabbit EL, but 16E7 did not.

Reference example 8

[0067] Binding affinities of anti-EL antibodies

The binding affinities of anti-EL antibodies were measured using Biacore. Anti-C2-tag antibody was immobilized on a sensor chip CM5 (GE HealthCare) using amine-coupling and baboon EL, cynomolgus monkey EL or human [1-305]-mouse chimeric EL heparin

extract was added and EL was captured on the sensor chip. Then, anti-EL antibodies were added and the binding affinities were calculated by bivalent fitting of BIAevaluation software. The results were summarized in Table 1 to 3.

[Table 1]

Affinity for Baboon EL			
Clone name	ka[1/Ms]	kd[1/s]	K_D [M]
55A1	3.5×10^{5}	4.2×10^{-4}	1.2×10^{-9}
7D4	7.8×10^{4}	3.5×10^{-4}	4.5×10^{-9}
14A1	1.9×10^{5}	6.2×10^{-4}	3.3×10^{-9}
2D5	7.7×10^{5}	1.7×10^{-4}	2.2×10^{-9}
53A11	1.7×10^{5}	2.6×10^{-4}	1.6×10^{-9}
13B3	6.1×10^{4}	3.1×10^{-4}	5.1×10^{-9}
23H8	1.5×10^{5}	4.4×10^{-4}	2.9×10^{-9}
16B3	3.1×10^{4}	9.8×10^{-5}	3.2×10^{-9}
16E7	5.3×10^{4}	2.5×10^{-4}	4.7×10^{-9}
14E1	1.5×10^{5}	8.5×10^{-4}	5.8×10^{-9}
19E7	6.7×10^{4}	8.3×10^{-4}	1.2×10^{-9}

[Table 2]

Affinity for Cynomolgus EL			
Clone name	ka[1/Ms]	kd[1/s]	K_D [M]
55A1	2.5×10^{5}	4.4×10^{-4}	1.7×10^{-9}
7D4	1.2×10^{5}	2.3×10^{-4}	1.9×10^{-9}
14A1	2.1×10^{5}	8.1×10^{-4}	3.9×10^{-9}
2D5	7.4×10^{5}	2.8×10^{-4}	3.8×10^{-9}
53A11	9.1×10^{5}	3.8×10^{-4}	4.2×10^{-9}
13B3	4.7×10^{4}	4.1×10^{-4}	8.7×10^{-9}
23H8	1.2×10^{5}	7.5×10^{-4}	6.1×10^{-9}
16B3	4.2×10^{5}	8.9×10^{-5}	2.1×10^{-9}
16E7	3.2×10^{4}	3.2×10^{-4}	3.7×10^{-9}
14E1	1.2×10^{5}	6.9×10^{-4}	5.9×10^{-9}
19E7	5.5×10^{4}	1.8×10^{-4}	3.3×10^{-9}

[Table 3]

Affinity for Human[1-305]-mouse chimeric EL				
No.	Clone name	ka[1/Ms]	kd[1/s]	K_D [nM]
1	55A1	1.9×10^{5}	1.4×10^{-4}	7.3×10^{-10}
2	7D4	1.1×10^{5}	1.1×10^{-4}	9.7×10^{-10}
3	14A1	2.1×10^{5}	1.0×10^{-4}	5.0×10^{-10}
4	2D5	8.5×10^{4}	9.3×10^{-5}	1.1×10^{-9}
5	53A11	1.8×10^{5}	1.1×10^{-4}	6.3×10^{-10}
6	13B3	1.5×10^{5}	1.4×10^{-4}	9.1×10^{-10}
7	23H8	1.2×10^{5}	1.1×10^{-4}	8.7×10^{-10}
8	16B3	5.1×10^{4}	1.9×10^{-4}	3.7×10^{-9}
9	16E7	9.5×10^{5}	1.0×10^{-4}	1.1×10^{-9}
10	14E1	4.2×10^{4}	2.3×10^{-4}	5.4×10^{-9}

[0068] From the results of Reference example 5 to 8, the characteristics of anti-EL antibodies were summarized in Table 4.

[Table 4]

No.	Clone name	Subclass	Neutralizing activity IC50 [nM]				a region of EL which contributes to antibody binding
			baboon EL	human-mouse chimeric EL	cynomolgus monkey EL	rabbit EL	
1	55A1	IgG2a	2.0	1.1	1.5	N.T.	1-157
2	7D4	IgG1	2.6	3.7	2.1	N.T.	1-157
3	14A1	IgG1	2.7	5.8	3.1	N.T.	1-157
4	2D5	IgG2a	2.9	2.7	3.0	N.T.	1-157
5	53A11	IgG2a	2.4	2.3	1.9	N.T.	1-157
6	13B3	IgG2a	2.6	4.1	1.7	13	1-157
7	23H8	IgG2a	3.2	1.7	2.7	67	1-157
8	16B3	IgG2a	3.0	1.3	1.9	6.3	202-305
9	16E7	IgG1	2.1	1.1	2.5	>40	202-305
10	14E1	IgG1	3.3	1.4	2.4	5.9	202-305
11	19E7	IgG2a	2.0	2.4	1.7	5.7	202-305

Reference example 9

[0069] Generation of anti-EL antibody binding to both human and mouse EL

The adenovirus which expresses mouse EL was obtained using the same method as Example 1 and immunized to EL knock-out mice. In the same manner as Example 4 and 5, anti-EL antibody (16F6) was achieved and subclass was IgG1. The neutralizing activity and binding affinity of 16F6 were measured and described in Table 5 and 6.

[Table 5]

Clone name	EL	neutralizing activity IC50 [nM]
16F6	baboon EL	2.8
	human (1-305) mouse chimeric EL	4.0
	mouse EL	2.5
	rabbit EL	2.3

[Table 6]

Clone name	EL	Affinity		
		ka[1/Ms]	kd[1/s]	K_D [M]
16F6	human [1-305] mouse chimeric EL	3.3×10^{5}	4.0×10^{-3}	1.4×10^{-8}
	mouse EL	2.2×10^{5}	1.5×10^{-4}	6.8×10^{-10}
	baboon EL	2.4×10^{5}	1.0×10^{-4}	4.2×10^{-10}

Reference example 10

[0070] Determination of EL regions contributing to antibody binding

The EL region which contributes to antibody binding was determined by the homology-scanning mutagenesis or alanine scanning mutagenesis. The binding activity of anti-EL antibody to EL mutant was analyzed by ELISA. The amino acid residues of baboon EL were mutated to alanine using QuikChange Site-Directed Mutagenesis Kit (Agilent Technologies), but the amino acid residues which were different from baboon EL and mouse EL were mutated to mouse EL amino acid residues. Mutated EL heparin extracts were prepared and binding activity to anti-EL antibody according to Example 2 and Example 8. The relative effect of each mutation was evaluated from the following formula; ([antibody concentration where A450 value showed 1.0]-mutated EL) / ([antibody concentration where A450 value showed 1.0]-wild type EL). The relative binding activity of mutated baboon EL to anti-EL antibodies (55A1, 7D4, 14A1, 2D5, 53A11, 13B3 or 23H8) was showed in Fig. 7A to G. The relative binding activity of mutated baboon EL to anti-EL antibodies (16B3, 16E7, 14E1, 19E7 or 16F6) was also showed in Fig. 7H to L.

[0071] From the information of Fig7A to 7G, it was shown that important amino acids in the binding of the 55A1, 7D4, 14A1, 2D5, 53A11, 13B3 or 23H8 antibody and EL are arginine at position 50, glutamic acid at position 60, histidine at position 61, tyrosine at position 65 and asparagine at position 100 in the amino acid sequence of SEQ ID NO: 1.

[0072] From the information of Fig7H to 7K , it was shown that important amino acids in the binding of the 16B3, 16E7, 14E1 or 19E7 antibody and EL are histidine at position 220, threonine at position 221, tyrosine at position 222, threonine at position 223, arginine at position 224, phenylalanine at position 226, glycine at position 227, glycine at position

231, isoleucine at position 232, glutamine at position 233, methionine at position 234, aspartic acid at position 240, tyrosine at position 242, proline at position 243, asparagine at position 244, glycine at position 246, glutamine at position 249, proline at position 250, glycine at position 251, leucine at position 254, leucine at position 258, tyrosine at position 263, valine at position 269 and glutamic acid at position 273 in the amino acid sequence of SEQ ID NO: 1.

Reference example 11

[0073] Analysis of the amino acid sequence of variable region of anti-EL antibodies

The amino acid sequence of variable region of anti-EL antibody was determined using conventional procedure and described in Fig. 4A to L.

[0074] The present invention is described below in more detail by the way of examples. However, the present invention is not limited to the following examples. Unless specifying otherwise as a procedure for preparing antibody, we used methods described in Immunochemistry in Practice (Blackwell Scientific Publications). Also unless specifying otherwise as the genetic engineering techniques, we used methods described in Molecular Cloning : A Laboratory Manual, 2nd Edition (Cold Spring Harbor Laboratory).

Example 1

[0075] Humanization of mouse monoclonal antibody

The seven mouse monoclonal antibodies (16B3, 55A1, 53A11, 23H8, 13B3 and 16F6) which were generated as described above and 12B10 which was described in WO2013/054830 were humanized. More specifically, humanization was performed by inserting the sequence of humanized variable region which is grafted CDRs of each mouse antibody into the pcDNA based plasmid encoding the constant region of human kappa or human gamma1 domain sequences.

In a same manner as described above, eleven humanized antibodies h16B3-S1, h16B3-S2, h16B3-S3, h16B3-S4, h16B3-S5, h16B3-S6, h16B3-S7, h16B3-S8, h16B3-F1, h16B3-F2 and h16B3-F3 were generated derived from mouse 16B3. The alignments of variable region of these humanized antibodies were shown in Fig. 8A to D.

In a same manner as described above, thirteen humanized antibodies h55A1-S1, h55A1-S2, h55A1-S3, h55A1-S4, h55A1-S5, h55A1-S6, h55A1-S7, h55A1-F1,

h55A1-F2, h55A1-F3, h55A1-F4, h55A1-F5 and h55A1-F6 were generated derived from mouse 55A1. The alignments of variable region of these humanized antibodies were shown in Fig. 9A to D.

In a same manner as described above, four humanized antibodies h53A11-S1, h53A11-S2, h53A11-S3 and h53A11-S4 were generated derived from mouse 53A11. The alignments of variable region of these humanized antibodies were shown in Fig. 10A to B.

In a same manner as described above, three humanized antibodies h23H8-S1, h23H8-S2 and h23H8-S3 were generated derived from mouse 23H8. The alignments of variable region of these humanized antibodies were shown in Fig. 11A to B.

In a same manner as described above, four humanized antibodies h13B3-S1, h13B3-S2, h13B3-S3 and h13B3-S4 were generated derived from mouse 13B3. The alignments of variable region of these humanized antibodies were shown in Fig. 12A to B.

In a same manner as described above, four humanized antibodies h12B10-S1, h12B10-S2, h12B10-S3 and h12B10-S4 were generated derived from mouse 12B10. The alignments of variable region of these humanized antibodies were shown in Fig. 13A to B.

In a same manner as described above, five humanized antibodies h16F6-S1, h16F6-S2, h16F6-S3, h16F6-S4 and h16F6-S5 were generated derived from mouse 16F6. The alignments of variable region of these humanized antibodies were shown in Fig. 14A to B.

The amino acid sequence of variable region of these forty four humanized antibodies were summarized in Table 7-1 to 7-2, and shown in Fig. 15 to 21.

[Table7-1]

mAb	Heavy chain			Light chain		
	VH	JH	Mutation	VK	JK	Mutation
h16B3-S1	3-23*04	6*01		4-1*01	2*01	
h16B3-S2	3-23*04	6*01	K94R	4-1*01	2*01	
h16B3-S3	3-23*04	6*01	K94R, R98K, Y100BF	4-1*01	2*01	
h16B3-S4	3-23*04	6*01	K94R, R98K, Y100BF	4-1*01	2*01	K93R
h16B3-S5	3-23*04	6*01	K94R, R98K, H100R, Y100BF, V102L	4-1*01	2*01	
h16B3-S6	3-23*04	6*01	K94R, R98K, H100R, Y100BF, V102L	4-1*01	2*01	K93R
h16B3-S7	3-23*04	6*01	G31A, E50D, K94R, R98K, H100R, Y100BF, V102L	4-1*01	2*01	
h16B3-S8	3-23*04	6*01	G31A, E50D, K94R, R98K, H100R, Y100BF, V102L	4-1*01	2*01	K93R
h16B3-F1	3-23*04	6*01	K94R	1-39*01	2*01	
h16B3-F2	3-23*04	6*01	K94R	3-15*01	2*01	
h16B3-F3	3-23*04	6*01	K94R	3-20*01	2*01	
h55A1-S1	7-4-1*01	6*03		7-3*01	4*02	
h55A1-S2	7-4-1*01	6*03	M34L, Y100BF	7-3*01	4*02	
h55A1-S3	7-4-1*01	6*03	M34L, Y100BF	7-3*01	4*02	Q90N
h55A1-S4	7-4-1*01	6*03	G33A, P57G, Y97F, Y100BF	7-3*01	4*02	
h55A1-S5	7-4-1*01	6*03	G33A, P57G, Y97F, Y100BF	7-3*01	4*02	Q90N
h55A1-S6	7-4-1*01	6*03	G33A, M34L, P57G, D62E, Y97F, Y100BF	7-3*01	4*02	
h55A1-S7	7-4-1*01	6*03	G33A, M34L, P57G, D62E, Y97F, Y100BF	7-3*01	4*02	Q90N
h55A1-F1	7-4-1*01	6*03		1-33*01	4*02	
h55A1-F2	1-18*01	6*03		3-15*01	4*02	

[Table 7-2]

h55A1-F3	1-18*01	6*03		1-39*01	4*02	
h55A1-F4	1-18*01	6*03		3-20*01	4*02	
h55A1-F5	1-46*01	6*03		1-39*01	4*02	
h55A1-F6	1-46*01	6*03		3-15*01	4*02	
h53A11-S1	1-3*01	6*02	R94K	3-15*01	2*01	P8L, Y49K
h53A11-S2	1-3*01	6*02	R94K	3-15*01	2*01	P8L
h53A11-S3	1-3*01	6*02	R94K	3-15*01	2*01	Y49K
h53A11-S4	1-3*01	6*02		3-15*01	2*01	Y49K
h23H8-S1	1-2*02	6*02		1-39*01	2*01	
h23H8-S2	1-2*02	6*02		1-39*01	2*01	Y49S, P80R
h23H8-S3	1-2*02	6*02		1-39*01	2*01	Y49S
h13B3-S1	1-46*03	6*01		3-20*01	4*01	
h13B3-S2	1-2*01	6*01		3-20*01	4*01	
h13B3-S3	1-46*03	6*01		3-11*01	4*01	
h13B3-S4	1-2*01	6*01		3-11*01	4*01	
h12B10-S1	3-33*01	5*01	S95D, Y96H, D97L, G98A, S99Y, P100Y, P101D, S102V	1-33*01	2*04	
h12B10-S2	3-33*01	5*01	S95D, Y96H, D97L, G98A, S99F, P100Y, P101D, S102L	1-33*01	2*04	
h12B10-S3	3-33*01	5*01	S95D, Y96H, D97L, G98A, S99F, P100F, P101D, S102L	1-33*01	2*04	
h12B10-S4	3-33*01	5*01	T31S, S95D, Y96H, D97L, G98V, S99F, P100F, P101D, S102L	1-33*01	2*04	
h16F6-S1	1-46*01	6*01	R94V	1-39*01	4*01	A43S
h16F6-S2	1-46*01	6*01	R94V	1-39*01	4*01	A43S, S67A
h16F6-S3	1-46*01	6*01	R94V	1-39*01	4*01	A43S, S63T, S67A
h16F6-S4	1-46*01	6*01	R94V	1-39*01	4*01	A43S, S63T, S67A, L73F
h16F6-S5	1-46*01	6*01	R94V	1-39*01	4*01	T20S, A43S, S63T, S67A, L73F

Example 2

[0076] Measurement of inhibitory activity of anti-EL humanized antibody

Humanized antibodies were produced from the plasmid vector as described in Example 1. The inhibitory activity of protein A column purified anti-EL humanized antibodies against human EL, human [1-305]-mouse chimeric EL, human [331-459]-mouse chimeric EL, cynomolgus monkey EL or mouse EL were measured as follows. Anti-EL humanized

antibody solution, assay buffer (20 mM Tris/HCl (pH 7.5), 0.5 % BSA, 4 mM $CaCl_2$, 150 mM NaCl) and 2 mg/mL human HDL (Athens Research & Technology) were mixed in a microtiter plate, followed by adding EL heparin extract. After incubation at 37 °C for 90 min, non-esterified Fatty Acid (NEFA) released from HDL was determined using a commercially available kit (NEFA C test-Wako, Wako). The NEFA amount was used as enzyme activity index. Enzyme activity in the case of adding no anti-EL humanized antibody was determined as control value and specific activity was calculated against the control value at each concentration of the anti-EL humanized antibody. The concentration of anti-EL humanized antibody where 50 % of EL activity was inhibited was calculated from the inhibition curve as IC50 value. The result was summarized in Table 8 to 11.

Mouse 16B3 derived humanized antibodies h16B3-S1, h16B3-S2, h16B3-S3, h16B3-S4, h16B3-S5, h16B3-S6, h16B3-S7, h16B3-S8, h16B3-F1, h16B3-F2 and h16B3-F3 showed about the same or increased neutralization activity. From the result, K or R at position 94 of heavy chain, G or A at position 31 of heavy chain, E or D at position 50 of heavy chain, R or K at position 98 of heavy chain, H or R at position 100 of heavy chain, Y or F at position 100B of heavy chain, V or L at position 102 of heavy chain and K or R at position 93 of light chain are considered to be acceptable. Additionally, human germline sequences IGKV4-1*01, IGKV1-39*01, IGKV3-15*01 or IGKV3-20*01 are considered to be used acceptors for mouse CDRs of light chain.

Mouse 55A1 derived humanized antibodies h55A1-S1, h55A1-S2, h55A1-S3, h55A1-S4, h55A1-S5, h55A1-S6, h55A1-S7, h55A1-F1, h55A1-F2, h55A1-F3, h55A1-F4, h55A1-F5 and h55A1-F6 showed about the same or increased neutralization activity. From the result, G or A at position 33 of heavy chain, M or L at position 34 of heavy chain, P or G at position 57 of heavy chain, D or E at position 62 of heavy chain , Y or F at position 97 of heavy chain, Y or F at position 100B of heavy chain and Q or N at position 90 of light chain are considered to be acceptable. Additionally, human germline sequences IGHV7-4-1*02, IGHV1-18*01 or IGHV1-46*01 are considered to be used acceptors for CDRs of heavy chain, and IGKV7-3*01, IGKV1-33*01, IGKV1-39*01, IGKV3-15*01 or IGKV3-20*01 are considered to be used acceptors for CDRs of light chain.

Mouse 53A11 derived humanized antibodies h53A11-S1, h53A11-S2 and h53A11-S3 showed about the same or increased neutralization activity although h53A11-S4 showed

decreased neutralization activity. From the result, combination of R94K mutation of heavy chain and P8L mutation of light chain, or combination of R94K mutation of heavy chain and Y49K mutation of light chain are considered to be desirable.

Mouse 23H8 derived humanized antibodies h23H8-S2 and h23H8-S3 showed about the same or increased neutralization activity although h23H8-S1 showed decreased neutralization activity. From the result, combination of Y49S and P80R mutations of light chain are considered to be desirable.

Mouse 13B3 derived humanized antibodies h13B3-S1, h13B3-S2, h13B3-S3 and h13B3-S4 showed about the same or increased neutralization activity.

Mouse 12B10 derived humanized antibodies h12B10-S1, h12B10-S2, h12B10-S3 and h12B10-S4 showed about the same or increased neutralization activity.

Mouse 16F6 derived humanized antibodies h16F6-S1, h16F6-S2, h16F6-S3, h16F6-F4, h16F6-F5 and h16F6-S5 showed about the same or increased neutralization activity. From the result, combination of R94V mutation of heavy chain and A43S mutation of light chain are considered to be desirable. Additionally, T or S at position 20 of light chain, S or T at position 63 of light chain, S or A at position 67 of light chain, L of F at position 73 of light chain are considered to be acceptable.

[Table 8]

mAb	Neutralizing activity IC50 [nM]
	Human EL
h16B3-S2	4.6
h55A1-S1	3.9
h53A11-S1	9.7
h23H8-S2	4.5
h13B3-S1	2.3

[Table 9-1]

mAb	Neutralizing activity IC50 [nM]
	Chimeric EL
16B3 (mouse mAb)	1.3
h16B3-S1	2.7
h16B3-S2	5.3
h16B3-S3	1.9
h16B3-S4	1.7
h16B3-S5	1.2
h16B3-S6	1.0
h16B3-S7	1.4
h16B3-S8	1.4
h16B3-F1	2.3
h16B3-F2	2.4
h16B3-F3	2.0
55A1 (mouse mAb)	1.1
h55A1-S1	2.2
h55A1-S2	1.1
h55A1-S3	1.2
h55A1-S4	1.1
h55A1-S5	1.3
h55A1-S6	1.2
h55A1-S7	1.0
h55A1-F1	1.9
h55A1-F2	2.1
h55A1-F3	1.1
h55A1-F4	2.4
h55A1-F5	1.3

[Table 9-2]

h55A1-F6	2.3
53A11 (mouse mAb)	2.6
h53A11-S1	2.1
h53A11-S2	2.7
h53A11-S3	1.8
23H8 (mouse mAb)	1.7
h23H8-S2	1.7
h23H8-S3	2.0
13B3 (mouse mAb)	4.1
h13B3-S1	3.0
h13B3-S2	9.0
h13B3-S3	2.1
h13B3-S4	2.6
12B10 (mouse mAb)	15
h12B10-S1	6.0
h12B10-S2	5.4
h12B10-S3	4.9
h12B10-S4	6.2

[Table 10]

mAb	Neutralizing activity IC50 [nM]
	Cynomolgus monkey EL
16B3 (mouse mAb)	1.8
h16B3-S1	3.6
h16B3-S2	1.9
55A1 (mouse mAb)	1.3
h55A1-S1	1.6
53A11 (mouse mAb)	2.7
h53A11-S1	1.7
h53A11-S2	1.8
h53A11-S3	1.2
h53A11-S4	12
23H8 (mouse mAb)	1.4
h23H8-S1	26
h23H8-S2	1.7
h23H8-S3	1.8
13B3 (mouse mAb)	3.1
h13B3-S1	2.4
h13B3-S2	3.6
h13B3-S3	4.1
h13B3-S4	2.9

[Table 11]

mAb	Neutralizing activity IC50 [nM]	
	Baboon EL	Mouse
h16F6-S1	2.6	3.1
h16F6-S2	3.3	3.0
h16F6-S3	3.1	3.3
h16F6-S4	2.6	2.0
h16F6-S5	2.0	2.1

Example 3

[0077] Measurement of inhibitory activity of anti-EL humanized antibody against HL and LPL

The DNA encoding human HL was cloned into pcDNA3.1 expression vector (Invitrogen). The expression vector was transfected into HEK293F cells and cultured at 37°C、8% CO2 for 2days. The cells were centrifuged and the cells were collected, the cells were suspended with PBS containing 20U/mL of Heparin (SIGMA). The cell suspension was incubated at 37°C for 45 min. The supernatant obtained by removing cells with centrifugation was used as human HL enzyme solution. Human LPL enzyme solution was prepared by using the same method. After adding anti-EL antibody to the solution containing 20 mM Tris-HCl Buffer (pH 7.5), 0.5 % bovine serum albumin, 4 mM $CaCl_2$, 150 mM NaCl and 0.5 mg/mL human VLDL (INTRACEL), human HL or human LPL

enzyme was added (total volume 10 μl). After reaction at 37 °C for 2 hr, free fatty acid (NEFA) made from VLDL by HL or LPL enzyme was determined using NEFA C-test Wako (Wako), the NFFA amount was used as enzyme activity index. Enzyme activity in the case of adding no anti-EL antibody was determined as control value and the specific activity was calculated against the control value at each concentration of the antibody. The concentration of anti-EL humanized antibody where 50 % of EL activity was inhibited was calculated from the inhibition curve as IC50 value. The result was shown in Table 12. As a result, it was shown that humanized antibodies h16B3-S2, h55A1-S1, h53A11-S1, h23H8-S2 and h13B3-S1 inhibited neither HL nor LPL enzyme activity.

[Table 12]

mAb	Neutralizing activity IC50 [nM]	
	Human HL	Human LPL
h16B3-S2	>400	>400
h55A1-S1	>1800	>1800
h53A11-S1	>400	>400
h23H8-S2	>400	>400
h13B3-S1	>400	>400

Example 4

[0078] Binding affinity of anti-EL humanized antibody

The binding affinities of anti-EL antibodies were measured using Biacore. Anti-C2-tag antibody was immobilized on a sensor chip CM5 (GE HealthCare) using amine-coupling and human [1-305]-mouse chimeric EL, human [331-459]-mouse chimeric EL, cynomolgus monkey EL or mouse EL heparin extract was added and EL was captured on the sensor chip. Then, anti-EL humanized antibodies were added and the binding affinities were calculated by bivalent fitting of BIAevaluation software. The results were summarized in Table 13 to 15

[Table 13-1]

mAb	Affinity for human-mouse chimeric EL		
	ka (1/Ms)	kd (1/s)	KD (M)
h16B3-S2	2.4×10^{4}	2.2×10^{-4}	9.3×10^{-9}
h16B3-S3	3.0×10^{4}	1.3×10^{-4}	4.5×10^{-9}
h16B3-S4	6.1×10^{4}	1.8×10^{-4}	3.0×10^{-9}
h16B3-S5	5.4×10^{4}	5.7×10^{-5}	1.0×10^{-9}
h16B3-S6	6.0×10^{4}	5.8×10^{-5}	1.0×10^{-9}
h16B3-S7	5.0×10^{4}	5.9×10^{-5}	1.2×10^{-9}
h16B3-S8	5.2×10^{4}	4.0×10^{-5}	7.8×10^{-10}
h16B3-F1	3.8×10^{4}	2.0×10^{-4}	5.2×10^{-9}
h16B3-F2	2.9×10^{4}	1.1×10^{-4}	3.8×10^{-9}
h16B3-F3	1.9×10^{4}	2.0×10^{-4}	1.0×10^{-8}
h55A1-S1	2.7×10^{4}	8.6×10^{-4}	3.1×10^{-8}
h55A1-S2	3.5×10^{4}	3.7×10^{-4}	1.1×10^{-8}
h55A1-S3	1.2×10^{5}	5.1×10^{-4}	4.2×10^{-9}
h55A1-S4	8.0×10^{4}	2.4×10^{-4}	3.0×10^{-9}
h55A1-S5	2.7×10^{4}	3.3×10^{-4}	1.2×10^{-8}
h55A1-S6	4.7×10^{4}	6.3×10^{-5}	1.4×10^{-9}
h55A1-S7	1.1×10^{5}	5.5×10^{-4}	5.1×10^{-9}

[Table 13-2]

h55A1-F1	2.0×10^{5}	1.7×10^{-5}	8.4×10^{-11}
h55A1-F2	1.6×10^{5}	2.6×10^{-5}	1.7×10^{-10}
h55A1-F3	1.1×10^{5}	3.3×10^{-5}	2.9×10^{-10}
h55A1-F4	1.4×10^{5}	3.0×10^{-5}	2.2×10^{-10}
h55A1-F5	1.4×10^{5}	1.6×10^{-5}	1.1×10^{-10}
h55A1-F6	1.6×10^{5}	4.8×10^{-6}	3.0×10^{-10}
h12B10-S1	1.9×10^{5}	3.5×10^{-4}	1.9×10^{-9}
h12B10-S2	2.4×10^{5}	3.3×10^{-5}	1.4×10^{-10}
h12B10-S3	1.5×10^{5}	1.7×10^{-5}	1.1×10^{-10}
h12B10-S4	5.5×10^{5}	3.9×10^{-5}	7.2×10^{-10}

[Table 14]

mAb	Affinity for Cynomolgus monkey EL		
	ka (1/Ms)	kd (1/s)	KD (M)
h16B3-S1	9.4×10^{4}	1.0×10^{-3}	1.1×10^{-8}
h16B3-S2	5.1×10^{4}	1.0×10^{-4}	2.0×10^{-9}
h55A1-S1	4.4×10^{5}	2.6×10^{-4}	5.9×10^{-10}
h53A11-S1	1.3×10^{5}	3.0×10^{-4}	2.3×10^{-9}
h53A11-S2	1.5×10^{5}	6.5×10^{-4}	4.3×10^{-9}
h53A11-S3	1.2×10^{5}	7.0×10^{-4}	5.8×10^{-9}
h23H8-S1	1.0×10^{5}	3.6×10^{-3}	3.6×10^{-8}
h23H8-S2	2.3×10^{5}	9.9×10^{-4}	4.3×10^{-9}
h23H8-S3	3.7×10^{5}	1.5×10^{-4}	4.1×10^{-10}
h13B3-S1	7.6×10^{4}	4.3×10^{-4}	5.7×10^{-9}
h13B3-S2	4.5×10^{4}	1.4×10^{-4}	3.1×10^{-9}
h13B3-S3	6.6×10^{4}	8.5×10^{-4}	1.3×10^{-8}
h13B3-S4	1.1×10^{5}	3.8×10^{-4}	3.5×10^{-9}

[Table 15]

mAb	Affinity for Baboon EL			Affinity for Mouse EL		
	ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)
h16F6-S1	1.3×10^{6}	7.4×10^{-4}	5.7×10^{-10}	1.2×10^{6}	1.9×10^{-4}	1.6×10^{-10}

Industrial applicability

[0079] The humanized monoclonal antibody which inhibits the enzymatic activity of vascular endothelial lipase of the present invention is useful as a drug for prevention and/or treatment of dyslipidemia, hyperlipidemia, arteriosclerosis, atherosclerosis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity and/or syndrome X because it has selectively inhibitory activity against vascular endothelial lipase.

Claims

1. A humanized monoclonal antibody or an antibody fragment thereof, selected from the group of

1) a humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2 as CDR1, the amino acid sequence of SEQ ID NO: 3 as CDR2 and the amino acid sequence of SEQ ID NO: 8 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 7 as CDR3;

2) a humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2 as CDR1, the amino acid sequence of SEQ ID NO: 3 as CDR2 and the amino acid sequence of SEQ ID NO: 8 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 9 as CDR3;

3) a humanized monoclonal antibody or an antibody fragment thereof, having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2 as CDR1, the amino acid sequence of SEQ ID NO: 3 as CDR2 and the amino acid sequence of SEQ ID NO: 10 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the

amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 7 as CDR3;

4) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 2 as CDR1, the amino acid sequence of SEQ ID NO: 3 as CDR2 and the amino acid sequence of SEQ ID NO: 10 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 9 as CDR3;

5) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11 as CDR1, the amino acid sequence of SEQ ID NO: 12 as CDR2 and the amino acid sequence of SEQ ID NO: 10 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 7 as CDR3;

6) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 11 as CDR1, the amino acid sequence of SEQ ID NO: 12 as CDR2 and the amino acid sequence of SEQ ID NO: 10 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 5 as CDR1, the amino acid sequence of SEQ ID NO: 6 as CDR2 and the amino acid sequence of SEQ ID NO: 9 as CDR3;

7) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 19 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2 and the amino acid sequence of SEQ ID NO: 20 as CDR3, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 18 as CDR3;
8) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 19 as CDR1, the amino acid sequence of SEQ ID NO: 14 as CDR2 and the amino acid sequence of SEQ ID NO: 20 as CDR3, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 21 as CDR3;
9) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 22 as CDR1, the amino acid sequence of SEQ ID NO: 23 as CDR2 and the amino acid sequence of SEQ ID NO: 24 as CDR3, and
a light chain variable region
including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 18 as CDR3;
10) a humanized monoclonal antibody or an antibody fragment thereof,
having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 22 as CDR1, the amino acid sequence of SEQ ID NO: 23 as CDR2 and the amino acid sequence of SEQ ID NO: 24 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 21 as CDR3;

11) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25 as CDR1, the amino acid sequence of SEQ ID NO: 106 as CDR2 and the amino acid sequence of SEQ ID NO: 24 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 18 as CDR3;

12) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25 as CDR1, the amino acid sequence of SEQ ID NO: 106 as CDR2 and the amino acid sequence of SEQ ID NO: 24 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 21 as CDR3;

13) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44 as CDR1, the

amino acid sequence of SEQ ID NO: 45 as CDR2 and the amino acid sequence of SEQ ID NO: 46 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47 as CDR1, the amino acid sequence of SEQ ID NO: 48 as CDR2 and the amino acid sequence of SEQ ID NO: 49 as CDR3;

14) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44 as CDR1, the amino acid sequence of SEQ ID NO: 45 as CDR2 and the amino acid sequence of SEQ ID NO: 50 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47 as CDR1, the amino acid sequence of SEQ ID NO: 48 as CDR2 and the amino acid sequence of SEQ ID NO: 49 as CDR3;

15) a humanized monoclonal antibody or an antibody fragment thereof,

having a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 44 as CDR1, the amino acid sequence of SEQ ID NO: 45 as CDR2 and the amino acid sequence of SEQ ID NO: 51 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47 as CDR1, the amino acid sequence of SEQ ID NO: 48 as CDR2 and the amino acid sequence of SEQ ID NO: 49 as CDR3;

16) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 52 as CDR1, the amino acid sequence of SEQ ID NO: 45 as CDR2 and the amino acid sequence of SEQ ID NO: 53 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 47 as CDR1, the amino acid sequence of SEQ ID NO: 48 as CDR2 and the amino acid sequence of SEQ ID NO: 49 as CDR3.

2. The humanized monoclonal antibody or an antibody fragment thereof according to claim 1, wherein said antibody fragment is Fab, $F(ab')_2$, Fab', scFv, dsFv or Diabody.

3. A humanized monoclonal antibody or an antibody fragment thereof,
selected from the group of
1) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61;
2) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61;
3) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61;
4) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 64;
5) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 61;
6) a humanized monoclonal antibody or an antibody fragment thereof,
having
a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and
a light chain variable region having the amino acid sequence of SEQ ID NO: 64;
7) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 61;

8) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64;

9) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67;

10) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68;

11) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69;

12) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

13) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

14) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

15) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

16) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

17) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

18) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

19) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

20) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

21) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

22) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

23) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

24) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

25) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83;

26) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84;

27) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 82, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85;

28) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 85;

29) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 88;

30) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 89;

31) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 87, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 90;

32) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92;

33) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 92;

34) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 91, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94;

35) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 93, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 94;

36) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 95, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96;

37) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 97, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96;

38) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 98, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96;

39) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 96;

40) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 101;

41) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 102;

42) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 103;

43) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 104; and

44) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 100, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 105.

4. The humanized monoclonal antibody or an antibody fragment thereof according to claim 3, wherein said antibody fragment is Fab, $F(ab')_2$, Fab', scFv, dsFv or Diabody.

5. A humanized monoclonal antibody or an antibody fragment thereof,

selected from the group of

1) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64;

2) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67;

3) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68;

4) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 60, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69;

5) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 62, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 64;

6) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67;

7) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68;

8) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 63, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69;

9) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67;

10) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68;

11) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 65, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69;

12) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 67;

13) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 68;

14) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 66, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 69;

15) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

16) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

17) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

18) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 70, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

19) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

20) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

21) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

22) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 72, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

23) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

24) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

25) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

26) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 74, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

27) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

28) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 78;

29) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 79;

30) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

31) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

32) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

33) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 77, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

34) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 71;

35) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 73;

36) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76;

37) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 81, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 80;

38) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 83; and

39) a humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 86, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 84.

6. The humanized monoclonal antibody or an antibody fragment thereof according to claim 5, wherein said antibody fragment is Fab, $F(ab')_2$, Fab', scFv, dsFv or Diabody.

7. A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody fragment thereof of claim 1.

8. The pharmaceutical composition of claim 7, wherein the disease related to vascular endothelial lipase is dyslipidemia.

9. A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody

fragment thereof of claim 3.

10. The pharmaceutical composition of claim 9, wherein the disease related to vascular endothelial lipase is dyslipidemia.

11. A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody fragment thereof of claim 5.

12. The pharmaceutical composition of claim 11, wherein the disease related to vascular endothelial lipase is dyslipidemia.

13. A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 25 as CDR1, the amino acid sequence of SEQ ID NO: 106 as CDR2 and the amino acid sequence of SEQ ID NO: 24 as CDR3, and

a light chain variable region

including three CDRs having the amino acid sequence of SEQ ID NO: 16 as CDR1, the amino acid sequence of SEQ ID NO: 17 as CDR2 and the amino acid sequence of SEQ ID NO: 18 as CDR3.

14. A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody fragment thereof of claim 13.

15. The pharmaceutical composition of claim 14, wherein the disease related to vascular endothelial lipase is dyslipidemia.

16. A humanized monoclonal antibody or an antibody fragment thereof,

having

a heavy chain variable region having the amino acid sequence of SEQ ID NO: 75, and

a light chain variable region having the amino acid sequence of SEQ ID NO: 76.

17. A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the humanized monoclonal antibody or the antibody fragment thereof of claim 16.

18. The pharmaceutical composition of claim 17, wherein the disease related to vascular endothelial lipase is dyslipidemia.