SPECIFICATION

Monoclonal antibody, inhibiting the enzymatic activity of vascular endothelial lipase

Technical field

[0001] The present invention relates to a 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 an antibody that selectively inhibits the enzymatic activity of EL, or a part 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) and rabbit EL consists of 500 amino acids (NCBI Accession number NO_001182567, SEQ ID NO: 2). 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 become 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 an antibody that selectively inhibits enzyme activity of EL, or a 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 monoclonal antibody that selectively inhibits the enzymatic activity of EL.

[0009] To be more specific, the present invention relates to:

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

(2) The monoclonal antibody of (1) or the antibody fragment thereof, wherein it recognizes at least one amino acid at positions of 50 to100 in an amino acid sequence of

SEQ ID NO: 1.

(3) The monoclonal antibody of (1) or (2) or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from arginine at position 50, glutamic acid at position 60, tyrosine at position 65 and asparagine at position 100 in an amino acid sequence of SEQ ID NO: 1.

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

(5) The monoclonal antibody of (4) or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 and asparagine at position 100 in an amino acid sequence of SEQ ID NO: 1.

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

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

(8) The monoclonal antibody of (6) or (7) or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 an amino acid sequence of SEQ ID NO: 1.

(9) The monoclonal antibody of (6) or (7) or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 an amino acid sequence of SEQ ID NO: 1.

(10) The monoclonal antibody of (6) or (7) or the antibody fragment thereof, wherein it recognizes all amino acids of 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 an amino acid sequence of SEQ ID NO: 1.

(11) The monoclonal antibody of any one of (1) to (10), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC 50 of 10nM or less.

(12) The monoclonal antibody of (11), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC 50 of 5nM or less.

(13) The monoclonal antibody of (11), wherein it inhibits the enzymatic activity of vascular endothelial lipase with an IC 50 of 2nM or less.

(14) A monoclonal antibody or a fragment thereof, selected from the group of

1) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16.

2) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

4) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24.

6) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

7) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

8) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID

NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

9) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32.

10) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

11) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

12) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

13) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40.

14) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of

SEQ ID NO: 48.

18) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least

one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56.

22) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of

SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64.

26) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ

ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68 and

a light chain variable region including three CDRs comprising amino acid sequence of

SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72.

30) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

32) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68, and

a light chain variable region including three CDRs, said three CDRs consisting of amino

acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80.

34) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76, and

a light chain variable region including three CDRs comprising amino acid sequence of

SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

36) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88.

38) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ

ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96.

42) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106.

46) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

(15) A monoclonal antibody or a fragment thereof, selected from the group of

1) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 9, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 13.

2) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 9, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 13,and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or

several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 9 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 13 and inhibiting the enzymatic activity of vascular endothelial lipase.

4) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 9 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 13,and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 17, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 21.

6) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 17, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 21,and

inhibiting the enzymatic activity of vascular endothelial lipase.

7) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 17 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 21 and inhibiting the enzymatic activity of vascular endothelial lipase.

8) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 17 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 21,and

inhibiting the enzymatic activity of vascular endothelial lipase.

9) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 25, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 29.

10) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 25, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 29,and

inhibiting the enzymatic activity of vascular endothelial lipase.

11) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 25 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 29 and

inhibiting the enzymatic activity of vascular endothelial lipase.

12) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 25 and

a light chain variable region comprising amino acids, said amino acids that are one or

several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 29,and

inhibiting the enzymatic activity of vascular endothelial lipase.

13) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 33, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 37.

14) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 33, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 37,and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 33 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 37 and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 33 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 37,and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 41, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 45.

18) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 41, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 45,and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 41 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 45 and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 41 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 45,and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 49, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 53.

22) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 49, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 53,and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 49 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 5 and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 49 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 53,and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 57, and

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

26) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 57, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 61,and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 57 and

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

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 57 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 61,and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A monoclonal antibody or a fragment thereof,

having

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

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

30) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 69,and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 65 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 69 and

inhibiting the enzymatic activity of vascular endothelial lipase.

32) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 65 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 69,and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 73, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 77.

34) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 73, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 77,and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 73 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 77 and

inhibiting the enzymatic activity of vascular endothelial lipase.

36) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of

SEQ ID NO: 73 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 77,and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A monoclonal antibody or a fragment thereof,

having

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

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

38) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 85,and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 81 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 85 and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 81 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 85,and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 89, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 93.

42) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 89, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 93,and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 89 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 93 and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 89 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 93,and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A monoclonal antibody or a fragment thereof,

having

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

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

46) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 103,and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 99 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 103 and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 99 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 103,and

inhibiting the enzymatic activity of vascular endothelial lipase.

(16) The pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the monoclonal antibody of any one of (1) to (15) or the antibody fragment thereof.

(17) The pharmaceutical composition of according to (16), wherein the disease related to vascular endothelial lipase is Dyslipidemia.

(18) The monoclonal antibody of any one of (1) to (15) or the antibody fragment thereof for the treatment or prevention of a disease related to vascular endothelial lipase.

(19) The monoclonal antibody of (18) or the antibody fragment thereof, wherein the disease related to vascular endothelial lipase is Dyslipidemia.

(20) A method for the treatment or prevention of a disease related to vascular endothelial

lipase characterized by administering to a monoclonal antibody of any one of (1) to (15) or the antibody fragment thereof.

(21) The method of (20), wherein the disease related to vascular endothelial lipase is Dyslipidemia.

Effect of the invention

[0010] As a monoclonal antibody of the present invention has the activity for selectively inhibiting enzymatic activity of EL, pharmaceutical compositions containing the 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

[0011] [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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting enzymatic activity of 55A1 antibody against human HL and human LPL.

[Fig. 2B] Fig. 2B shows measurement results of inhibiting enzymatic activity of 7D4 antibody against human HL and human LPL..

[Fig. 2C] Fig. 2C shows measurement results of inhibiting enzymatic activity of 14A1 antibody against human HL and human LPL.

[Fig. 2D] Fig. 2D shows measurement results of inhibiting enzymatic activity of 2D5 antibody against human HL and human LPL.

[Fig. 2E] Fig. 2E shows measurement results of inhibiting enzymatic activity of 53A11 antibody against human HL and human LPL.

[Fig. 2F] Fig. 2F shows measurement results of inhibiting enzymatic activity of 13B3 antibody against human HL and human LPL.

[Fig. 2G] Fig. 2G shows measurement results of inhibiting enzymatic activity of 23H8 antibody against human HL and human LPL.

[Fig. 2H] Fig. 2H shows measurement results of inhibiting enzymatic activity of 16B3 antibody against human HL and human LPL.

[Fig. 2I] Fig. 2I shows measurement results of inhibiting enzymatic activity of 16E7 antibody against human HL and human LPL..

[Fig. 2J] Fig. 2J shows measurement results of inhibiting enzymatic activity of 14E1 antibody against human HL and human LPL.

[Fig. 2K] Fig. 2K shows measurement results of inhibiting enzymatic activity of

19E7 antibody human HL and human LPL.

[Fig. 2L] Fig. 2L shows measurement results of inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 inhibiting 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 amino acid sequence of a variable region of 55A1 antibody.

[Fig. 4B] Fig. 4B shows amino acid sequence of a variable region of 7D4 antibody.

[Fig. 4C] Fig. 4C shows amino acid sequence of a variable region of 14A1 antibody.

[Fig. 4D] Fig. 4D shows amino acid sequence of a variable region of 2D5 antibody.

[Fig. 4E] Fig. 4E shows amino acid sequence of a variable region of 53A11 antibody.

[Fig. 4F] Fig. 4F shows amino acid sequence of a variable region of 13B3 antibody.

[Fig. 4G] Fig. 4G shows amino acid sequence of a variable region of 23H8 antibody.

[Fig. 4H] Fig. 4H shows amino acid sequence of a variable region of 16B3 antibody.

[Fig. 4I] Fig. 4I shows amino acid sequence of a variable region of 16E7 antibody.

[Fig. 4J] Fig. 4J shows amino acid sequence of a variable region of 14E1 antibody.

[Fig. 4K] Fig. 4K shows amino acid sequence of a variable region of 19E7 antibody.

[Fig. 4L] Fig. 4L shows amino acid sequence of a variable region 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.

Mode for carrying out the invention

[0012] The present invention provides a 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.

[0013] It is important to use peptide having consecutive amino acid residues containing amino acid sequence at positions of 1 to 157 or 202 to 305 region in 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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).

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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).

[0025] 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.*

[0026] 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).

[0027] 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.

[0028] 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, 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.

[0029] Effective concentration (IC50) of antibody which shows 50% inhibition of EL enzyme activity is often used as an indicator of EL inhibitory activity.

[0030] In the present invention, a monoclonal antibody or a fragment thereof inhibiting the enzymatic activity of vascular endothelial lipase with an IC 50 of 10nM or less means a monoclonal antibody or a fragment thereof showing IC 50 of 10nM or less measured by method of said [0027]-[0029]. Any species EL may be used for the measurement if the EL is derived from a mammal. If a monoclonal antibody or a fragment thereof inhibits the enzymatic activity of EL of any kind of mammal species with an IC 50 of 10nM or less, the monoclonal antibody or a fragment thereof is a monoclonal antibody or a fragment thereof showing IC 50 of 10nM or less.

[0031] 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.

[0032] 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 2days. The cell cultures are centrifuged, the cells are collected, 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 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, 4mM CaCl2, 150mM NaCl and 0.5mg/mL human VLDL (INTRACEL), HL or LPL enzyme solution is added . After reaction at 37°C for 2hr, 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.

[0033] 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.

[0034] The monoclonal antibody of the present invention includes recombinant monoclonal antibodies that are artificially modified for the purpose of lowering heterologous antigenicity against human, for example, chimera monoclonal antibody, humanized monoclonal antibody and human monoclonal antibody.

[0035] The monoclonal antibody of the present invention may be a conjugate antibody bound to various molecules such as polyethylene glycol (PEG), radioactive material, toxin. These conjugate antibodies can be obtained by chemically modifying obtained antibodies. The techniques of modification of antibody are well known in this field. These conjugate antibodies are included in monoclonal antibodies of the present invention.

[0036] And the monoclonal antibody of the present invention may fuse to the other proteins at the N terminal or C terminal of the antibody (Clinical Cancer Research, 2004, 10, 1274-1281). Those skilled in the art may properly select fusion protein.

[0037] 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. 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).

[0038] A monoclonal antibody of the present invention or a fragment thereof is useful as a pharmaceutical composition. Therefore, a pharmaceutical composition containing a monoclonal antibody of the present invention or a fragment thereof 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 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 monoclonal antibody of the invention has the specific binding ability to against vascular endothelial lipase.

[0039] A monoclonal antibody of the present invention or a fragment thereof is characterized of recognizing at least one amino acid at positions of 1 to 157 in an amino acid sequence of SEQ ID NO: 1 or recognizing at least one amino acid at positions of 202 to 305 in an amino acid sequence of SEQ ID NO: 1. Recognizing at least one amino acid at positions of 1 to 157 in an amino acid sequence of SEQ ID NO: 1 means that a monoclonal antibody or a fragment thereof recognizes at least one amino acid in this region.

[0040] 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 of the present invention or a fragment thereof 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.

[0041] 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

[0042] 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/cm³ 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. The amino acid sequence of baboon EL-C2 tag was described in SEQ ID NO: 2.

Example 2

[0043] Preparation of EL heparin extract

The DNA encoding baboon EL 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 cell culture was centrifuged and the cells were collected, the cells were suspended with PBS containing 20U/mL of Heparin. The cell suspension was incubated at 37°C for 45 min. The supernatant obtained by removing cells with centrifugation was used as baboon EL enzyme solution. Using the same method, 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 heparin extract were prepared. The amino acid sequences of 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 with C2 tag were described SEQ ID NO: 2, 3, 4, 5, 6, 7, 96 and 97.

Example 3

[0044] 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.

Example 4

[0045] 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.

Example 5

[0046] Screening of a hybridoma cells which produces 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.

Example 6

[0047] 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~K). The concentration of anti-EL antibody where 50 % of EL activity was inhibited was calculated from the inhibition curve as IC50 value.

Example 7

[0048] 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~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.

Example 8

[0049] 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~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.

Example 9

[0050] 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 1~3.

[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}

[0051] From the results of Example 5, 6, 8 and 9, 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

Example 10

[0052] Generation of anti-EL antibody which neutralizes both human and mouse EL

[0053] 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}

Example 11

[0054] Determination of EL regions which contribute 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, 23H8, 16B3, 16E7, 14E1 and 19E7) was showed in Fig. 7A~L.

[0055] From the information of Fig7A-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 an amino acid sequence of SEQ ID NO: 1.

[0056] From the information of Fig7H-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 an amino acid sequence of SEQ ID NO: 1.

Example 12

[0057] Analysis of 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~L.

Example 13

[0058] Alignment of amino acid sequences of variable region of 55A1, 7D4, 2D5, 53A11, 13B3 and 23H8

The amino acid sequences of variable region of 55A1, 7D4, 2D5, 53A11, 13B3 and 23H8 were aligned by GENETYX software (Fig 5A~D). Fig. 5A and 5B indicated that all six CDRs of heavy and light chain of 55A1, 7D4, 14A1 and 2D5 had high similarity. Fig. 5C indicated that CDR1 and CDR2 of heavy chain of 53A11, 13B3 and 23H8 had high similarity.

[0059] The analysis of CDRs of heavy and light chain of 55A1, 7D4, 14A1 and 2D5 revealed the following things.

The amino acid sequences of heavy chain CDR1 was consisted of 5 amino acids, NYGMN.

The amino acid sequences of heavy chain CDR2 was consisted of 17 amino acids, WINTYSGVPTY (A or T) (G or D) DFKG.

The amino acid sequences of heavy chain CDR3 was consisted of 11 amino acids, (R or F) (G or S) YYGR (R or H) YFD (V or Y).

The amino acid sequences of light chain CDR1 was consisted of 15 amino acids, KASQSVDYD (V or G) DSYM (H or N).

The amino acid sequences of light chain CDR2 was consisted of 7 amino acids, AASNLXS. “X” represents given amino acid.

The amino acid sequences of light chain CDR3 was consisted of 10 amino acids, (H or Q) Q (T or S) (I or T or N) (E or D) DPP (- or W) T. “-” represents deletion of amino acid.

[0060] The analysis of CDRs of heavy and light chain of 53A11, 13B3 and 23H8 revealed the following things.

The amino acid sequences of heavy chain CDR1 was consisted of 5 amino acids, (D or

E) (Y or N) T (M or I) H.

The amino acid sequences of heavy chain CDR2 was consisted of 17 amino acids, XINPYYGGTX (Y or N) NEKFKD. “X” represents given amino acid.

There was no commonality of amino acid residues in heavy chain CDR3.

Example 14

[0061] Alignment of amino acid sequences of variable region of 16B3, 16E7, 14E1 and 19E7

The amino acid sequences of variable region of 16B3, 16E7, 14E1 and 19E7 were aligned by GENETYX software (Fig 6A~D). Fig. 6A and 6B indicated that all six CDRs of heavy and light chain of 16B3 and 16E7 had high similarity.

[0062] The analysis of CDRs of heavy and light chain of 16B3, 16E7, 14E1 and 19E7 revealed the following things.

The amino acid sequences of heavy chain CDR1 was consisted of 5 amino acids, (G or S) YTMS.

The amino acid sequences of heavy chain CDR2 was consisted of 17 amino acids, EISF (A or T) R (D or S) RAFYPDTVKG.

The amino acid sequences of heavy chain CDR3 was consisted of 13 amino acids, LGG (R or N) N (H or Y) DYWYFDV.

The amino acid sequences of light chain CDR1 was consisted of 15 amino acids, RASESVEYYGTSLMQ.

The amino acid sequences of light chain CDR2 was consisted of 7 amino acids, AASNVES.

The amino acid sequences of light chain CDR3 was consisted of 9 amino acids, QQSWKVPFT.

Industrial applicability

[0063] The 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.

Sequence list

Claims

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

[2] The monoclonal antibody of claim1 or the antibody fragment thereof, wherein it recognizes at least one amino acid at positions of 50 to100 in an amino acid sequence of SEQ ID NO: 1.

[3] The monoclonal antibody of claim 1 or claim 2 or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from arginine at position 50, glutamic acid at position 60, tyrosine at position 65 and asparagine at position 100 in an amino acid sequence of SEQ ID NO: 1.

[4] The monoclonal antibody of claim 1 or claim 2 or the antibody fragment thereof, wherein it recognizes at least tyrosine at position 65 in an amino acid sequence of SEQ ID NO: 1.

[5] The monoclonal antibody of claim 4 or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 and asparagine at position 100 in an amino acid sequence of SEQ ID NO: 1.

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

[7] The monoclonal antibody of claim 6 or the antibody fragment thereof, wherein it recognizes at least one amino acid at positions of 220 to 273 in an amino acid sequence of SEQ ID NO: 1.

[8] The monoclonal antibody of claim 6 or 7 or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 an amino acid sequence of SEQ ID NO: 1.

[9] The monoclonal antibody of claim 6 or 7 or the antibody fragment thereof, wherein it recognizes at least one amino acid selected from 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 an amino acid sequence of SEQ ID NO: 1.

[10] The monoclonal antibody of claim 6 or 7 or the antibody fragment thereof, wherein it recognizes all amino acids of 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 an amino acid sequence of SEQ ID NO: 1.

[11] A monoclonal antibody or a fragment thereof, selected from the group of

1) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region

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

a light chain variable region

including three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16.

2) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region

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

a light chain variable region

including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 14,

amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region

including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12, and

a light chain variable region

including three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

4) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 10, amino acid sequence of SEQ ID NO: 11 and amino acid sequence of SEQ ID NO: 12, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 14, amino acid sequence of SEQ ID NO: 15 and amino acid sequence of SEQ ID NO: 16, and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region

including three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino

acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24.

6) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

7) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence of SEQ ID NO: 20, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

8) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 18, amino acid sequence of SEQ ID NO: 19 and amino acid sequence

of SEQ ID NO: 20, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 22, amino acid sequence of SEQ ID NO: 23 and amino acid sequence of SEQ ID NO: 24, and

inhibiting the enzymatic activity of vascular endothelial lipase.

9) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32.

10) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

11) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence

of SEQ ID NO: 28, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

12) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 26, amino acid sequence of SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 30, amino acid sequence of SEQ ID NO: 31 and amino acid sequence of SEQ ID NO: 32, and

inhibiting the enzymatic activity of vascular endothelial lipase.

13) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40.

14) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36 and

a light chain variable region including three CDRs, said three CDRs consisting of

amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 34, amino acid sequence of SEQ ID NO: 35 and amino acid sequence of SEQ ID NO: 36, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 38, amino acid sequence of SEQ ID NO: 39 and amino acid sequence of SEQ ID NO: 40, and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of

SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48.

18) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence

of SEQ ID NO: 42, amino acid sequence of SEQ ID NO: 43 and amino acid sequence of SEQ ID NO: 44, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 46, amino acid sequence of SEQ ID NO: 47 and amino acid sequence of SEQ ID NO: 48, and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56.

22) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence

of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 50, amino acid sequence of SEQ ID NO: 51 and amino acid sequence of SEQ ID NO: 52, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 54, amino acid sequence of SEQ ID NO: 55 and amino acid sequence of SEQ ID NO: 56, and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64.

26) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 58, amino acid sequence of SEQ ID NO: 59 and amino acid sequence of SEQ ID NO: 60, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 62, amino acid sequence of SEQ ID NO: 63 and amino acid sequence of SEQ ID NO: 64, and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72.

30) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

32) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in

at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 66, amino acid sequence of SEQ ID NO: 67 and amino acid sequence of SEQ ID NO: 68, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 70, amino acid sequence of SEQ ID NO: 71 and amino acid sequence of SEQ ID NO: 72, and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80.

34) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in

at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

36) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 74, amino acid sequence of SEQ ID NO: 75 and amino acid sequence of SEQ ID NO: 76, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 78, amino acid sequence of SEQ ID NO: 79 and amino acid sequence of SEQ ID NO: 80, and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88.

38) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of

SEQ ID NO: 84 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 82, amino acid sequence of SEQ ID NO: 83 and amino acid sequence of SEQ ID NO: 84, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 86, amino acid sequence of SEQ ID NO: 87 and amino acid sequence of SEQ ID NO: 88, and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96.

42) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of

amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 90, amino acid sequence of SEQ ID NO: 91 and amino acid sequence of SEQ ID NO: 92, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 94, amino acid sequence of SEQ ID NO: 95 and amino acid sequence of SEQ ID NO: 96, and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102 and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106.

46) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102 and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of

amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said the three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102, and

a light chain variable region including three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs ,said the three CDRs comprising amino acid sequence of SEQ ID NO: 100, amino acid sequence of SEQ ID NO: 101 and amino acid sequence of SEQ ID NO: 102, and

a light chain variable region including three CDRs, said three CDRs consisting of amino acids that are one or several amino acids are depleted, substituted or added in at least one of the three CDRs, said three CDRs comprising amino acid sequence of SEQ ID NO: 104, amino acid sequence of SEQ ID NO: 105 and amino acid sequence of SEQ ID NO: 106, and

inhibiting the enzymatic activity of vascular endothelial lipase.

[12] A monoclonal antibody or a fragment thereof, selected from the group of

1) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 9, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 13.

2) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 9, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 13,and

inhibiting the enzymatic activity of vascular endothelial lipase.

3) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 9 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 13 and

inhibiting the enzymatic activity of vascular endothelial lipase.

4) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 9 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 13, and

inhibiting the enzymatic activity of vascular endothelial lipase.

5) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 17, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 21.

6) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 17, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 21, and

inhibiting the enzymatic activity of vascular endothelial lipase.

7) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of

SEQ ID NO: 17 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 21 and inhibiting the enzymatic activity of vascular endothelial lipase.

8) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 17 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 21,and

inhibiting the enzymatic activity of vascular endothelial lipase.

9) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 25, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 29.

10) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 25, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 29,and

inhibiting the enzymatic activity of vascular endothelial lipase.

11) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 25 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 29 and inhibiting the enzymatic activity of vascular endothelial lipase.

12) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 25 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 29,and

inhibiting the enzymatic activity of vascular endothelial lipase.

13) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 33, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 37.

14) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 33, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 37,and

inhibiting the enzymatic activity of vascular endothelial lipase.

15) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 33 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 37 and

inhibiting the enzymatic activity of vascular endothelial lipase.

16) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 33 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of

SEQ ID NO: 37,and

inhibiting the enzymatic activity of vascular endothelial lipase.

17) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 41, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 45.

18) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 41, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 45,and

inhibiting the enzymatic activity of vascular endothelial lipase.

19) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 41 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 45 and

inhibiting the enzymatic activity of vascular endothelial lipase.

20) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 41 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 45,and

inhibiting the enzymatic activity of vascular endothelial lipase.

21) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 49, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 53.

22) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 49, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 53,and

inhibiting the enzymatic activity of vascular endothelial lipase.

23) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 49 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 53 and

inhibiting the enzymatic activity of vascular endothelial lipase.

24) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 49 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 53,and

inhibiting the enzymatic activity of vascular endothelial lipase.

25) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 57, and

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

26) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 57, and

a light chain variable region comprising amino acids, said amino acids that are one or

several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 61,and

inhibiting the enzymatic activity of vascular endothelial lipase.

27) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 57 and

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

inhibiting the enzymatic activity of vascular endothelial lipase.

28) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 57 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 61,and

inhibiting the enzymatic activity of vascular endothelial lipase.

29) A monoclonal antibody or a fragment thereof,

having

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

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

30) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 69,and

inhibiting the enzymatic activity of vascular endothelial lipase.

31) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 65 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 69 and inhibiting the enzymatic activity of vascular endothelial lipase.

32) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 65 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 69,and

inhibiting the enzymatic activity of vascular endothelial lipase.

33) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 73, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 77.

34) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 73, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 77,and

inhibiting the enzymatic activity of vascular endothelial lipase.

35) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 73 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 77 and inhibiting the enzymatic activity of vascular endothelial lipase.

36) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 73 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 77,and

inhibiting the enzymatic activity of vascular endothelial lipase.

37) A monoclonal antibody or a fragment thereof,

having

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

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

38) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 85,and

inhibiting the enzymatic activity of vascular endothelial lipase.

39) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 81 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 85 and

inhibiting the enzymatic activity of vascular endothelial lipase.

40) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 81 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 85,and

inhibiting the enzymatic activity of vascular endothelial lipase.

41) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 89, and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 93.

42) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acid sequence of SEQ ID NO: 89, and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 93,and

inhibiting the enzymatic activity of vascular endothelial lipase.

43) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 89 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 93 and

inhibiting the enzymatic activity of vascular endothelial lipase.

44) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 89 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 93,and

inhibiting the enzymatic activity of vascular endothelial lipase.

45) A monoclonal antibody or a fragment thereof,

having

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

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

46) A monoclonal antibody or a fragment thereof,

having

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

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 103,and

inhibiting the enzymatic activity of vascular endothelial lipase.

47) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 99 and

a light chain variable region comprising amino acid sequence of SEQ ID NO: 103 and

inhibiting the enzymatic activity of vascular endothelial lipase.

48) A monoclonal antibody or a fragment thereof,

having

a heavy chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 99 and

a light chain variable region comprising amino acids, said amino acids that are one or several amino acids are depleted, substituted or added in amino acids sequence of SEQ ID NO: 103,and

inhibiting the enzymatic activity of vascular endothelial lipase.

[13] A pharmaceutical composition for treating or preventing a disease related to vascular endothelial lipase, comprising the monoclonal antibody of any one of claims (1) to (12) or the antibody fragment thereof.

[14] A pharmaceutical composition of claim 13, wherein the disease related to vascular endothelial lipase is Dyslipidemia.