and glycan structure for immunosuppression. (Anthony, *et al.*, 2008, Science 320: 373-376 and WO 2007/117505).

However, only a minor population of IgG in IVIG have glycans terminating in α2,6 sialic acids (sFc) and the anti-inflammatory activity. As a result, for the suppression of autoantibody triggered inflammation in a variety of clinical settings, one has to administer IVIG at high doses (1-2g/kg), to enrich sialylated IgGs, or otherwise to increase the sialylation of IgGs (US Application Nos. 20080206246, and 20090004179, and Nimmerjahn *et al. Annu Rev Immunol* 26, 513-533 (2008)).

The present invention addresses and meets the above-mentioned needs by identifying sialylation–free anti-inflammatory polypeptides.

SUMMARY

This disclosure relates to agents, such as polypeptides and antibodies, and methods for treating inflammatory disorders, e.g., autoimmune diseases.

In one aspect, the present invention refers to an isolated polypeptide comprising a modified sequence that is at least 75% identical to an IgG Fc region and has a conservative substitution at a position corresponding to F241 of SEQ ID No: 1, wherein the modified sequence is free of sialylation and the polypeptide has an anti-inflammatory activity that is higher than that of a parent polypeptide. In one ~~aspect~~example, the present invention provides an isolated polypeptide comprising a modified sequence that is at least 75% identical to an IgG Fc region, wherein the modified sequence is free of sialylation and the polypeptide has an anti-inflammatory activity that is higher than that of a parent polypeptide.

Accordingly, one example of this disclosure features an isolated polypeptide comprising a modified sequence that is at least 75% (e.g., any number between 75% and 100%, inclusive, e.g., 70 %, 80%, 85%, 90%, 95%, 99%, and 100%) identical to an IgG Fc region. The modified sequence is free of sialylation and the polypeptide has an anti-inflammatory activity that is higher than that of a parent polypeptide. The parent polypeptide can comprise the IgG Fc region, such as the sequence of SEQ ID NO: 1 listed below. In some examples, the polypeptide has ability to bind to DC-SIGN, and to bind to hFcγRIIA or RIIB. In one example, the isolated polypeptide has an ability to bind to hFcγRIIA or RIIB at a K_D of $2x10^{-5}$ M or lower (i.e., K_A of 5.0×10^4 M^{-1} or higher). Preferably, the modified sequence has a FA241 mutation. The modified sequence can be at least 75% (e.g., any number between 75% and 100%, inclusive, e.g., 70 %, 80%, 85%, 90%, 95%, 99%, and 100%) identical to SEQ ID NO: 2. In some examples, the modified sequence comprises or consists essentially of SEQ ID NO: 2.

In another aspect, the present invention refers to a method for making a polypeptide having an anti-inflammatory activity, the method comprising: providing a parent polypeptide having the sequence of an IgG Fc region or a first nucleic acid sequence encoding the parent polypeptide; and modifying the parent polypeptide to obtain a modified polypeptide so that the modified polypeptide is free of sialylation and mimics the structure of a sialylated form of the IgG Fc region, wherein the modifying step comprises introducing a conservative substitution at a position corresponding to F241 of SEQ ID No: 1. In another ~~aspect~~example, the present invention provides a method for making a polypeptide having an anti-inflammatory activity, the method comprising:

providing a parent polypeptide having the sequence of an IgG Fc region or a first nucleic acid sequence encoding the parent polypeptide; and

modifying the parent polypeptide to obtain a modified polypeptide so that the modified polypeptide is free of sialylation and mimics the structural of a sialylated form of the IgG Fc region.

In another example, the disclosure provides a method for making a polypeptide having an anti-inflammatory activity. The method includes, among others, steps of providing a parent polypeptide having the sequence of an IgG Fc region or a first nucleic acid sequence encoding the parent polypeptide; and modifying the parent polypeptide to obtain a modified polypeptide so that the modified polypeptide is free of sialylation and

CLAIMS

WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising a modified sequence that is at least 75% identical to an IgG Fc region and has a conservative substitution at a position corresponding to F241 of SEQ ID No: 1, wherein the modified sequence is free of sialylation and the polypeptide has an anti-inflammatory activity that is higher than that of a parent polypeptide.

2. The isolated polypeptide of claim 1, wherein the parent polypeptide comprises the IgG Fc region.

3. The isolated polypeptide of claim 1 or 2, wherein the IgG Fc region comprises the sequence of SEQ ID NO: 1.

4. The isolated polypeptide of any one of claims 1-3, wherein the isolated polypeptide has an ability to bind to DC-SIGN.

5. The isolated polypeptide of any one of claims 1-4, wherein the isolated polypeptide has an ability to bind to hFcγRIIA or RIIB

6. The isolated polypeptide of any one of claims 1-5, wherein the isolated polypeptide has an ability to bind to hFcγRIIA or RIIB at a K_D of $2x10^{-5}$ M or lower (i.e., K_A of 5.0×10^4 M^{-1} or higher).

7. The isolated polypeptide of any one of claims 1-6, wherein the modified sequence has a FA241 mutation.

8. The isolated polypeptide of any one of claims 1-7, wherein the modified sequence is at least 75% identical to SEQ ID NO: 2.

9. The isolated polypeptide of claim 8, wherein the modified sequence is at least 80% identical to SEQ ID NO: 2.

10. The isolated polypeptide of claim 9, wherein the modified sequence is at least 90% identical to SEQ ID NO: 2.

11. The isolated polypeptide of claim 10, wherein the modified sequence is at least 95% identical to SEQ ID NO: 2.

12. The isolated polypeptide of claim 11, wherein the modified sequence is at least 99% identical to SEQ ID NO: 2.

13. The isolated polypeptide of claim 12, wherein the modified sequence comprises SEQ ID NO: 2.

14. The isolated polypeptide of claim 9, wherein the modified sequence consists essentially of SEQ ID NO: 2.

15. A method for making a polypeptide having an anti-inflammatory activity, the method comprising:

providing a parent polypeptide having the sequence of an IgG Fc region or a first nucleic acid sequence encoding the parent polypeptide; and

modifying the parent polypeptide to obtain a modified polypeptide so that the modified polypeptide is free of sialylation and mimics the structure of a sialylated form of the IgG Fc region, wherein the modifying step comprises introducing a conservative substitution at a position corresponding to F241 of SEQ ID No: 1.

16. The method of claim 15, wherein the modifying step is conducted by modifying the first nucleic acid sequence to obtain a second nucleic acid encoding the modified polypeptide.

17. A polypeptide made by the method of claim 15 or 16.

18. An isolated nucleic acid comprising a sequence encoding the polypeptide of any of claims 1-14 and 17.