

We claim:

1. CLAIMS

1. A method for identifying regions in a receptor Fc fusion protein that contribute to the viscosity of the receptor Fc fusion protein, comprising:
 - microdialysing samples of the receptor Fc fusion protein in a microdialysis cartridge against a buffer comprising deuterium for at least two different time periods;
 - subsequently quenching the microdialysis of the samples;
 - analyzing the quenched samples in an hydrogen/deuterium exchange mass spectrometry system to determine regions of the receptor Fc fusion protein in the sample that have reduced levels of deuterium relative to other regions of the receptor Fc fusion protein, wherein regions of the receptor Fc fusion protein that have reduced levels of deuterium contribute to the viscosity of the receptor Fc fusion protein.
2. The method of claim 1, wherein samples of the receptor Fc fusion protein comprise between 10 mg/mL to 200 mg/mL of protein.
3. The method of any one of claims 1 or 2, wherein samples of the receptor Fc fusion protein in the microdialysing step are in a buffer having a pH between 5.0 and 7.5.
4. The method of any one of claims 1-3, wherein the samples of receptor Fc fusion protein in the microdialysing step are in 10 mM Histidine at pH 6.0.
5. The method of any one of claims 1-4, wherein the buffer comprising deuterium comprises 10 mM Histidine at pH 6.0.
6. The method of any one of claims 1-5, wherein the microdialysis is performed at 2 to 6 °C.
7. The method of any one of claims 1-6, wherein at least one sample is microdialysed for 4 hours and at least another sample is microdialysed for 24 hours.
8. The method of any one of claims 1-7, wherein the quenching step is performed at -2 to 2 °C for 1 to 5 minutes.

9. The method of any one of claims 1-8, further comprising digesting the receptor Fc fusion protein into peptides before mass spectrometry analysis.
10. A method of modifying the viscosity of a receptor Fc fusion protein drug, comprising:
——identifying regions of the receptor Fc fusion protein drug that contribute to the viscosity of the receptor Fc fusion protein drug according to the method of any one of claims 1-9,
——modifying one or more of the regions identified as contributing to the viscosity of the receptor Fc fusion protein drug to modify the viscosity of the receptor Fc fusion protein drug.
11. The method of claim 10, wherein at least one of the regions identified as contributing to the viscosity of the receptor Fc fusion protein drug are modified by substituting one or more amino acids in the at least one region.
12. The method of any one of claims 10 or 11, wherein the one or more regions identified as contributing to the viscosity of the receptor Fc fusion protein drug are modified to reduce the viscosity of the receptor Fc fusion protein drug.
13. The method of any one of claims 1-12, wherein the receptor Fc fusion protein is selected from the group consisting of an antibody, a fusion protein, a recombinant protein, or a combination thereof.
14. The method of any one of claims 10-13, wherein the receptor Fc fusion protein drug is a concentrated monoclonal antibody.
15. ~~The~~ A receptor Fc fusion protein drug produced by ~~the~~a method comprising the steps of any:
a) identifying regions of the receptor Fc fusion protein drug that contribute to the viscosity of the receptor Fc fusion protein drug by:
i) microdialysing samples of the receptor Fc fusion protein in a microdialysis cartridge, without dilution, against a buffer comprising deuterium for at least two different time periods;
ii) subsequently quenching the microdialysis of the samples; and
iii) analyzing the quenched samples in an hydrogen/deuterium exchange mass spectrometry system to determine regions of the receptor Fc fusion protein in

the sample that have reduced levels of deuterium relative to other regions of the receptor Fc fusion protein, wherein regions of the receptor Fc fusion protein that have reduced levels of deuterium contribute to the viscosity of the receptor Fc fusion protein; and

b) modifying one of claims 10-14 or more of the regions identified as contributing to the viscosity of the receptor Fc fusion protein drug to modify the viscosity of the receptor Fc fusion protein drug.