IMMUNOSUPPRESSIVE COMPOSITION FOR USE IN TREATING IMMUNOLOGICAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of Singapore provisional application No. 10201606949Q, filed 19 August 2016, the contents of it being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of molecular biology. In particular, the present invention relates to compositions for the treatment of immunological disorders.

BACKGROUND OF THE INVENTION

[0003] Mesenchymal stromal cell (MSC) therapy has been shown to be effective in, for example, modulating immunological disorders, alloimmune disease (graft versus host disease (GVHD) after allogeneic hematopoietic cell transplantations) and autoimmune diseases systemic lupus erythematosus (SLE), lupus nephritis, type-I diabetes mellitus, systemic sclerosis, inflammatory bowel disease (IBD), Crohn's disease, etc.). However, MSC therapy trials still face challenges regarding unforeseen long-term complications, potential tumorigenicity and uncontrolled differentiation to unwanted cells or tissue types. Also, the use of human mesenchymal stromal cells raises the question of the equivalence of cells isolated from different sources and using different expansion methods.

[0004] Therefore, there is a need for a replacement for mesenchymal stromal cell (MSC) therapy for the treatment of immunological diseases.

SUMMARY

[0005] In one aspect, the present disclosure refers to the use of a pharmaceutical composition comprising CXCL5 (ENA-78) in the manufacture of a medicament for the treatment of an immunological disorder, wherein the immunological disorder is an alloimmune or an autoimmune disease.

[0005a] In another aspect, the present disclosure refers to the use of a pharmaceutical composition comprising at least one antibody and/or at least one mesenchymal stromal cell-derived protein, wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β),

CCL-1 (I-309) and CCL24 (Eotaxin-2); wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-3), CCL8 (MCP-2), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2), wherein the immunological disorder is an alloimmune or an autoimmune disease, and wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C19a	IL-10; OPG; CXCL5; CXCL6
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
C27a	CXCL5

C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG
C33a	OPG; CXCL5
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5
C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

[0005b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising at least one antibody and at least one mesenchymal stromal cell-derived protein, wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2); wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-3), CCL8 (MCP-2), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2), and wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24

C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5
C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

[0005c] In yet another aspect, the present disclosure refers to a pharmaceutical composition as disclosed herein for modulating the immune system.

[0005d] In still another aspect, the present disclosure refers to a kit comprising at least one antibody and at least one mesenchymal stromal cell-derived protein as disclosed herein.

~~[0005]~~ [0005e] In one ~~aspect~~example, the present ~~invention~~ disclosure refers to a pharmaceutical composition comprising at least one antibody and at least one mesenchymal stromal cell-derived protein, wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2); wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-2), CCL8 (MCP-3), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2).

[0006] In one example, the present application discloses the pharmaceutical composition described herein, wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C19a	IL-10; OPG; CXCL5; CXCL6
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
C28a	anti-CCL1; anti-CCL24
C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG

C32a	anti-CCL24; CXCL5
C33a	OPG; CXCL5
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5
C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

[0007] In another example, the present application discloses the pharmaceutical composition as described herein, wherein the pharmaceutical composition comprises CXCL5 and an anti-CCL24 antibody (C32a).

[0008] In yet another example, the present application discloses the pharmaceutical composition as described herein, wherein the antibody is present in a concentration of about 0.05µg/ml to about 5µg/ml.

[0009] In a further example, the present application discloses the pharmaceutical composition as described herein, wherein the antibody is present in a concentration of about 1µg/ml or about 2µg/ml.

[0010] In one example, the present application discloses the pharmaceutical composition as described herein, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 0.5ng/ml to about 75ng/ml.

[0011] In another example, the present application discloses the pharmaceutical composition as described herein, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 10ng/ml or 50ng/ml.

[0012] In another ~~aspect~~example, the present ~~invention refers to~~application discloses a method of treating an immunological disorder, the method comprising administration of a pharmaceutical composition comprising at least one antibody and/or at least one mesenchymal stromal cell-derived protein, wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2); wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-2), CCL8 (MCP-3), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2).

[0013] In yet another ~~aspect~~example, the present ~~invention refers to~~application discloses a method of modulating the immune system, the method comprising administration of a pharmaceutical composition as described herein.

[0014] In one example, the present application discloses the method described herein, wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C19a	IL-10; OPG; CXCL5; CXCL6
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
C24a	anti-CCL1

C25a	anti-CCL24
C26a	OPG
C27a	CXCL5
C28a	anti-CCL1; anti-CCL24
C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG
C32a	anti-CCL24; CXCL5
C33a	OPG; CXCL5
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5
C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

[0015] In another example, the present application discloses the method as described herein, wherein the pharmaceutical composition comprises CXCL5 and an anti-CCL24 antibody (C32a).

[0016] In yet another example, the present application discloses the method as described herein, wherein the immunological disorder is an alloimmune disease or an autoimmune disease.

[0017] In a further example, the present application disclose the method as described herein, wherein the alloimmune disease is selected from the group consisting of graft versus host disease (GVHD) after allogeneic hematopoietic cell transplantations, alloimmune disease resulting from skin transplant, alloimmune disease resulting from kidney transplant, alloimmune disease resulting from liver transplant, and hemolytic disease of the foetus and newborn.

[0018] In yet another example, the present application discloses the method as described herein, wherein the autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), lupus nephritis, type-I diabetes mellitus, systemic sclerosis, inflammatory bowel disease (IBD) and Crohn's disease.

[0019] In a further example, the present application discloses the method as disclosed herein, wherein the pharmaceutical composition results in a decrease in the concentration of one or more

of the circulating pro-inflammatory cytokines selected from the group consisting of IFN-γ, IL-6, IL-17A, IL-8, MIP-1β and MCP-1 in the subject.

[0020] In one example, the present invention discloses the method as described herein, wherein the pharmaceutical composition results an increase or a decrease in the concentration of at least one mesenchymal stromal cell-derived protein in a subject results in an immunosuppressive effect, wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7, CCL8, CCL20, IL-10, CXCL5, CXCL6, M-CSF, IL-1β, CCL-1 and CCL24.

[0021] In a further ~~aspect~~example, the present ~~invention~~ disclosure refers to a kit comprising at least one antibody and at least one mesenchymal stromal cell-derived protein as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0023] **Figure 1** shows a column graph with data indicating that the immunosuppressive effect of BM-MSC is mainly attributable to soluble factors. Mixed lymphocyte reaction (MLR) experiments were initiated with 1.6×10^5 of two HLA-mismatched UCB-MNCs at 15:1 E/T ratio for 20 hours. Cell mediated cytotoxicity was determined by LDH detection. Transwell inserts with a pore size of 8μm were used. The different distance between insert and well bottom was varied. Results were expressed as mean ± S.D. For multiple comparisons, Bonferroni's test was used to correct the p-value for t-test (* $p<0.05$; ** $p<0.01$; *** $p<0.001$).

[0024] **Figure 2** shows images of a cytokine antibody array assay, whereby supernatant from cultures of MLR, BM-MSCs and MLR with BM-MSCs was collected and applied on Raybio human cytokine antibody array G series 1000 (containing 120 kinds of cytokines antibody) according to the manufacturer's instructions. Incubated slides were scanned and analysed by Axon Genepix 6.1. Positive and negative control wells were marked by white boxes, while wells with more than 3-fold change in protein expression level were marked by grey box (upregulated) and black box (downregulated).

[0025] **Figure 3** shows dose response curves showing the determination of the optimal working concentration of each factor. (A-C) Dose response curves of upregulated factors. (D)

Claims

1. An pharmaceutical composition comprising at least one antibody and at least one mesenchymal stromal cell-derived protein,
wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2);
wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-2), CCL8 (MCP-3), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2).

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20

~~C19a~~	~~IL-10; OPG; CXCL5; CXCL6~~
~~C20a~~	~~anti-CCL24; OPG; CXCL6; CCL20~~
~~C21a~~	~~anti-CCL24; OPG; CXCL5; anti-CCL1~~
~~C22a~~	~~anti-CCL24; IL-10; CXCL6; anti-CCL1~~
~~C23a~~	~~anti-CCL24; IL-10; CXCL5; CCL20~~
~~C28a~~	~~anti-CCL1; anti-CCL24~~
~~C29a~~	~~anti-CCL1; OPG~~
~~C30a~~	~~anti-CCL1; CXCL5~~
~~C31a~~	~~anti-CCL24; OPG~~
~~C32a~~	~~anti-CCL24; CXCL5~~
~~C33a~~	~~OPG; CXCL5~~
~~C34a~~	~~anti-CCL1; anti-CCL24; OPG~~
~~C35a~~	~~anti-CCL1; anti-CCL24; CXCL5~~
~~C36a~~	~~anti-CCL1; OPG; CXCL5~~
~~C37a~~	~~anti-CCL24; OPG; CXCL5~~
~~C38a~~	~~anti-CCL1; anti-CCL24; OPG; CXCL5~~

~~3. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises CXCL5 and an anti-CCL24 antibody (C32a).~~

~~4. The pharmaceutical composition of any one of the preceding claims, wherein the antibody is present in a concentration of about 0.05µg/ml to about 5µg/ml~~

~~5. The pharmaceutical composition of claim 4, wherein the antibody is present in a concentration of about 1µg/ml or about 2µg/ml.~~

~~6. The pharmaceutical composition of any one of the preceding claims, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 0.5ng/ml to about 75ng/ml.~~

~~7. The pharmaceutical composition of claim 6, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 10ng/ml or 50ng/ml.~~

1. Use of a pharmaceutical composition comprising CXCL5 (ENA-78) in the manufacture of a medicament for the treatment of an immunological disorder, wherein the immunological disorder is an alloimmune or an autoimmune disease.

~~8.~~2. ~~A method of treating an immunological disorder, the method comprising administration~~Use of a pharmaceutical composition comprising at least one antibody and/or at least one mesenchymal stromal cell-derived protein,

wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2);

wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7 (MCP-~~2~~3), CCL8 (MCP-~~3~~2), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2), wherein the immunological disorder is an alloimmune or an autoimmune disease, and ~~.~~

~~9. A method of modulating the immune system, the method comprising administration of a pharmaceutical composition as defined in claim 8 to a subject.~~

~~10. The method of any one of claims 8 to 9,~~ wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF

C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C19a	IL-10; OPG; CXCL5; CXCL6
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
~~C24a~~	~~anti-CCL1~~
~~C25a~~	~~anti-CCL24~~
~~C26a~~	~~OPG~~
C27a	CXCL5
~~C28a~~	~~anti-CCL1; anti-CCL24~~
C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG
~~C32a~~	~~anti-CCL24; CXCL5~~
C33a	OPG; CXCL5
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5
C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

~~11. The method of claim 10, wherein the pharmaceutical composition comprises CXCL5 and an anti-CCL24 antibody (C32a).~~

~~12. The method of claim 10, wherein the immunological disorder is an alloimmune disease or an autoimmune disease.~~

~~13.~~3. The use according to claim 1 or 2~~method of claim 12~~, wherein the alloimmune disease is selected from the group consisting of graft versus host disease (GVHD) after allogeneic hematopoietic cell transplantations, alloimmune disease resulting from skin transplant, alloimmune disease resulting from kidney transplant, alloimmune disease resulting from liver transplant, and hemolytic disease of the foetus and newborn.

~~14.~~4. The use according to claim 1 or 2~~method of claim 12~~, wherein the autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), lupus nephritis, type-I diabetes mellitus, systemic sclerosis, rheumatoid arthritis, vasculitis, inflammatory bowel disease (IBD) and Crohn's disease.

~~15.~~5. The ~~method~~ use ~~of any one of claims 8 to 9~~according to claim 1 or 2, wherein the pharmaceutical composition results in a decrease in the concentration of one or more of the circulating pro-inflammatory cytokines selected from the group consisting of IFN-γ, IL-6, IL-17A, IL-8, MIP-1β and MCP-1 in the subject.

~~16. The method of any one of claims 8 to 9, wherein the pharmaceutical composition results an increase or a decrease in the concentration of at least one mesenchymal stromal cell-derived protein in a subject results in an immunosuppressive effect, wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2), OPG, CCL7, CCL8, IL-10, CCL20, CXCL5, CXCL6, M-CSF, IL-1β, CCL-1 and CCL24.~~

6. A pharmaceutical composition comprising at least one antibody and at least one mesenchymal stromal cell-derived protein,
wherein the antibody targets one or more of the cytokines selected from the group consisting of macrophage colony-stimulating factor (M-CSF), Interleukin-1beta (IL-1β), CCL-1 (I-309) and CCL24 (Eotaxin-2); wherein the mesenchymal stromal cell-derived protein is selected from the group consisting of PGE2 (prostaglandin E2),

OPG, CCL7 (MCP-3), CCL8 (MCP-2), CCL20 (MIP-3α), CXCL5 (ENA-78), IL-10 and CXCL6 (GCP-2), and wherein the pharmaceutical composition is as shown in the table below:

Composition	
C2a	CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF; anti-CCL24
C3a	CCL8; CCL7; OPG; IL-10; anti-CCL24
C4a	CCL8; CCL7; OPG; IL-10; CXCL5; anti-CCL1; anti-IL1b; anti-M-CSF
C5a	CCL20; CXCL6; OPG; IL-10; anti-IL1b; anti-M-CSF
C6a	CCL20; CXCL6; OPG; IL-10; CXCL5; anti-CCL1; anti-CCL24
C7a	CCL20; CXCL6; CCL8; CCL7; anti-IL1b; anti-M-CSF; anti-CCL24
C8a	CCL20; CXCL6; CCL8; CCL7; CXCL5; anti-CCL1
C9a	PGE2; CXCL6; CCL7; IL-10; anti-CCL1; anti-M-CSF
C10a	PGE2; CXCL6; CCL7; IL-10; CXCL5; anti-IL1b; anti-CCL24
C11a	PGE2; CXCL6; CCL8; OPG; anti-CCL1; anti-M-CSF; anti-CCL24
C12a	PGE2; CXCL6; CCL8; OPG; CXCL5; anti-IL1b
C13a	PGE2; CCL20; CCL7; OPG; anti-CCL1; anti-IL1b
C14a	PGE2; CCL20; CCL7; OPG; CXCL5; anti-M-CSF; anti-CCL24
C15a	PGE2; CCL20; CCL8; IL-10; anti-CCL1; anti-IL1b; anti-CCL24
C16a	PGE2; CCL20; CCL8; IL-10; CXCL5; anti-M-CSF
C17a	CXCL5; CXCL6; anti-CCL1; CCL20
C18a	IL-10; OPG; anti-CCL1; CCL20
C20a	anti-CCL24; OPG; CXCL6; CCL20
C21a	anti-CCL24; OPG; CXCL5; anti-CCL1
C22a	anti-CCL24; IL-10; CXCL6; anti-CCL1
C23a	anti-CCL24; IL-10; CXCL5; CCL20
C29a	anti-CCL1; OPG
C30a	anti-CCL1; CXCL5
C31a	anti-CCL24; OPG
C34a	anti-CCL1; anti-CCL24; OPG
C35a	anti-CCL1; anti-CCL24; CXCL5

C36a	anti-CCL1; OPG; CXCL5
C37a	anti-CCL24; OPG; CXCL5
C38a	anti-CCL1; anti-CCL24; OPG; CXCL5

7. The pharmaceutical composition of claim 6, wherein the antibody is present in a concentration of about 0.05µg/ml to about 5µg/ml

8. The pharmaceutical composition of claim 7, wherein the antibody is present in a concentration of about 1µg/ml or about 2µg/ml.

9. The pharmaceutical composition of any one of claims 6 to 8, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 0.5ng/ml to about 75ng/ml.

10. The pharmaceutical composition of claim 9, wherein the mesenchymal stromal cell-derived protein is present in a concentration of about 10ng/ml or 50ng/ml.

11. A pharmaceutical composition according to any one of claims 6 to 10 for modulating the immune system.

~~17.~~12. A kit comprising at least one antibody and at least one mesenchymal stromal cell-derived protein as defined in any one of claims ~~1~~ 6 to ~~7~~10.