Claims

1. A method of producing at least two antibodies, wherein at least one antibody is a multispecific antibody, comprising

- providing cells with nucleic acid that encodes the at least two antibodies;
- culturing said cells;
- collecting the at least two antibodies from the culture; and
- separating the produced antibodies from half antibodies by ion exchange chromatography (IEX);

the method characterized in that the at least two antibodies exhibit IEX retention times that deviate by 10% or less from the average of the retention times of the at least two individual antibodies under the IEX conditions used.

2. The method of claim 1, further comprising selecting at least two antibodies that exhibit IEX retention times that deviate by 10% or less from the average of the retention times of the at least two individual antibodies under the conditions used for the IEX.

3. The method of claim 1 or 2, wherein the collection of the at least two antibodies from the culture comprises purifying antibodies from other proteins by antibody affinity purification, preferably by protein A extraction.

4. The method of claim 3, wherein the at least two affinity purified antibodies are further subjected to size-exclusion chromatography, gel-filtration chromatography and/or anion-exchange chromatography.

5. The method of any one of claims 1-4, wherein subsequent to the IEX the at least two collected antibodies are quantitatively analyzed for relative expression levels by hydrophobic interaction chromatography (HIC).

6. The method of claim 5, wherein the specificity of the at least two collected antibodies is verified by ELISA.

7. The method of any one of claims 1-6, wherein the retention times of the respective half antibodies are outside the range spanned by the retention times of the at least two antibodies.

8. The method of claim 7, wherein the cells produce 3 heavy chains.

9. The method of claim 8, wherein said heavy chains comprise domains for efficient heterodimerization of heavy chains.

10. The method of any one of claims 1-9, wherein at least one of said antibodies is a monospecific antibody.

11. The method of any one of claims 1-10, wherein at least two of said antibodies are multispecific antibodies.

12. The method of any one of claims 1-11, wherein at least two of said antibodies are bispecific antibodies.

13. The method of any one of claims 1-12, wherein at least two of said antibodies share an identical heavy chain.

14. The method of any one of claims 1-13, wherein said antibodies have isoelectric points (pI) that differ by 0.4 units or less from the average pI of said at least two antibodies.

15. The method of any one of claims 1-14, wherein the at least two antibodies are selected for having heavy and light chain combinations of the respective half antibodies that have retention times that differ by more than 10% of the average of the retention times of the full antibodies under the IEX conditions used.

16. The method of claim 15, wherein the pI of heavy and light chain combinations of the respective half antibodies differ by more than 0.4 units from the average pI of said at least two antibodies.

17. The method of any one of claims 1-16, wherein the at least two antibodies have heavy chains comprising a CH3 domain that favors heterodimerization of heavy chains.

18. The method of any one of claims 1-17, wherein said at least two antibodies have IgG heavy chains.

19. The method of any one of claims 8-18, wherein said cells produce three or more heavy chains, wherein one heavy chain comprises the amino acid substitutions L351K

and T366K (EU numbering) in the CH3 region and another heavy chain comprises the amino acid substitutions L351D and L368E in the CH3 region.

20. A method of producing at least two antibodies, wherein at least one antibody is a multispecific antibody, comprising

- providing cells with nucleic acid that encodes the at least two antibodies;
- culturing said cells;
- collecting the at least two antibodies from the culture; and
- separating the produced antibodies from half antibodies by ion exchange chromatography (IEX);

the method characterized in that the at least two antibodies exhibit IEX retention times that deviate by 10% or less from the average of the retention times of the individual antibodies under the IEX conditions used and wherein subsequent to the IEX the at least two collected antibodies are quantitatively analyzed for relative expression levels by hydrophobic interaction chromatography (HIC) and the specificity of the at least two collected antibodies is verified by ELISA.

21. A composition comprising 2-10 recombinant antibodies, characterized in that the IEX retention times of at least two of said antibodies deviate by 10% or less from the average of the retention times of the individual antibodies under the IEX conditions, wherein at least one of said antibodies is a multispecific antibody.

22. A composition comprising 2-10 recombinant antibodies, characterized in that the pI of at least two of said antibodies differ by 0.4 units or less from the average pI of said at least two antibodies, wherein at least one of said antibodies is a multispecific antibody.

23. The composition of claim 21 or 22, characterized in that the IEX retention times of all the antibodies deviate by 10% or less from the average of the retention times of the individual antibodies under the IEX conditions used and/or the pI of all the antibodies differ by 0.4 units or less from the average pI of said at least two antibodies.

24. The composition of any one of claims 21-23, wherein at least one of said antibodies is a monospecific antibody.

25. The composition of any one of claims 21-24, wherein at least two of the antibodies are multispecific antibodies.

26. The composition of any one of claims 21-25, wherein at least two of the antibodies are bispecific antibodies.

27. The composition of any one of claims 21-26, wherein at least two of said antibodies share an identical heavy chain.