transplantation of a complementarity determining region (CDR) of a mammalian antibody other than human antibody, e.g., a mouse antibody into a CDR of a human antibody, and gene recombination techniques therefor are generally known. Specifically, a DNA sequence including a CDR of a mouse antibody linked to a framework region (FR) of a human antibody is synthesized through PCR using several oligonucleotides which are produced to have overlapped part at an end thereof. The thus-obtained DNA fragment is linked to a DNA fragment encoding the constant region of the human antibody, subsequently the resultant fragment is incorporated into an expression vector and the vector is incorporated into host cells to thereby produce the humanized antibody (see EP239400 A and WO 96/02576 A). The FR of the human antibody linked via the CDR is selected from FRs having a CDR which forms a suitable antigen-binding site. If needed, an amino acid in the FR of the variable region of the antibody may be substituted such that a CDR of the reshaped antibody forms an appropriate antigen-binding site (Sato, K. *et al.*, Cancer Res., 1993, 53, 851-856).

[0015]

The amino acid sequence of the chimeric antibody or humanized antibody preferably has an identity of 100% to that of the Vh or Vl region of cDNA expressing a deposited hybridoma. Due to genetic modification, an antibody having an identity in amino acid sequence of 90% or higher is also preferred. In the process of humanization or chimerization,

there has been conventionally carried out such controlled residue substitution for improving binding to an antigen. Such an antibody having a partially modified sequence is essentially considered to be an antibody originating from the original hybridoma.

[0016]

Methods for producing a chimeric antibody and a humanized antibody based on a genetic engineering technique have been already known. Specifically, the Vh and VL sequences of a monoclonal antibody serving as a confirmed group is genetically modified, and then chimerization or humanization is performed through a routine technique.

[0017]

The method for recovering a human antibody is also known. In one procedure, human lymphocytes are sensitized in vitro with an antigen of interest or with cells expressing the antigen, and the thus-sensitized lymphocytes are fused with human myeloma cells, e.g., U266, to thereby produce a human antibody of interest having a binding activity to the antigen (see JP-B-1989-59878). Alternatively, a human antibody of interest may be recovered through immunization, with an antigen of interest, of a transgenic animal having a complete repertory of the human antibody gene (see WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO96/34096, and WO96/33735). Also known is a technique for recovering a human antibody through panning by use of a human antibody library. In one procedure, a variable region of a human

D-set sense primer (mixture of the following 2 primers)

5′-ATGAGGRCCCCTGCTCAGWTTYTTGGIWTCTT-3′: SEQ ID NO: 28

5′-ATGGGCWTCAAGATGRAGTCACAKWYYCWGG-3′: SEQ ID NO: 29

E-set sense primer (mixture of the following 3 primers)

5′-ATGAGTGTGCYCACTCAGGTCCTGGSGTT-3′: SEQ ID NO: 30

5′-ATGTGGGGAYCGKTTTYAMMCTTTTCAATTG-3′: SEQ ID NO: 31

5′-ATGGAAGCCCCAGCTCAGCTTCTCTTCC-3′: SEQ ID NO: 32

F-set sense primer (mixture of the following 4 primers)

5′-ATGAGIMMKTCIMTTCAITTCYTGGG-3′: SEQ ID NO: 33

5′-ATGAKGTHCYCIGCTCAGYTYCTIRG-3′: SEQ ID NO: 34

5′-ATGGTRTCCWCASCTCAGTTCCTTG-3′: SEQ ID NO: 35

5′-ATGTATATATGTTTGTTGTCTATTTCT-3′: SEQ ID NO: 36

G-set sense primer (mixture of the following 4 primers)

5′-ATGAAGTTGCCTGTTAGGCTGTTGGTGCT-3′: SEQ ID NO: 37

5′-ATGGATTTWCARGTGCAGATTWTCAGCTT-3′: SEQ ID NO: 38

5′-ATGGTYCTYATVTCCTTGCTGTTCTGG-3′: SEQ ID NO: 39

5′-ATGGTYCTYATVTTRCTGCTGCTATGG-3′: SEQ ID NO: 40

KVL antisense primer

ACTGGATGGTGGGAAGATGGA: SEQ ID NO: 41

[0064]

B. Primers for use in PCR amplification of a gene encoding mouse H-chain V-region

The following two primer sets were employed 4-set primers having, at the 5' end, a homology to the mouse H-chain signal part and a primer having, at the 3' end, a homology to the KC part; and 1-set primers having, at the 5' end, a homology to the FR1 part and 2-set primers having, at

confirmed.

Next, a gene encoding the human Cκ region was linked to the cloned gene encoding the V region of the L-chain of the anti-CDH3 antibody, and a gene encoding the human Cκ1 region was linked to the gene encoding the V region of the H-chain. The thus-designed L-chain and H-chain chimeric antibody genes were synthesized in full length by GenScript. At the time, frequency of codon usage was optimized so as to obtain efficient gene expression in producing cells (according to a method disclosed in Kim *et al.*, Codon optimization for high-level expression of human erythropoietin (EPO) in mammalian cells, Gene, 199, 1997, p. 293-301). Specifically, in the case of L-chain, for the purpose of effective translation, an essential DNA sequence (Kozak, M., J., At least six nucleotides preceding the AUG initiator codon enhance translation in mammalian cells. J. Mol. Biol. 196, p. 947-950, 1987), signal peptide of mouse IGKV, the V region of the L-chain of the anti-CDH3 antibody, and the human Cκ region were juxtaposed in this order, and restriction enzyme sites were added to both ends (*Nhe*I on the 5' side and *EcoR*I on the 3' side). The chimera H-chain was prepared in the same manner. Each of the synthesized genes was cut with *Nhe*I and *EcoR*I, and the cut fragment was incorporated into an expression vector pCAGGS between the *Nhe*I site and the *EcoR*I site, to thereby produce an anti-CDH3 chimeric antibody L-chain expression vector pCAGGS-IGK and H-chain expression vector pCAGGS-IGH.

[Sequence Listing]

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<150> JP 2010-028028

<151> 2010-02-10

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Cys Trp Leu Gln Cys Ala Ala Ser Glu Pro Cys Arg Ala Val Phe Arg

20 25 30

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35 40 45

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Gln Ala Leu Gly Lys Val Phe Met Gly Cys Pro Gly Gln Glu Pro Ala

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Leu Phe Ser Thr Asp Asn Asp Asp Phe Thr Val Arg Asn Gly Glu Thr

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Val Gln Glu Arg Arg Ser Leu Lys Glu Arg Asn Pro Leu Lys Ile Phe
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Pro Ser Lys Arg Ile Leu Arg Arg His Lys Arg Asp Trp Val Val Ala
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Asn Gln Leu Lys Ser Asn Lys Asp Arg Asp Thr Lys Ile Phe Tyr Ser
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gta 480

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165 170 175

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180 185 190

gcc tca gtg gag gac ccc atg aac atc tcc atc atc gtg acc gac cag 624

Ala Ser Val Glu Asp Pro Met Asn Ile Ser Ile Ile Val Thr Asp Gln

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Thr
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tcc 768
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Ser
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att 816
Ile His Ser Gln Glu Pro Lys Asp Pro His Asp Leu Met Phe Thr
Ile
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cgg 864
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Arg
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gat 912

Glu Lys Val Pro Glu Tyr Thr Leu Thr Ile Gln Ala Thr Asp Met Asp

290 295 300

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Gly Asp Gly Ser Thr Thr Thr Ala Val Ala Val Val Glu Ile Leu Asp

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gag 1344

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485 490 495

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acg 1776

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19

transplantation of a complementarity determining region (CDR) of a mammalian antibody other than human antibody, e.g., a mouse antibody into a CDR of a human antibody, and gene recombination techniques therefor are generally known. Specifically, a DNA sequence including a CDR of a mouse antibody linked to a framework region (FR) of a human antibody is synthesized through PCR using several oligonucleotides which are produced to have overlapped part at an end thereof. The thus-obtained DNA fragment is linked to a DNA fragment encoding the constant region of the human antibody, subsequently the resultant fragment is incorporated into an expression vector and the vector is incorporated into host cells to thereby produce the humanized antibody (see EP239400 A and WO 96/02576 A). The FR of the human antibody linked via the CDR is selected from FRs having a CDR which forms a suitable antigen-binding site. If needed, an amino acid in the FR of the variable region of the antibody may be substituted such that a CDR of the humanized antibody forms an appropriate antigen-binding site (Sato, K. *et al.*, Cancer Res., 1993, 53, 851-856).

[0015]

The amino acid sequence of the chimeric antibody or humanized antibody preferably has an identity of 100% to that of the VH or VL region of cDNA expressing a deposited hybridoma. Due to genetic modification, an antibody having an identity in amino acid sequence of 90% or higher is also preferred. In the process of humanization or chimerization,

there has been conventionally carried out such controlled residue substitution for improving binding to an antigen. Such an antibody having a partially modified sequence is essentially considered to be an antibody originating from the original hybridoma.

[0016]

Methods for producing a chimeric antibody and a humanized antibody based on a genetic engineering technique have been already known. Specifically, the VH and VL sequences of a monoclonal antibody serving as a confirmed group is genetically modified, and then chimerization or humanization is performed through a routine technique.

[0017]

The method for recovering a human antibody is also known. In one procedure, human lymphocytes are sensitized in vitro with an antigen of interest or with cells expressing the antigen, and the thus-sensitized lymphocytes are fused with human myeloma cells, e.g., U266, to thereby produce a human antibody of interest having a binding activity to the antigen (see JP-B-1989-59878). Alternatively, a human antibody of interest may be recovered through immunization, with an antigen of interest, of a transgenic animal having a complete repertory of the human antibody gene (see WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO96/34096, and WO96/33735). Also known is a technique for recovering a human antibody through panning by use of a human antibody library. In one procedure, a variable region of a human

D-set sense primer (mixture of the following 2 primers)

5′-ATGAGGRCCCCTGCTCAGWTTYTTGGIWTCTT-3′: SEQ ID NO: 28

5′-ATGGGCWTCAAGATGRAGTCACAKWYYCWGG-3′: SEQ ID NO: 29

E-set sense primer (mixture of the following 3 primers)

5′-ATGAGTGTGCYCACTCAGGTCCTGGSGTT-3′: SEQ ID NO: 30

5′-ATGTGGGGAYCGKTTTYAMMCTTTTCAATTG-3′: SEQ ID NO: 31

5′-ATGGAAGCCCCAGCTCAGCTTCTCTTCC-3′: SEQ ID NO: 32

F-set sense primer (mixture of the following 4 primers)

5′-ATGAGIMMKTCIMTTCAITTCYTGGG-3′: SEQ ID NO: 33

5′-ATGAKGTHCYCIGCTCAGYTYCTIRG-3′: SEQ ID NO: 34

5′-ATGGTRTCCWCASCTCAGTTCCTTG-3′: SEQ ID NO: 35

5′-ATGTATATATGTTTGTTGTCTATTTCT-3′: SEQ ID NO: 36

G-set sense primer (mixture of the following 4 primers)

5′-ATGAAGTTGCCTGTTAGGCTGTTGGTGCT-3′: SEQ ID NO: 37

5′-ATGGATTTWCARGTGCAGATTWTCAGCTT-3′: SEQ ID NO: 38

5′-ATGGTYCTYATVTCCTTGCTGTTCTGG-3′: SEQ ID NO: 39

5′-ATGGTYCTYATVTTRCTGCTGCTATGG-3′: SEQ ID NO: 40

KVL antisense primer

ACTGGATGGTGGGAAGATGGA: SEQ ID NO: 41

[0064]

B. Primers for use in PCR amplification of a gene encoding mouse H-chain V-region

The following two primer sets were employed 4-set primers having, at the 5' end, a homology to the mouse H-chain signal part and a primer having, at the 3' end, a homology to the IGHC part; and 1-set primers having, at the 5' end, a homology to the FR1 part and 2-set primers having, at

confirmed.

Next, a gene encoding the human Cκ region was linked to the cloned gene encoding the V region of the L-chain of the anti-CDH3 antibody, and a gene encoding the human Cγ1 region was linked to the gene encoding the V region of the H chain. The thus-designed L-chain and H-chain chimeric antibody genes were synthesized in full length by GenScript. At the time, frequency of codon usage was optimized so as to obtain efficient gene expression in producing cells (according to a method disclosed in Kim *et al.*, Codon optimization for high-level expression of human erythropoietin (EPO) in mammalian cells, Gene, 199, 1997, p. 293-301). Specifically, in the case of L-chain, for the purpose of effective translation, an essential DNA sequence (Kozak, M., J., At least six nucleotides preceding the AUG initiator codon enhance translation in mammalian cells. J. Mol. Biol. 196, p. 947-950, 1987), signal peptide of mouse IGKV, the V region of the L-chain of the anti-CDH3 antibody, and the human Cκ region were juxtaposed in this order, and restriction enzyme sites were added to both ends (*Nhe*I on the 5' side and *EcoR*I on the 3' side). The chimera H-chain was prepared in the same manner. Each of the synthesized genes was cut with *Nhe*I and *EcoR*I, and the cut fragment was incorporated into an expression vector pCAGGS between the *Nhe*I site and the *EcoR*I site, to thereby produce an anti-CDH3 chimeric antibody L-chain expression vector pCAGGS-IGK and H-chain expression vector pCAGGS-IGH.

[Sequence Listing]

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<150> JP 2010-028028

<151> 2010-02-10

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tgc tgg ctg cag tgc gcg gcc tcc gag ccg tgc cgg gcg gtc ttc agg 96

Cys Trp Leu Gln Cys Ala Ala Ser Glu Pro Cys Arg Ala Val Phe Arg

20 25 30

gag gct gaa gtg acc ttg gag gcg gga ggc gcg gag cag gag ccc ggc 144

Glu Ala Glu Val Thr Leu Glu Ala Gly Gly Ala Glu Gln Glu Pro Gly

35 40 45

cag gcg ctg ggg aaa gta ttc atg ggc tgc cct ggg caa gag cca gct 192

Gln Ala Leu Gly Lys Val Phe Met Gly Cys Pro Gly Gln Glu Pro Ala

50 55 60

ctg ttt agc act gat aat gat gac ttc act gtg cgg aat ggc gag aca 240

Leu Phe Ser Thr Asp Asn Asp Asp Phe Thr Val Arg Asn Gly Glu Thr

65 70 75 80

gtc cag gaa aga agg tca ctg aag gaa agg aat cca ttg aag atc ttc 288
Val Gln Glu Arg Arg Ser Leu Lys Glu Arg Asn Pro Leu Lys Ile Phe
85 90 95

cca tcc aaa cgt atc tta cga aga cac aag aga gat tgg gtg gtt gct 336
Pro Ser Lys Arg Ile Leu Arg Arg His Lys Arg Asp Trp Val Val Ala
100 105 110

cca ata tct gtc cct gaa aat ggc aag ggt ccc ttc ccc cag aga ctg 384
Pro Ile Ser Val Pro Glu Asn Gly Lys Gly Pro Phe Pro Gln Arg Leu
115 120 125

aat cag ctc aag tct aat aaa gat aga gac acc aag att ttc tac agc 432
Asn Gln Leu Lys Ser Asn Lys Asp Arg Asp Thr Lys Ile Phe Tyr Ser
130 135 140

atc acg ggg ccg ggg gca gac agc ccc cct gag ggt gtc ttc gct

gta 480

Ile Thr Gly Pro Gly Ala Asp Ser Pro Pro Glu Gly Val Phe Ala Val

145 150 155 160

gag aag gag aca ggc tgg ttg ttg aat aag cca ctg gac cgg gag 528

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165 170 175

gag att gcc aag tat gag ctc ttt ggc cac gct gtg tca gag aat ggt 576

Glu Ile Ala Lys Tyr Glu Leu Phe Gly His Ala Val Ser Glu Asn Gly

180 185 190

gcc tca gtg gag gac ccc atg aac atc tcc atc atc gtg acc gac cag 624

Ala Ser Val Glu Asp Pro Met Asn Ile Ser Ile Ile Val Thr Asp Gln

195 200 205

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225 230 235 240

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His Arg Ser Thr Gly Thr Ile Ser Val Ile Ser Ser Gly Leu Asp Arg
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gaa aaa gtc cct gag tac aca ctg acc atc cag gcc aca gac atg

gat 912

Glu Lys Val Pro Glu Tyr Thr Leu Thr Ile Gln Ala Thr Asp Met Asp

290 295 300

ggg gac ggc tcc acc acc acg gca gtg gca gta gtg gag atc ctt gat 960

Gly Asp Gly Ser Thr Thr Thr Ala Val Ala Val Val Glu Ile Leu Asp

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325 330 335

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Val Pro Glu Asn Ala Val Gly His Glu Val Gln Arg Leu Thr Val Thr

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Asp Leu Asp Ala Pro Asn Ser Pro Ala Trp Arg Ala Thr Tyr Leu Ile

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385 390 395 400

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Lys Asn Gln His Thr Leu Tyr Val Glu Val Thr Asn Glu Ala Pro Phe
405 410 415

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Lys Asn Gln His Thr Leu Tyr Val Glu Val Thr Asn Glu Ala Pro Phe

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Ala

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770 775 780

Ser Gly Ser Asp Ala Ala Ser Leu Ser Ser Leu Thr Ser Ser Ala Ser

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19