to be degraded or to induce toxicity of the expression system by accumulating in the intracellular environment of the expression system. Thus, an antibody may be expressed as a fusion protein comprising a preferred N-terminal sequence fused to a mature sequence of the heavy chain or the light chain of an antibody.

[0006] To effectively use this technique, the signal peptides must be identified. However, the amino acid sequence of most recombinant therapeutic antibodies disclosed in publicly available databases does not include the sequences of the signal peptides. Furthermore, the signal peptide information required for production in mammalian cell culture is also absent in the case of monoclonal antibodies isolated through methods such as phage display.

[0007] Rituxan is the only antibody for which heavy and light chain signal peptide sequence information is available in public database. However, the availability of the information does not entail that the original signal peptide is optimized for the secretion of the antibody in the desired host cell selected for production.

[0008] Another issue associated with production of recombinant antibodies comprising a signal peptide is the cleavage heterogeneity. Cleavage heterogeneity may arise from nonspecific cleavage of a signal peptide by a signal peptidase. As cleavage of the signal peptide occurs within the variable region in the N-terminus of both the heavy and light chains, non-specific cleavage may affect antigen recognition.

[0009] Recombinant IgG production may also be affected by glycan heterogeneity that is present at the *N*-glycosylation site of the C_H2 constant domain of the heavy chains. One recent study explored an LC/MS with a column-switching system to rapidly evaluate glycan heterogeneity.

[0010] Thus, there is a need to provide further signal peptides to create recombinant antibodies that are efficiently secreted and produced in expression systems.

SUMMARY OF THE INVENTION

[0011] Described below are antibodies of interest with a light chain and heavy chain fused to signal peptides to enhance secretion of the antibody during production and methods of determining a signal peptide for enhancing secretion of an antibody of interest.

Thus, in one aspect, there is provided an antibody an antibody of interest comprising a heavy chain

signal peptide and a light chain signal peptide, wherein the heavy chain signal peptide comprises a N-domain, a H-domain and a C-domain, wherein the heavy chain signal peptide is bound to the antibody via the C-terminal end of the C-domain; wherein the amino acid sequence of the N-domain of the heavy chain signal peptide is selected from the group consisting of MELGLS (SEQ ID NO: 293), MELGLR (SEQ ID NO: 294) and MEFGLS (SEQ ID NO: 297), wherein the amino acid sequence of the C-domain of the heavy chain signal peptide is selected from the group consisting of KGVQC (SEQ ID NO: 298), EGVQC (SEQ ID NO: 299), TGVQS (SEQ ID NO: 302) and RGVQC (SEQ ID NO: 303), and wherein the amino acid sequence of the H-domain of the heavy chain signal peptide is selected from the group consisting of WIFLLAIL (SEQ ID NO: 304), FLFVVAAA (SEQ ID NO: 308), WLFLVAIL (SEQ ID NO: 309) and WVFLVALF (SEQ ID NO: 310), wherein the amino acid sequence of the light chain signal peptide comprises MDMRVP (SEQ ID NO: 311) or MKYLLP (SEQ ID NO: 312), and wherein the antibody of interest is selected from the group consisting of trastuzumab (Herceptin, CAS number 180288-69-1), bevacizumab (Avastin, CAS number 216974-75-3), infliximab (Remicade, CAS number 170277-31-3), rituximab (Rituxan, CAS number 174722-31-7) and adalimumab (Humira, CAS number 331731-18-1).

[0012] ~~Thus, in a first aspect~~In one example, there is provided an antibody of interest comprising a heavy chain signal peptide, wherein the heavy chain signal peptide comprises a N-domain, a H-domain and a C-domain, wherein the heavy chain signal peptide is bound to the antibody via

the C-terminal end of the C-domain; wherein the H-domain comprises an amino acid sequence of formula (I):

$$X_{aa6}\text{-}X_{aa7}\text{-}X_{aa8}\text{-}X_{aa9}\text{-}X_{aa10}\text{-}X_{aa11}\text{-}X_{aa12}\text{-}X_{aa13},$$

wherein X_{aa6} is any one of Trp, Phe or Ile; X_{aa7} is any one of Val, Ile or Leu; X_{aa8} is Phe or Leu; X_{aa9} is Leu or Val; X_{aa10} is Val or Leu; X_{aa11} is Ala; X_{aa12} is any one of Leu, Ile or Ala; X_{aa13} is any one of Phe, Leu, Pro or Ala; and wherein the amino acid sequence of formula (I) has optionally one or two mutations; provided that an antibody showing the lowest secretion is excluded, wherein the lowest secretion is determined by a) fusing polynucleotides encoding the heavy chain of the antibody of interest to a polynucleotide encoding the heavy chain signal peptide as defined herein, to obtain different combinations of heavy chain signal peptides and antibody of interest; b) creating at least one expression vector comprising the polynucleotides defined under a); and c) quantifying secretion of the antibody of interest encoded by the vector referred to under b) after transfection into an expression system to determine the antibody with the lowest secretion.

[0013] In ~~a second aspect~~another example, there is provided an antibody of interest comprising a light chain signal peptide, wherein the light chain signal peptide comprises an amino acid sequence of formula (IV):

$$X_{bb6}\text{-}X_{bb7}\text{-}X_{bb8}\text{-}X_{bb9}\text{-}X_{bb10}\text{-}X_{bb11}\text{-}X_{bb12}\text{-}X_{bb13}\text{-}X_{bb14},$$

wherein X_{bb6} is Ala or Thr; X_{bb7} is Gln or Ala; X_{bb8} is Leu or Ala; X_{bb9} is Leu or Ala; X_{bb10} is Gly; X_{bb11} to X_{bb14} is Leu; or wherein the amino acid sequence of the formula (IV) has one or two mutations; provided that an antibody showing the lowest secretion is excluded, wherein the lowest secretion is determined by a) fusing polynucleotides encoding the light chain of the antibody of interest to a polynucleotide encoding the light chain signal peptide as defined herein to obtain different combinations of light chain signal peptides and antibody of interest; b) creating at least one expression vector comprising the polynucleotides defined under a); and c) quantifying secretion of the antibody of interest encoded by the vector referred to under b) after transfection into an expression system to determine the antibody with the lowest secretion.

[0014] In ~~a third~~another aspect, there is provided a polynucleotide encoding the antibody as described herein.

[0015] In a ~~fourth~~further aspect, there is provided a vector comprising the polynucleotide as defined above.

[0016] In a ~~fifth~~further aspect there is provided a host cell comprising the nucleotide as described hereinbefore and/or the vector as described hereinbefore.

[0017] In ~~a sixth aspect~~one example, there is provided a hybridoma cell line capable of producing the antibody as described above.

[0018] In ~~a seventh~~one aspect, there is provided an amino acid sequence comprising the amino acid sequence for trastuzumab (Herceptin, CAS number 180288-69-1); a heavy chain signal peptide of SEQ ID NO: 1 fused to the heavy chain amino acid sequence of trastuzumab; and a light chain signal peptide of SEQ ID NO: 2 fused to the light chain amino acid sequence of trastuzumab.

[0019] In ~~an eight~~another aspect, there is provided an amino acid sequence comprising the amino acid sequence for bevacizumab (Avastin, CAS number 216974-75-3); a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of bevacizumab; and a light chain signal peptide of SEQ ID NO: 5 fused to the light chain amino acid sequence of bevacizumab.

[0020] In ~~a ninth~~yet another aspect, there is provided an amino acid sequence comprising the amino acid sequence for infliximab (Remicade, CAS number 170277-31-3); a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of infliximab; and a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of infliximab.

[0021] In a ~~tenth~~further aspect, there is provided an amino acid sequence comprising the amino acid sequence for rituximab (Rituxan, CAS number 174722-31-7); a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of rituximab; and a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of rituximab.

[0022] In ~~an eleventh~~yet a further aspect, there is provided an amino acid sequence comprising the amino acid sequence for adalimumab (Humira, CAS number 331731-18-1); a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of adalimumab; and a light chain signal peptide of SEQ ID NO: 5 fused to the light chain amino acid sequence of adalimumab.

[0023] In ~~a twelfth aspect~~one example, there is provided a nucleotide encoding an antibody as described above.

[0024] In ~~a thirteenth~~one aspect, there is provided a polynucleotide sequence encoding the amino acid sequence as described herein.

[0025]

In ~~a fourteenth~~another aspect, there is provided a vector comprising a polynucleotide sequence as described herein. In a further aspect, there is provided a method of determining a signal peptide for enhancing secretion of an antibody of interest, wherein the method comprises:

(i) fusing

(a) a polynucleotide encoding the heavy chain of the antibody of interest to a polynucleotide encoding the amino acid sequence selected from the group consisting of MELGLSWIFLLAILKGVQC (H1, SEQ ID NO: 5), MELGLRWVFLVAILEGVQC (H2, SEQ ID NO: 6), MKHLWFFLLLVAAPRWVLS (H3, SEQ ID NO: 7), MDWTWRILFLVAAATGAHS (H4, SEQ ID NO: 8), MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), MEFGLSWLFLVAILKGVQC (H6, SEQ ID NO: 9), MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO:3) and MDLLHKNMKHLWFFLLLVAAPRWVLS (H8, SEQ ID NO: 11), and

(b) a polynucleotide encoding the light chain of the antibody of interest to a polynucleotide encoding the amino acid sequence MDMRVPAQLLGLLLLWLSGARC (L1, SEQ ID NO: 2) or MKYLLPTAAAGLLLLAAQPAMA (L2, SEQ ID NO: 4),

(ii) creating (a) at least one vector comprising a polynucleotide resulted from (i)(a) and (b) at least one vector comprising a polynucleotide resulted from (i)(b); and

(iii) quantifying and comparing secretion of the antibody after transfection of the at least one vector from (ii)(a) and the at least one vector from (ii)(b) into an expression system to determine the combination of heavy and light chain signal peptides that enhance expression and secretion of the antibody of interest the most.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0027] **Fig. 1** is a hierarchical clustering dendogram of signal peptides using agglomerative nesting to search for sequence similarity in (A) heavy chain signal peptides from a database of 173 human Ig heavy chains and (B) kappa (κ) light chain signal peptides from a database of 62

human kappa chains. Fig. 1 C to F is an enlargement of the dendogram obtained in Fig. 1 A showing the amino acid sequence of the signal peptides present in each of the created clusters H1 to H8, representative of the Ig heavy chain signal peptides. The selected amino acid sequence of SEQ ID: 1, 3, and 5 to 10 is highlighted for each one of the clusters H1 to H8. Fig. 1 G is an enlargement of the dendogram shown in Fig. 1 B showing the specific amino acid sequences of each of the 57 human kappa chains that were used to create the database. The specific amino acid sequence of the two clusters, L1 and L2, having the amino acid sequence of SEQ ID NO: 2 and 4, are highlighted.

[0028] **Fig. 2** is a table providing the amino acid sequences and DNA sequences of the heavy and light chain signal peptides that were selected for testing of the antibodies' improved production and secretion. The amino acid sequences correspond to the amino acid sequence already highlighted in Fig. 1 C to G.

Fig. 3 is a series of histogram plots showing the amount of Herceptin heavy chain produced when fused with one of the eight heavy chain signal peptides selected from H1 to H8, as described above, and when co-expressed with the Herceptin kappa light chain fused either to L1 or L2 signal peptide described above. Fig. 3 A and C: Ig ELISA results were plotted showing the monoclonal antibody titer (in ng/ml) with eight different heavy chain signal peptides and two different light chain signal peptides. Fig. 3A shows results when heavy chains were paired with light chain signal peptide 1 (L1), while Fig. 3C shows results when heavy chains were paired with light chain signal peptide 2 (L2). Fig. 3 B and D: The

Claims

1. An antibody of interest comprising a heavy chain signal peptide and a light chain signal peptide, wherein the heavy chain signal peptide comprises a N-domain, a H-domain and a C-domain, wherein the heavy chain signal peptide is bound to the antibody via the C-terminal end of the C-domain; wherein the amino acid sequence of the N-domain of the heavy chain signal peptide is selected from the group consisting of MELGLS (SEQ ID NO: 293), MELGLR (SEQ ID NO: 294) and MEFGLS (SEQ ID NO: 297),

wherein the amino acid sequence of the C-domain of the heavy chain signal peptide is selected from the group consisting of KGVQC (SEQ ID NO: 298), EGVQC (SEQ ID NO: 299), TGVQS (SEQ ID NO: 302) and RGVQC (SEQ ID NO: 303), and

wherein the amino acid sequence of the H-domain of the heavy chain signal peptide is selected from the group consisting of WIFLLAIL (SEQ ID NO: 304), FLFVVAAA (SEQ ID NO: 308), WLFLVAIL (SEQ ID NO: 309) and WVFLVALF (SEQ ID NO: 310), wherein the amino acid sequence of the light chain signal peptide comprises MDMRVP (SEQ ID NO: 311) or MKYLLP (SEQ ID NO: 312), and wherein the antibody of interest is selected from the group consisting of trastuzumab (Herceptin, CAS number 180288-69-1), bevacizumab (Avastin, CAS number 216974-75-3), infliximab (Remicade, CAS number 170277-31-3), rituximab (Rituxan, CAS number 174722-31-7) and adalimumab (Humira, CAS number 331731-18-1).

2. The antibody according to claim 1, wherein the amino acid sequence of the heavy chain signal peptide is selected from the group consisting of MELGLSWIFLLAILKGVQC (H1, SEQ ID NO: 5), MELGLRWVFLVAILEGVQC (H2, SEQ ID NO: 6), MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), MEFGLSWLFLVAILKGVQC (H6, SEQ ID NO: 9), MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO:3) and MDLLHKNMKHLWFFLLLVAAPRWVLS (H8, SEQ ID NO: 11).

3. The antibody according to claim 2, wherein the heavy chain of the antibody of interest is fused to a signal peptide selected from the group consisting of: MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), and MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO: 3).

4. The antibody according to any one of claims 1 to 3, wherein the amino acid sequence of the light chain signal peptide further comprises SGARC (SEQ ID NO: 313) or QPAMA (SEQ ID NO: 314).

5. The antibody according to any one of claims 1 to 4, wherein the amino acid sequence of the light chain signal peptide further comprises AQLLGLLLLWL (SEQ ID NO: 315) or TAAAGLLLLAA (SEQ ID NO: 316).

6. The antibody according to any one of claims 1 to 5, wherein the amino acid sequence of the light chain signal peptide is MDMRVPAQLLGLLLLWLSGARC (L1, SEQ ID NO: 2) or MKYLLPTAAAGLLLLAAQPAMA (L2, SEQ ID NO: 4).

7. A polynucleotide encoding an antibody of any one of claims 1 to 6.

8. A vector comprising the polynucleotide according to claim 7.

9. A host cell comprising the polynucleotide of claim 7 and/or the vector of claim 8.

10. An amino acid sequence comprising

a) the amino acid sequence for trastuzumab (Herceptin, CAS number 180288-69-1);
b) a heavy chain signal peptide of SEQ ID NO: 1 fused to the heavy chain amino acid sequence of trastuzumab; and
c) a light chain signal peptide of SEQ ID NO: 2 fused to the light chain amino acid sequence of trastuzumab.

11. An amino acid sequence comprising

a) the amino acid sequence for bevacizumab (Avastin, CAS number 216974-75-3);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of bevacizumab; and

c) a light chain signal peptide of SEQ ID NO: 2 fused to the light chain amino acid sequence of bevacizumab.

12. An amino acid sequence comprising

a) the amino acid sequence for infliximab (Remicade, CAS number 170277-31-3);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of infliximab; and

c) a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of infliximab.

13. An amino acid sequence comprising

a) the amino acid sequence for rituximab (Rituxan, CAS number 174722-31-7);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of rituximab; and

c) a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of rituximab.

14. An amino acid sequence comprising

a) the amino acid sequence for adalimumab (Humira, CAS number 331731-18-1);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of adalimumab; and

c) a light chain signal peptide of SEQ ID NO: 2 fused to the light chain amino acid sequence of adalimumab.

15. A polynucleotide sequence encoding the amino acid sequence of any one of claims 10 to 14.

16. A vector comprising a polynucleotide sequence according to claim 15.

17. The antibody of any one of claims 1 to 6, wherein the expression system is a host cell.

18. The antibody of any one of claims 1 to 6, wherein the host cell is a mammalian or bacterial cell.

19. The antibody of claim 17, wherein the expression system is selected from the group consisting of Chinese Hamster Ovary Cell (CHO cell), baculovirus expression vector system, *Leishmania tarentolae* expression system, galline cell, yeast expression system, and plant expression system.

20. A method of determining a signal peptide for enhancing secretion of an antibody of interest, wherein the method comprises:

(i) fusing

(a) a polynucleotide encoding the heavy chain of the antibody of interest to a polynucleotide encoding the amino acid sequence selected from the group consisting of MELGLSWIFLLAILKGVQC (H1, SEQ ID NO: 5), MELGLRWVFLVAILEGVQC (H2, SEQ ID NO: 6), MKHLWFFLLLVAAPRWVLS (H3, SEQ ID NO: 7), MDWTWRILFLVAAATGAHS (H4, SEQ ID NO: 8), MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), MEFGLSWLFLVAILKGVQC (H6, SEQ ID NO: 9), MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO:3) and MDLLHKNMKHLWFFLLLVAAPRWVLS (H8, SEQ ID NO: 11), and

(b) a polynucleotide encoding the light chain of the antibody of interest to a polynucleotide encoding the amino acid sequence MDMRVPAQLLGLLLLWLSGARC (L1, SEQ ID NO: 2) or MKYLLPTAAAGLLLLAAQPAMA (L2, SEQ ID NO: 4),

(ii) creating (a) at least one vector comprising a polynucleotide resulted from (i)(a) and (b) at least one vector comprising a polynucleotide resulted from (i)(b); and

(iii) quantifying and comparing secretion of the antibody after transfection of the at least one vector from (ii)(a) and the at least one vector from (ii)(b) into an expression system to determine the combination of heavy and light chain signal peptides that enhance expression and secretion of the antibody of interest the most.

21. The method of claim 20, wherein the expression system is a host cell.

22. The method of claim 21, wherein the host cell is a eukaryotic cell or a prokaryotic cell.

23. The method of claim 22, wherein the eukaryotic cell is selected from the group consisting of a mammalian cell, an avian cell, an insect cell, a fungal cell, a yeast cell or a plant cell.

24. The method of claim 20, wherein the expression system is selected from the group consisting of Chinese Hamster Ovary Cell (CHO cell), baculovirus expression vector system, *Leishmania tarentolae* expression system, galline cell, yeast expression system, and plant expression system.

25. The method of any one of claims 20 to 24, wherein the antibody is a monoclonal antibody.

26. The method of any one of claims 20 to 25, wherein the antibody has an isotype selected from the group consisting of mammalian IgG, IgM, IgD, IgA and IgE.

Claims

1. An antibody of interest comprising a heavy chain signal peptide, wherein the heavy chain signal peptide comprises a N-domain, a H-domain and a C-domain, wherein the heavy chain signal peptide is bound to the antibody via the C-terminal end of the C-domain; wherein the H-domain comprises an amino acid sequence of formula (I):

X_{aa6}-X_{aa7}-X_{aa8}-X_{aa9}-X_{aa10}-X_{aa11}-X_{aa12}-X_{aa13} (SEQ ID NO: 277),

wherein

X_{aa6} is any one of Trp, Phe or Ile;

X_{aa7} is any one of Val, Ile or Leu;

X_{aa8} is Phe or Leu;

X_{aa9} is Leu or Val;

X_{aa10} is Val or Leu;

X_{aa11} is Ala;

X_{aa12} is any one of Leu, Ile or Ala;

X_{aa13} is any one of Phe, Leu, Pro or Ala; and

wherein the amino acid sequence of formula (I) has optionally one or two mutations;

provided that an antibody showing the lowest secretion is excluded, wherein the lowest secretion is determined by a) fusing polynucleotides encoding the heavy chain of the antibody of interest to a polynucleotide encoding the heavy chain signal peptide as defined herein to obtain different combinations of heavy chain signal peptides and antibody of interest; b) creating at least one expression vector comprising the polynucleotides defined under a); and c) quantifying secretion of the antibody of interest encoded by the vector referred to under b) after transfection into an expression system to determine the antibody with the lowest secretion.

2. The antibody according to claim 1, wherein the N-domain comprises an amino acid sequence of formula (II):

M-X_{aa1}-X_{aa2}-X_{aa3}-X_{aa4}-X_{aa5} (SEQ ID NO: 278),

wherein

X_{aa1} is any one of Asp, Asn or Lys;

X_{aa2} is any one of Phe, Leu, His or Trp;

X_{aa3} is any one of Gly, Leu or Thr;

X_{aa4} is Leu or Trp;

X_{aa5} is any one of Ser, Arg or Phe;

wherein the amino acid sequence of formula (II) has optionally one or two mutations.

3. The antibody according to claim 1 or claim 2, wherein the C-domain comprises an amino acid sequence of the formula (III),

X_{aa14}-X_{aa15}-X_{aa16}-X_{aa17}-X_{aa18} (SEQ ID NO: 279),

wherein

X_{aa14} is any one of Arg, Lys, Asp or Thr;

X_{aa15} is Gly or Trp;

X_{aa16} is Val or Ala;

X_{aa17} is any one of Glu, Leu, or His;

X_{aa18} is Cys or Ser;

wherein the amino acid sequence of formula (III) has optionally one or two mutations.

4. The antibody according any one of the preceding claims further excluding antibodies whose secretion is no more than 1.5 fold higher when compared to the secretion of the antibody with the lowest secretion.

5. The antibody according to any one of the preceding claims, further excluding antibodies whose secretion is no more than 2 fold higher when compared to the secretion of the antibody with the lowest secretion.

6. The antibody according to any one of the preceding claims, wherein the amino acid sequence of the N-domain of the heavy chain signal peptide is selected from the group consisting of MELGLS (SEQ ID NO: 293), MELGLR (SEQ ID NO: 294), MKHLWF (SEQ ID NO: 295), MDWTWR (SEQ ID NO: 296) and MEFGLS (SEQ ID NO: 297).

7. The antibody according to any one of the preceding claims wherein the amino acid sequence of the C-domain of the heavy chain signal peptide is selected from the group consisting of KGVQC (SEQ ID NO: 298), EGVQC (SEQ ID NO: 299), RWVLS (SEQ

ID NO: 300), TGAHS (SEQ ID NO: 301), TGVQS (SEQ ID NO: 302) and RGVQC (SEQ ID NO: 303).

8. The antibody according to any one of the preceding claims wherein the amino acid sequence of the H-domain of the heavy chain signal peptide is selected from the group consisting of WIFLLAIL (SEQ ID NO: 304), WVFLVAIL (SEQ ID NO: 305), ILLLVAAP (SEQ ID NO: 306), ILFLVAAA (SEQ ID NO: 307), FLFVVAAA (SEQ ID NO: 308), WLFLVAIL (SEQ ID NO: 309) and WVFLVALF (SEQ ID NO: 310).

9. The antibody according to any one of the preceding claims, wherein the amino acid sequence of the heavy chain signal peptide is selected from the group consisting of MELGLSWIFLLAILKGVQC (H1, SEQ ID NO: 5), MELGLRWVFLVAILEGVQC (H2, SEQ ID NO: 6), MKHLWFFLLLVAAPRWVLS (H3, SEQ ID NO: 7), MDWTWRILFLVAAATGAHS (H4, SEQ ID NO: 8), MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), MEFGLSWLFLVAILKGVQC (H6, SEQ ID NO: 9), MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO:3) and MDLLHKNMKHLWFFLLLVAAPRWVLS (H8, SEQ ID NO: 11).

10. The antibody according to claim 9, wherein the heavy chain of the antibody of interest is fused to a signal peptide selected from the group consisting of: MDWTWRFLFVVAAATGVQS (H5, SEQ ID NO: 1), and MEFGLSWVFLVALFRGVQC (H7, SEQ ID NO: 3).

11. The antibody of any one of the preceding claims wherein the antibody of interest comprises the heavy chain signal peptide comprising one or two or three or four mutations in the heavy chain signal peptide.

12. An antibody of interest comprising a light chain signal peptide, wherein the light chain signal peptide comprises an amino acid sequence of formula (IV):

X_{bb6}-X_{bb7}-X_{bb8}-X_{bb9}-X_{bb10}-X_{bb11}-X_{bb12}-X_{bb13}-X_{bb14} (SEQ ID NO: 280),

wherein

X_{bb6} is Ala or Thr;

X_{bb7} is Gln or Ala;

X_{bb8} is Leu or Ala;

X_{bb9} is Leu or Ala;

X_{bb10} is Gly;

X_{bb11} to X_{bb14} is Leu; or

wherein the amino acid sequence of the formula (IV) has one or two mutations;

provided that an antibody showing the lowest secretion is excluded, wherein the lowest secretion is determined by a) fusing polynucleotides encoding the light chain of the antibody of interest to a polynucleotide encoding the light chain signal peptide as defined herein to obtain different combinations of light chain signal peptides and antibody of interest; b) creating at least one expression vector comprising the polynucleotides defined under a); and c) quantifying secretion of the antibody of interest encoded by the vector referred to under b) after transfection into an expression system to determine the antibody with the lowest secretion.

13. The antibody according to claim 12, wherein the light signal peptide is selected from signal peptides of mammalian kappa light chains.

14. The antibody according to claim 12 or claim 13, wherein the antibody further comprises an amino acid sequence of the formula (V):

$M\text{-}X_{bb1}\text{-}X_{bb2}\text{-}X_{bb3}\text{-}X_{bb4}\text{-}X_{bb5}$ (SEQ ID NO: 281),

wherein

X_{bb1} is Asp or Lys;

X_{bb2} is Met or Tyr;

X_{bb3} is Arg or Leu;

X_{bb4} is Val or Leu;

X_{bb5} is Pro; and

wherein the amino acid sequence of formula (V) has optionally one or two mutations.

15. The antibody according to any one of claim 12 to 14, wherein the antibody further comprises an amino acid sequence of the formula (VI):

$X_{bb15}\text{-}X_{bb16}\text{-}X_{bb17}\text{-}X_{bb18}\text{-}X_{bb19}\text{-}X_{bb20}\text{-}X_{bb21}$ (SEQ ID NO: 282),

wherein

X_{bb15} is Ala or Trp;

X_{bb16} is Ala or Leu;

X_{bb17} is Ser or Glu;

X_{bb18} is Gly or Pro;

X_{bb19} is Ala;

X_{bb20} is Arg or Met;

X_{bb21} is Ala or Cys; and

wherein the amino acid sequence of formula (VI) has optionally one or two mutations.

16. The antibody according any one of claims 12 to 15 further excluding antibodies whose secretion is no more than 1.5 fold higher when compared to the secretion of the antibody with the lowest secretion.

17. The antibody according to any one of claims 12 to 16 further excluding antibodies whose secretion is no more than 2.0 fold higher when compared to the secretion of the antibody with the lowest secretion.

18. The antibody according to any one of claims 12 to 17, wherein the amino acid sequence of the light chain signal peptide comprises MDMRVP (SEQ ID NO: 311) or MKYLLP (SEQ ID NO: 312).

19. The antibody according to any one of claims 12 to 18 wherein the amino acid sequence of the light chain signal peptide further comprises SGARC (SEQ ID NO: 313) or QPAMA (SEQ ID NO: 314).

20. The antibody according to any one of claims 12 to 19 wherein the amino acid sequence of the light chain signal peptide further comprises AQLLGLLLLWL (SEQ ID NO: 315) or TAAAGLLLLAA (SEQ ID NO: 316).

21. The antibody according to any one of claims 12 to 20, wherein the amino acid sequence of the light chain signal peptide is MDMRVPAQLLGLLLLWLSGARC (L1, SEQ ID NO: 2) or MKYLLPTAAAGLLLLAAQPAMA (L2, SEQ ID NO: 4).

22. The antibody according to any one of claims 12 to 21 wherein the antibody of interest comprises the light chain signal peptide comprising one or two or three or four mutations in the light chain signal peptide.

23. The antibody of any one of the preceding claims, wherein the antibody of interest comprises combinations of one heavy and one light chain signal peptide defined in claims 1 to 11 for the heavy chain and claim 12 to 22 for the light chain.

24. The antibody according to any one of the preceding claims, wherein the antibody of interest is a monoclonal antibody.

25. The antibody according to any one of the preceding claims, wherein the antibody of interest is selected from the group consisting of IgG, IgM, IgD, IgA and IgE.

26. The antibody according to any one of the preceding claims, wherein the antibody of interest is selected from the group consisting of an antibody used for the treatment of breast cancer, colorectal cancer, lung cancer, glioblastoma, kidney cancer and ovarian cancer; an autoimmune disease, lymphoma, leukemia, and transplant rejection.

27. The antibody according to claim 26, wherein the antibody of interest used for the treatment of breast cancer is trastuzumab (Herceptin, CAS number 180288-69-1) or bevacizumab (Avastin, CAS number 216974-75-3).

28. The antibody according to claim 26, wherein the antibody of interest used for the treatment of colorectal cancer, lung cancer, glioblastoma, kidney cancer and ovarian cancer is bevacizumab (Avastin, CAS number 216974-75-3).

29. The antibody according to claim 26, wherein the antibody of interest used for the treatment of an autoimmune disease is infliximab (Remicade, CAS number 170277-31-3) or rituximab (Rituxan, CAS number 174722-31-7) or adalimumab (Humira, CAS number 331731-18-1).

30. The antibody according to claim 29, wherein the autoimmune disease is selected from the group consisting of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis.

31. The antibody according to claim 26, wherein the antibody of interest used for the treatment of lymphoma, leukemia and transplant rejection is rituximab (Rituxan, CAS number 174722-31-7).

32. A polynucleotide encoding an antibody of any one of claims 1 to 31.

33. A vector comprising the polynucleotide according to claim 32.

34. A host cell comprising the polynucleotide of claim 32 and/or the vector of claim 33.

35. A hybridoma cell line capable of producing the antibody of any one of claims 1 to 31.

36. An amino acid sequence comprising
    a) the amino acid sequence for trastuzumab (Herceptin, CAS number 180288-69-1);
    b) a heavy chain signal peptide of SEQ ID NO: 1 fused to the heavy chain amino acid sequence of trastuzumab; and
    c) a light chain signal peptide of SEQ ID NO: 2.

37. An amino acid sequence comprising
    a) the amino acid sequence for bevacizumab (Avastin, CAS number 216974-75-3);
    b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of bevacizumab; and
    c) a light chain signal peptide of SEQ ID NO: 5 fused to the light chain amino acid sequence of bevacizumab.

38. An amino acid sequence comprising
    a) the amino acid sequence for infliximab (Remicade, CAS number 170277-31-3);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of infliximab; and

c) a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of infliximab.

39. An amino acid sequence comprising

a) the amino acid sequence for rituximab (Rituxan, CAS number 174722-31-7);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of rituximab; and

c) a light chain signal peptide of SEQ ID NO: 4 fused to the light chain amino acid sequence of rituximab.

40. An amino acid sequence comprising

a) the amino acid sequence for adalimumab (Humira, CAS number 331731-18-1);

b) a heavy chain signal peptide of SEQ ID NO: 3 fused to the heavy chain amino acid sequence of adalimumab; and

c) a light chain signal peptide of SEQ ID NO: 5 fused to the light chain amino acid sequence of adalimumab.

41. A polynucleotide sequence encoding the amino acid sequence of any one of claims 36 to 40.

42. A vector comprising a polynucleotide sequence according to claim 41.

43. The antibody of any one of claims 1 to 31, wherein the expression system is a host cell.

44. The antibody of any one of claims 1 to 31, wherein the host cell is a mammalian or bacterial cell.

45. The antibody of claim 43, wherein the expression system is selected from the group consisting of Chinese Hamster Ovary Cell (CHO cell), baculovirus expression vector

system, *Leishmania tarentolae* expression system, galline cell, yeast expression system, and plant expression system.