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 ~~invention~~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 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 ~~aspect~~example of this ~~invention~~ 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 ~~embodiments~~examples, the polypeptide has ability to bind to DC-SIGN, and to bind to hFcγRIIA or RIIB. In one ~~embodiment~~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 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 ~~aspect~~example, the ~~invention~~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

mimics the structural of a sialylated form of the IgG Fc region. The modifying step can be conducted by modifying the first nucleic acid sequence to obtain a second nucleic acid encoding the modified polypeptide. The ~~invention~~disclosure also provides a polypeptide made by the just-described method.

In another aspect, the present invention provides an isolated nucleic acid comprising a sequence encoding the polypeptide described above.

In another aspect, the present invention provides an expression vector comprising a nucleic acid.

In another aspect, the present invention provides a host cell comprising a nucleic acid.

In ~~a third aspect~~another example, the invention features an isolated nucleic acid comprising a sequence encoding the polypeptide described above; an expression vector comprising the nucleic acid; and a host cell comprising the nucleic acid. In another aspect, the present invention provides a method of producing a polypeptide, comprising culturing the host cell in a medium under conditions permitting expression of a polypeptide encoded by the nucleic acid, and purifying the polypeptide from the cultured cell or the medium of the cell.

The ~~invention~~disclosure also features a method of producing a polypeptide. The method includes culturing the host cell in a medium under conditions permitting expression of a polypeptide encoded by the nucleic acid, and purifying the polypeptide from the cultured cell or the medium of the cell.

In another aspect, the present invention provides a pharmaceutical formulation comprising (i) the polypeptide or a nucleic acid and (ii) a pharmaceutically acceptable carrier. In ~~a fourth aspect~~another example, the ~~invention~~ disclosure features a pharmaceutical formulation comprising (i) the polypeptide or nucleic acid described above, and (ii) a pharmaceutically acceptable carrier.

In another aspect, the present invention provides use of the polypeptide of the present invention, or a nucleic acid encoding the polypeptide in the manufacture of a medicament for treating an inflammatory disease. In ~~a fifth aspect~~another example, the ~~invention~~disclosure provides a method of treating an inflammatory disease. The method includes administering to a subject in need thereof a therapeutically effective amount of the above-described polypeptide or nucleic acid encoding the polypeptide. Also provided is use of the polypeptide or nucleic acid in the manufacture of a medicament for treating an inflammatory disease. In another aspect, the present invention provides use of a polypeptide or a nucleic acid in the manufacture of a medicament for treating an inflammatory disease.

The ~~invention~~disclosure also features an isolated polypeptide, nucleic acid, expression vector, host cell, composition, or method for treating an inflammatory disease substantially as shown and described herein.

The details of one or more ~~embodiments~~examples of the ~~invention~~disclosure are set forth in the description below. Other features, objects, and advantages of the ~~invention~~disclosure will be apparent from the description and from the claims.

DESCRIPTION OF DRAWINGS

FIGs. 1a-c are diagrams and photographs showing that α2,6-linked sialic acid conferred DC-SIGN binding activity to recombinant human IgG1 Fc.

FIGs. 2a-b are diagrams and photographs showing that disrupting Fc-glycan interactions conferred DC-SIGN binding activity to recombinant human IgG1 Fc.

FIG. 3 is as set of diagrams showing that the FA241 mutation in hIgG1 Fc recapitulates anti-inflammatory activity of α2,6 sFc.

19. An expression vector comprising a nucleic acid of claim 18.

20. A host cell comprising a nucleic acid of claim 18.

21. A method of producing a polypeptide, comprising culturing the host cell of claim 20 in a medium under conditions permitting expression of a polypeptide encoded by the nucleic acid, and purifying the polypeptide from the cultured cell or the medium of the cell.

22. A pharmaceutical formulation comprising (i) the polypeptide of any of claims 1-14 and 17 or a nucleic acid of claim 18, and (ii) a pharmaceutically acceptable carrier.

23. ~~A method of treating an inflammatory disease, comprising administering to a subject in need thereof a therapeutically effective amount~~ Use of the polypeptide of any of claims 1-14 and 17, or a nucleic acid encoding the polypeptide in the manufacture of a medicament for treating an inflammatory disease.

24. ~~An isolated polypeptide, nucleic acid, expression vector, host cell, or composition substantially as shown and described herein~~.

~~25. A method for treating an inflammatory disease substantially as shown and described herein.~~

~~26.~~ Use of a polypeptide of any of claims 1-14 and 17 or a nucleic acid of claim 18 in the manufacture of a medicament for treating an inflammatory disease.