CLAIMS:

1. A mixed mode chromatography method for separating a correctly folded etanercept from an incorrectly folded etanercept, comprising the steps of:

(a) binding a first etanercept-containing protein mixture comprising both correctly folded and incorrectly folded conformations of etanercept to a mixed mode chromatography resin having both ion exchange moieties and hydrophobic moieties;

(b) eluting the correctly folded etanercept from the mixed mode resin by contacting the mixed mode resin with a salt solution to obtain a second etanercept-containing protein mixture comprising a higher proportion of correctly folded etanercept than the first etanercept mixture.

2. The method of claim 1 wherein the mixed mode chromatography resin is a Capto™ MMC mixed mode chromatography resin or Capto™ Adhere mixed mode chromatography resin.

3. The method of claim 1, wherein the incorrectly folded etanercept constitutes less than about 10 wt.% of the eluate obtained in step (b); the correctly folded etanercept constitutes more than about 90 wt.% of the eluate obtained in step (b); and a combined amount of correctly folded and incorrectly folded etanercept constitutes at least about 95 wt.% of the eluate obtained in step (b).

4. The method of claim 3, wherein the mixed mode resin is Capto^{TM} Adhere and steps (a) and (b) are conducted at a pH of about 4.5 to about 8.5; and said salt solution optionally further comprises arginine.

5. The method of claim 3, wherein the salt solution is applied in step (b) through a gradient whereby the salt concentration is gradually increased.

6. The method of claim 1, wherein, during step (b), the pH of the salt solution contacting the resin in step (b) is gradually changed.

7. The method of claim 1, wherein the amount of correctly folded protein is at least about 70 wt.% of the amount of protein present in the protein mixture introduced to the resin in step (a).

8. The method of claim 1, wherein a protein mixture comprising at least 90 wt.% correctly folded etanercept is obtained without performing, or without need to perform any chromatographic separation or purification steps to separate correctly folded from incorrectly folded etanercept, other than the following:

(1) one or more purification steps, where such step(s) are employed solely to remove non-etanercept based impurities;

(2) the mixed mode chromatographic steps (a) and (b) recited in claim 1; and

(3) SEC, HIC or other analytical chromatographic steps performed solely for purposes of analysis.

9. The method of claim 1, wherein the method is practiced two or more times in the following manner:

performing a first mixed mode separation (separation #1) by carrying out steps (a) and (b); followed by

performing a second mixed mode separation (separation #2): by carrying out steps (a) and (b) again;

wherein the eluate obtained in step (b) of separation #1 is used as the solution containing a protein mixture in step (a) of separation #2.

10. The method of claim 9, wherein separation #1 and separation #2 are carried out in a manner selected from the following combinations:

Separation # 1 uses CAPTO MMC as the mixed mode chromatography resin and
Separation # 2 uses CAPTO ADHERE as the mixed mode chromatography resin;

Separation # 1 uses CAPTO ADHERE as the mixed mode chromatography resin and Separation # 2 uses CAPTO MMC as the mixed mode chromatography resin;

Separation # 1 uses CAPTO MMC as the mixed mode chromatography resin and
Separation # 2 uses CAPTO MMC as the mixed mode chromatography resin; or

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Separation # 1 uses CAPTO ADHERE as the mixed mode chromatography resin and
Separation # 2 uses CAPTO ADHERE as the mixed mode chromatography resin.

11. A method for producing an etanercept-containing protein mixture having high purity with respect to the amount of correctly folded versus incorrectly folded etanercept present therein, said method comprising the steps of:

(1) expressing etanercept in a mammalian expression system to obtain a harvest cell culture fluid containing an etanercept-containing protein mixture comprising both correctly folded and incorrectly folded etanercept;

(2) subjecting the harvest cell culture fluid obtained in step 1 to a purification process whereby an etanercept-containing protein mixture is obtained with a reduced amount of, or substantially free of, undesired impurities present in the harvest cell culture fluid produced in step (1);

(3) contacting the etanercept-containing protein mixture obtained in step (2) one or more times with a mixed mode chromatographic resin having both ion exchange moieties and hydrophobic interaction moieties in order to affix proteins contained in the mixture to the resin; and

4) contacting the resin having protein bound thereon from step 3 with a solution to elute correctly folded etanercept from the mixed mode resin to obtain an eluate comprising an etanercept-containing protein mixture having a higher proportion of correctly folded etanercept versus incorrectly

folded etanercept than the etanercept-containing mixture introduced to the resin in step 3;

wherein:

(i) the amount of protein present in the etanercept-containing protein mixture obtained from purification of step 2 is at least about 80 wt.% of the amount of the etanercept-based protein mixture present in the harvest cell culture fluid obtained in step 1.

(ii) the combined amount of correctly and incorrectly folded etanercept protein present in the protein mixture eluted in step 4 is at least about 60 wt.% of the amount thereof present in the protein mixture obtained from step 2;

(iii) the amount of correctly folded etanercept present in the eluate of step 4 is at least about 30 wt.%of the amount of etanercept-containing protein mixture present in the harvest cell culture fluid obtained in step 1; and

(iv) said correctly folded etanercept constitutes at least about 90 wt.% of the eluate obtained in step 4.

12. The method of claim 11, wherein the mixed mode resin is selected from the group consisting of CAPTO MMC and CAPTO ADHERE.

13. The method of claim 12, comprising the following additional steps:

Step (5): contacting the protein mixture obtained in the eluate of step 4 with a mixed mode chromatographic resin having both ion exchange moieties and

hydrophobic interaction moieties in order to affix the proteins contained in the mixture to the resin, and then;

step (6) contacting the resin with a solution to elute correctly folded etanercept therefrom to obtain an eluate comprising a protein mixture having a higher proportion of correctly folded versus incorrectly etanercept;

wherein the mixed mode resin used in said additional steps 5 and 6 is the same as, or different from the mixed mode resin used in steps 3 and 4.

14. The method of claim 1, which excludes use of single mode hydrophobic interaction chromatography as a means of separating correctly folded etanercept from incorrectly folded etanercept, except when performed solely for purposes of analysis.