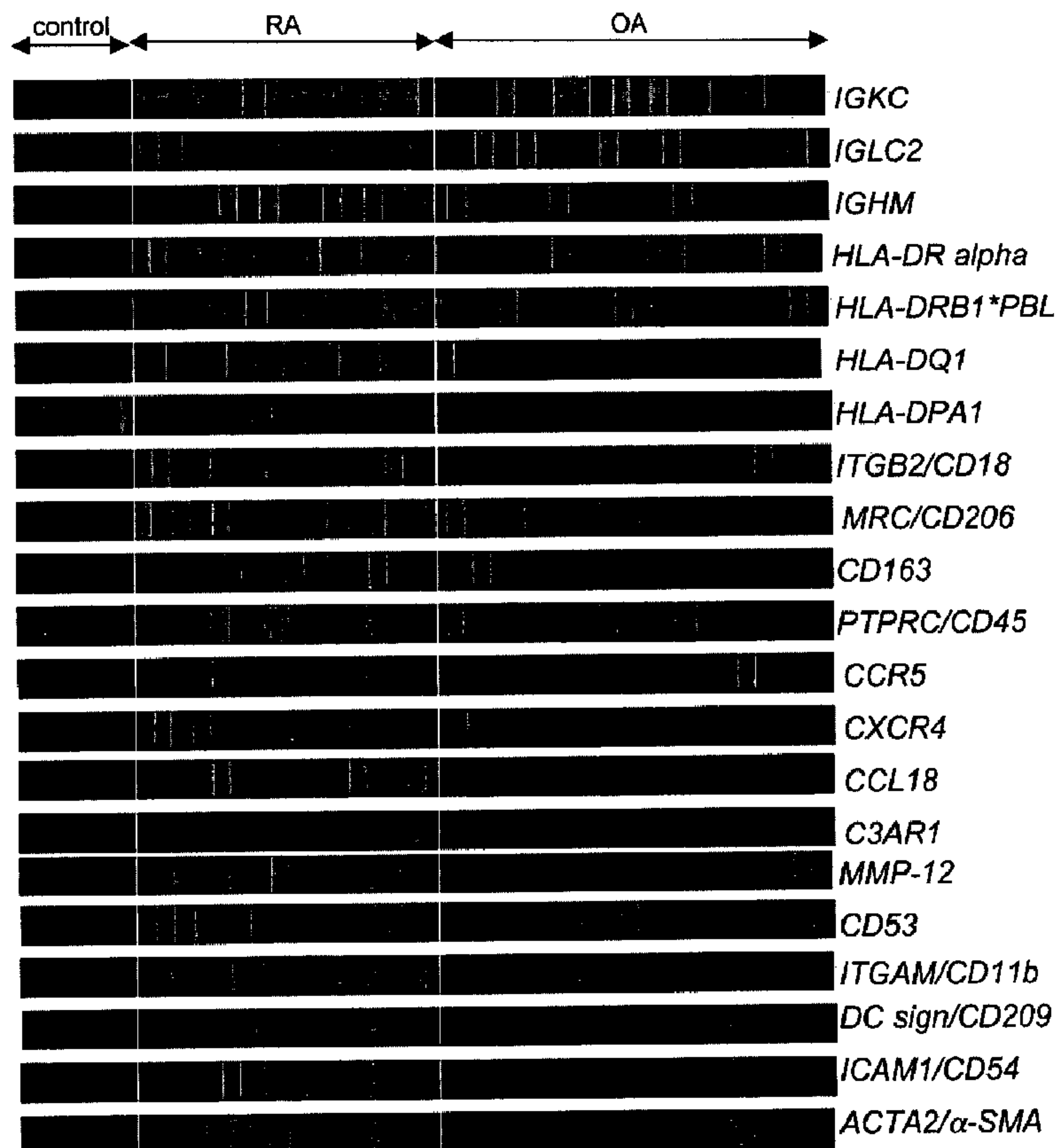




(86) **Date de dépôt PCT/PCT Filing Date:** 2007/05/25
 (87) **Date publication PCT/PCT Publication Date:** 2007/12/06
 (45) **Date de délivrance/Issue Date:** 2016/11/08
 (85) **Entrée phase nationale/National Entry:** 2008/10/29
 (86) **N° demande PCT/PCT Application No.:** CA 2007/000919
 (87) **N° publication PCT/PCT Publication No.:** 2007/137405
 (30) **Priorité/Priority:** 2006/05/25 (US60/808,294)

(51) **Cl.Int./Int.Cl. C12Q 1/68** (2006.01),
C12Q 1/04 (2006.01), **C12Q 1/06** (2006.01),
G01N 33/48 (2006.01)
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(54) **Titre : DIAGNOSTIC ET TRAITEMENT DE L'ARTHRITE RHUMATOIDE ET DE L'ARTHROSE**
 (54) **Title: METHODS OF DIAGNOSING AND TREATING RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS**



Gene expression levels in ST FLS cells: Affymetrix analysis

(57) **Abrégé/Abstract:**

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(57) Abrégé(suite)/Abstract(continued):

diagnosing or monitoring rheumatoid arthritis and/or osteoarthritis using gene expression profiles, protein expression profiles, and/or protein phosphorylation profiles of different cell types, including the novel precursor, CD3+ cells, synovial tissue fibroblast-like synovial cells and fibrocytes. The invention also includes methods to identify substances to treat or prevent rheumatoid arthritis and/or osteoarthritis.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 December 2007 (06.12.2007)

PCT

(10) International Publication Number
WO 2007/137405 A1

(51) International Patent Classification:

C12Q 1/68 (2006.01) *C12Q 1/06* (2006.01)
C12Q 1/04 (2006.01) *G01N 33/48* (2006.01)

(21) International Application Number:

PCT/CA2007/000919

(22) International Filing Date: 25 May 2007 (25.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/808,294 25 May 2006 (25.05.2006) US

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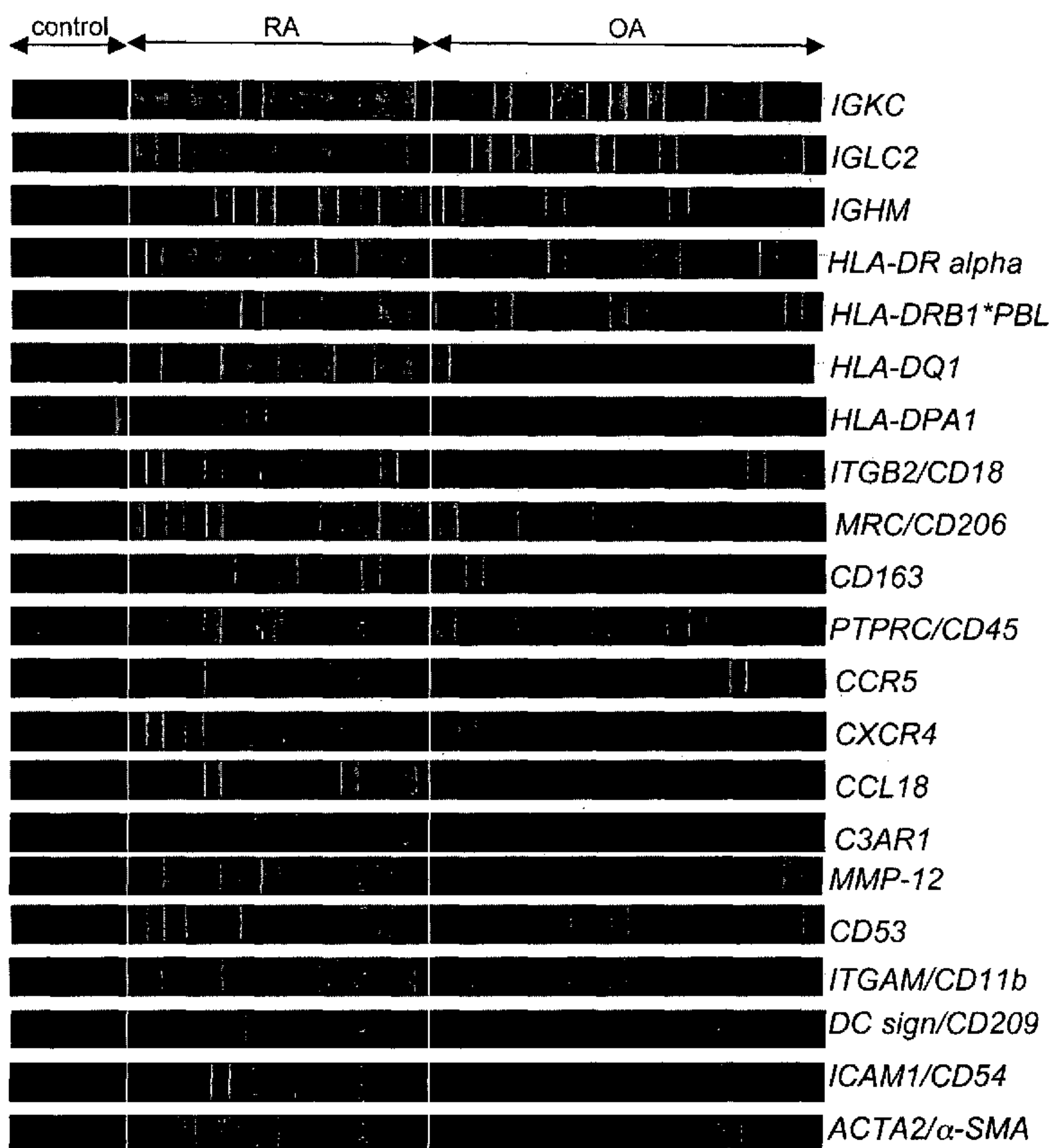
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY,

[Continued on next page]

(54) Title: METHODS OF DIAGNOSING AND TREATING RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS



(57) Abstract: The invention provides a novel cell that is a precursor of a fibroblast-like synovial cell. The novel cell is a circulating synovial tissue cell that stains positive for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14. The invention also relates to methods of diagnosing or monitoring rheumatoid arthritis and/or osteoarthritis using gene expression profiles, protein expression profiles, and/or protein phosphorylation profiles of different cell types, including the novel precursor, CD3+ cells, synovial tissue fibroblast-like synovial cells and fibrocytes. The invention also includes methods to identify substances to treat or prevent rheumatoid arthritis and/or osteoarthritis.

Gene expression levels in ST FLS cells: Affymetrix analysis

WO 2007/137405 A1

WO 2007/137405 A1

MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,

PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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TITLE: Methods of Diagnosing and Treating Rheumatoid Arthritis and Osteoarthritis

FIELD OF THE INVENTION

[0001] The invention relates to a novel cell that is a precursor of a fibroblast-like synovial cell. The invention also relates to methods of diagnosing or monitoring rheumatoid arthritis and/or osteoarthritis using gene expression profiles, protein expression profiles, and/or protein phosphorylation profiles of different cell types, including the novel precursor, CD3+ cells, fibroblast-like synovial cells, and fibrocytes.

10 **BACKGROUND OF THE INVENTION**

[0002] Rheumatoid arthritis (RA) is a common, relapsing autoimmune disease affecting 0.8-1% of the population worldwide (1) (2). RA presents clinically with joint swelling, deformity, pain, stiffness, and weakness (3). The primary sites of tissue damage are joints, but systemic involvement of the eyes, kidneys, chest and lungs may also occur (4). The rheumatoid synovial environment is an area of intense immunological activity. The cellular composition of the affected RA joint is characterized by proliferation of synovial lining cells, pannus accumulation over articular cartilage and the infiltration of inflammatory cells, including mononuclear cells and lymphocytes.

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20 Fibroblast-like synovial (FLS) cells are thought to be responsible for pannus formation and contribute to bone and cartilage destruction.

[0003] One of the hallmarks of RA is synovial hyperplasia. Two critical resident cells types in affected synovial tissue (ST) are: a CD68+/MHCII+ macrophage-like synoviocyte (MLS) and a CD68-/MHCII- FLS cell (5). The intimal layer increases from several cells to 15 cells deep, due to increased FLS cell numbers, through a combination of increased proliferation, decreased apoptosis and decreased senescence (5). FLS cells synthesize and secrete many pro-inflammatory mediators – cytokines, chemokines, growth factors - that are involved in autocrine and paracrine regulation of inflammation (5) and, therefore, are critical effectors in regulating the inflammatory response in RA. FLS cells are found in the intima and subintima, and FLS cells in RA are thought to transform into cells that proliferate in an

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anchorage-independent manner, lack contact inhibition and secrete cytokines constitutively. Many growth factors, such as PDGF, bFGF, TGF- β and activin are expressed in RA and drive fibroblast proliferation *in vitro* (6) (7) (8) (9) (10).

5 **SUMMARY OF THE INVENTION**

[0004] The present inventors have identified a precursor of a fibroblast-like synovial cell that comprises a circulating cell that stains positive for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14. The activation status of the novel precursor is useful to diagnose or monitor rheumatoid arthritis in a
10 subject.

[0005] Accordingly, the invention includes an isolated precursor of a fibroblast-like synovial cell, comprising a circulating cell that stains positive for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14.

[0006] The invention also includes a method of diagnosing or
15 monitoring rheumatoid arthritis in a subject, comprising the steps:

- (a) determining the number of isolated precursor cells of the invention in a sample from the subject; and
- (b) comparing the number of isolated precursor cells from the sample with a control;

20 wherein a difference in the number of isolated precursor cells in the sample from the subject as compared to the control is indicative of rheumatoid arthritis.

[0007] Another aspect of the invention, is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- 25
- (a) determining the activation state of the isolated precursor cell of the invention from a sample from the subject; and
 - (b) (b) comparing the activation state of the isolated precursor cell from the sample with a control;

30 wherein the activation state of the precursor cell is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the isolated precursor cell as compared to the control is indicative of rheumatoid arthritis.

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[0008] The invention also includes the use of the isolated precursor cell of the invention to diagnose or monitor rheumatoid arthritis.

[0009] An additional aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 5 (a) determining the number of isolated precursor cells of the invention in a sample from a subject treated with a substance; and
- (b) comparing the number of isolated precursor cells from the sample with a control;

10 wherein a difference in the number of isolated precursor cells in the sample from the subject as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

[0010] A further aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 15 (a) determining the activation state of the isolated precursor cell of the invention from a sample from a subject treated with a substance; and
- (b) comparing the activation state of the isolated precursor cell from the sample with a control;

20 wherein the activation state of the precursor cell is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the isolated precursor cell as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

25 **[0011]** In addition, the invention includes the use of the isolated precursor cell of the invention to identify a substance to treat or prevent rheumatoid arthritis.

[0012] The inventors have also analyzed the activation status of circulating CD3+ cells and have determined that increases in phosphorylation
30 of various signaling molecules correlates with the progression of rheumatoid arthritis.

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[0013] Accordingly, the invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

(a) determining the activation state of a CD3+ cell from a sample from the subject; and

5 (b) comparing the activation state of the CD3+ cell from the sample with a control;

wherein, the activation state of the CD3+ cell is determined by measuring the phosphorylation levels of signaling molecules, and

10 wherein a difference in the activation state of the CD3+ cell as compared to the control is indicative of rheumatoid arthritis.

[0014] The invention also includes the use of a CD3+ cell to diagnose or monitor rheumatoid arthritis in subject.

[0015] Another aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis comprising the steps:

15 (a) determining the activation state of a CD3+ cell from a sample from a subject treated with a substance; and

(b) comparing the activation state of the CD3+ cell from the sample with a control;

20 wherein the activation state of the CD3+ cell is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the CD3+ cell as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

25 **[0016]** The invention also includes the use of a CD3+ cell to identify a substance to treat or prevent rheumatoid arthritis.

[0017] The inventors have also characterized the gene and protein expression profiles of synovial tissue fibroblast-like synovial cells, and the protein phosphorylation profiles of these cells in samples from individuals with rheumatoid arthritis or osteoarthritis.

30 **[0018]** Accordingly, the invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- 5 -

- (a) determining the gene expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the gene expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

5 wherein a difference in the gene expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of rheumatoid arthritis.

[0019] Another aspect of the invention is a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

- 10 (a) determining the gene expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the gene expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

 wherein a difference in the gene expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of

15 osteoarthritis.

[0020] An additional aspect of the invention is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- 20 (a) determining the protein expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the protein expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

 wherein a difference in the protein expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of

25 rheumatoid arthritis.

[0021] A further aspect of the invention is a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

- 30 (a) determining the protein expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the protein expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

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wherein a difference in the protein expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of osteoarthritis.

[0022] An additional aspect of the invention is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- (a) determining the protein phosphorylation profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

wherein a difference in the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of rheumatoid arthritis.

[0023] Another aspect of the invention is a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

- (a) determining the protein phosphorylation profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

wherein a difference in the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of osteoarthritis.

[0024] The methods of the invention can also be used to identify substances to treat or prevent rheumatoid arthritis or osteoarthritis.

[0025] A further aspect of the invention is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- (a) determining the number of circulating fibrocytes in a sample from the subject; and

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- (b) comparing the number of fibrocytes from the sample with a control;

wherein a difference in the number of fibrocytes in the sample from the subject as compared to the control is indicative of rheumatoid arthritis.

5 **[0026]** Another aspect of the invention, is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- (a) determining the activation state of a circulating fibrocyte from a sample from the subject; and

10 (b) comparing the activation state of the fibrocyte from the sample with a control;

wherein the activation state of the fibrocyte is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the fibrocyte as compared to the control is indicative of rheumatoid arthritis.

15 **[0027]** The invention also includes using circulating fibrocytes to diagnose or monitor rheumatoid arthritis.

[0028] An additional aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

20 (a) determining the number of circulating fibrocytes in a sample from a subject treated with a substance; and

- (b) comparing the number of fibrocytes from the sample with a control;

25 wherein a difference in the number of fibrocytes in the sample from the subject as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

[0029] A further aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

(a) determining the activation state of circulating fibrocytes from a sample from a subject treated with a substance; and

30 (b) comparing the activation state of the fibrocyte from the sample with a control;

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wherein the activation state of the fibrocyte is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the fibrocyte as compared to the control is indicative of a substance to treat or prevent rheumatoid
5 arthritis.

[0030] In addition, the invention includes the use of circulating fibrocytes to identify a substance to treat or prevent rheumatoid arthritis.

[0031] Other features and advantages of the present invention will become apparent from the following detailed description. It should be
10 understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

[0032] The invention will now be described in relation to the drawings in which:

[0033] Figure 1 is heat map representation showing the gene expression levels of synovial tissue fibroblast-like synovial cells in controls or
20 subjects with rheumatoid arthritis or osteoarthritis.

[0034] Figure 2 is a heat map representation showing the phospho-
25 protein signature profiles of synovial tissue fibroblast-like synovial cells (ST FLS) from subjects with rheumatoid arthritis or osteoarthritis. Cell lysates derived from ST FLS cells from affected joints from 2 OA patients (LHS panel) and 3 RA patients (RHS panel) were analyzed using customized BD phospho-protein PowerBlots. Heat map representation: phospho-protein expression
30 profiles are represented as a "heat-map".

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Each array map represents 80 phosphospecificities. Similar patterns are indicative of similar phospho-protein profiles. This is evident for the 2 representative OA ST FLS cell specimens. These are distinguishable from the 3 RA ST FLS cell signature profiles. Interestingly, in regard to the RA specimens, although exhibiting similar phosphorylation-activation of many signaling effectors and kinases, there are clusters of distinctive patterns, allowing for stratification of the RA specimens into 3 sub-groups, exemplified by the 3 profiles provided.

5
10 **[0035]** Figure 3 shows the protein expression in synovial tissue fibroblast-like synovial cells derived from individuals with rheumatoid arthritis or osteoarthritis.

[0036] Figure 4 shows the immunostaining results of peripheral blood fibrocytes for various markers. (A) FACS analysis of a population of peripheral blood fibrocytes. (B) Confocal microscopy of a single peripheral blood fibrocyte. Images were collected using an upright Leica SP2 confocal laser-scanning microscope (Leica Microsystems Heidelberg GmbH, Mannheim, Germany), 100X oil immersion lens (1.4 NA) and 4X digital zoom.

[0037] Figure 5 shows the results of an intracellular analysis of phospho-STAT3 in CD3-, collagen+ peripheral blood fibrocytes.

20 **[0038]** Figure 6 shows the results of an intracellular analysis of phospho-STAT5 in CD3-, collagen+ peripheral blood fibrocytes.

[0039] Figure 7 shows the results of an intracellular analysis of phospho-ERK in CD3-, collagen+ peripheral blood fibrocytes.

25 **[0040]** Figure 8 shows the results of an intracellular analysis of phospho-p38 MAPK in CD3-, collagen+ peripheral blood fibrocytes.

[0041] Figure 9 shows protein phosphorylation profiles of sub-populations and primary cells.

[0042] Figure 10 shows the results of an intracellular analysis of phospho-STAT3 and phospho-p38 in CD3+ cells from healthy individuals, early rheumatoid arthritis patients and late rheumatoid arthritis patients.

30 **[0043]** Figure 11 depicts a signaling cascade.

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[0044] Figure 12 shows circulating fibrocytes in CIA. Mice with CIA exhibit obvious swelling of the paws/joints compared to naïve animals (A-1, II). Affected joints were scored on a scale of 0-16 and the cumulative disease score is shown in panel B. Mice with CIA cumulative score of 6/individual paw score of 2, show obvious swelling and cellular infiltrates in the dermis (C III, magnification 100X; C IV, magnification 200X *) compared to control animals (C I, magnification 100X; C II, magnification 200X). The majority of the inflammatory infiltrate were neutrophils (PMN) but macrophages (M), lymphocytes (L) and plasma cells (P) were also observed (C V, 1000X magnification). Swelling (**) and early inflammatory infiltrates (&) were observed in the intra-articular spaces (C VI, 200X magnification). PBMC were collected by cardiac puncture at different stages of disease and FACS analysis performed to detect the α -SMA/CI fibrocyte population (D). Panel E describes the α -SMA/CI fibrocyte population on day 30. Large granular cells were gated by FSC/SSC and double positive cells are shown. Notably, the number of circulating fibrocytes was higher in mice with higher disease scores.

[0045] Figure 13 shows evidence of increased p-STAT5 in circulating fibrocytes from animals with early stages of CIA. PBMC were isolated from the peripheral blood of control and CIA mice at stage 1-2. The cells were stained for Collagen I-Alexa647, α -SMA-FITC and p-STAT5-PE and analyzed by FACS. The Coll+ cells were gated and the percentage of α -SMA/p-STAT5 double positive cells are shown (A, R2 gate and B).

[0046] Figure 14 shows immunohistochemistry of paraffin embedded joints from mice with collagen induced arthritis stained with α -SMA-FITC (green) and CD45-PE (red). α -SMA also stains smooth muscle and is clearly identified surrounding an artery (open arrow). A profound cellular influx of leukocytes is evident (*) in the CIA joint tissue and the majority of these cells do not stain with α -SMA (overlay). α -SMA/CD45 fibrocytes/myofibroblasts were easily identified in the CIA joints (closed arrow) and were more abundant than in normal joints.

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[0047] Figure 15 shows immunohistochemistry of plastic embedded joints from mice with collagen induced arthritis stained with α -SMA-FITC (green) and CD45-PE (red). α -SMA/CD45 double positive fibrocytes/myofibroblasts were identified in the CIA joints.

5 **DETAILED DESCRIPTION OF THE INVENTION**

[0048] The inventors have discovered a precursor of a fibroblast-like synovial cell. This cell is a circulating cell and can migrate to affected joints in subjects with rheumatoid arthritis, and is able to transform into resident myofibroblasts and fibroblast-like synovial cells. The precursor cell stains
10 positive for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14, and can be isolated from the circulatory system, for example from peripheral blood mononuclear cells from healthy individuals and individuals with rheumatoid arthritis.

[0049] Accordingly, the invention provides an isolated precursor of a
15 fibroblast-like synovial cell, comprising a circulating cell that stains positive for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14.

[0050] The term "isolated precursor of a fibroblast-like synovial cell" as used herein refers to the precursor cells of the invention substantially free of
20 other cell types. In another embodiment, the cells are also substantially free of cellular debris or other cellular material, or culture medium.

[0051] The invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- (a) determining the number of isolated precursor cells of the invention in a sample from the subject; and
- 25 (b) comparing the number of isolated precursor cells from the sample with a control;

wherein a difference in the number of isolated precursor cells in the sample from the subject as compared to the control is indicative of rheumatoid arthritis.

30 **[0052]** The inventors also analyzed the activation state of this circulating precursor cell in healthy individuals and subjects with early rheumatoid arthritis and subjects with later stages of disease. The activation

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state of the precursor cell was determined by analyzing the phosphorylation levels of signaling molecules, including STAT3, STAT5, ERK and /or p38 MAPK.

[0053] Accordingly, the invention includes a method of diagnosing or
5 monitoring rheumatoid arthritis in a subject, comprising the steps:

(a) determining the activation state of the isolated precursor cell of the invention from a sample from the subject; and

(b) comparing the activation state of the isolated precursor cell from the sample with a control;

10 wherein the activation state of the precursor cell is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the isolated precursor cell as compared to the control is indicative of rheumatoid arthritis.

[0054] The phrase "diagnosing or monitoring rheumatoid arthritis" as
15 used herein refers to a method or process of determining if a subject has or does not have rheumatoid arthritis, or determining the severity or degree of rheumatoid arthritis.

[0055] The term "subject" as used herein refers to any member of the animal kingdom, preferably a human being.

20 **[0056]** The term "sample" as used here refers to any fluid, cell or tissue sample from an individual which includes the precursor cell of the invention. In one embodiment, the sample is from the circulatory system of the individual.

[0057] The term "control" as used herein refers to a sample from a subject or a group of subjects who are either known as having rheumatoid
25 arthritis or not having rheumatoid arthritis, or who are known as having a particular severity or degree of rheumatoid arthritis or not. A subject known not to have rheumatoid arthritis is also referred to as a "healthy individual" herein. For example, the control can be from a healthy individual, a subject with early stage rheumatoid arthritis or a subject with late stage rheumatoid
30 arthritis. A person skilled in the art will appreciate that a subject with early stage rheumatoid arthritis can be defined to include individuals within the first year of onset of symptoms with 3 swollen joints.

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[0058] The phrase "difference in number of isolated precursor cells in the sample from the subject as compared to the control is indicative of rheumatoid arthritis" refers to the difference in frequency of cells. There are generally greater numbers of the isolated precursor cells in samples from
5 subjects with rheumatoid arthritis as compared to healthy individuals. In addition, there are greater numbers of the isolated precursor cells in samples from subjects as the disease progresses. For example, there are greater numbers of the isolated precursor cell from subjects with late stage
10 rheumatoid arthritis as compared to subjects with early stage rheumatoid arthritis. Thus, if the control is a healthy individual, then there are greater numbers of the isolated precursor cells in the samples from subjects with rheumatoid arthritis as compared to the control. If the control is a subject with early stage rheumatoid arthritis, then there are greater numbers of the precursor cells in samples with late stage rheumatoid arthritis as compared to
15 the control.

[0059] The "activation state of the isolated precursor cell" can be determined by measuring the activation status of signaling molecules within the isolated precursor cell. For example, the activation status of signaling molecules can be determined by measuring the phosphorylation levels of
20 signaling molecules, such as STAT3, STAT5, ERK and/or p38 MAPK.

[0060] The phrase "difference in the activation state of the isolated precursor cell as compared to the control is indicative of rheumatoid arthritis" refers to a difference in the frequency or levels of phosphorylation of signaling molecules in the isolated precursor cell, including STAT3, STAT5, ERK and
25 p38 MAPK, as compared to the control. There are more frequent and/or higher levels of phosphorylation of signaling molecules in samples from subjects with rheumatoid arthritis as compared to healthy individuals. There are generally more frequent and/or higher levels of phosphorylation of signaling molecules in samples from subjects as the disease progresses. For
30 example, there are more frequent and/or higher levels of phosphorylation of signaling molecules in samples from subjects with late stage rheumatoid arthritis as compared to subjects with early stage rheumatoid arthritis. Thus, if

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the control is a healthy individual, then there are more frequent and/or higher levels of phosphorylation of signaling molecules in precursor cells in samples from subjects with rheumatoid arthritis as compared to the control. If the control is a subject with early stage rheumatoid arthritis, then there are more frequent and/or higher levels of phosphorylation of signaling molecules in precursor cells in samples from subjects with late stage rheumatoid arthritis as compared to the control.

[0061] The invention also includes the use of the isolated precursor cell of the invention to diagnose or monitor rheumatoid arthritis.

10 **[0062]** The isolated precursor cell of the invention can also be used in methods of drug discovery or methods to identify substances that can treat or prevent rheumatoid arthritis. For example, an additional aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 15 (a) determining the number of isolated precursor cells of the invention in a sample from a subject treated with a substance; and
- (b) comparing the number of isolated precursor cells from the sample with a control;

20 wherein a difference in the number of isolated precursor cells in the sample from the subject as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

[0063] In another example, the invention includes a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 25 (a) determining the activation state of the isolated precursor cell of the invention from a sample from a subject treated with a substance; and
- (b) comparing the activation state of the isolated precursor cell from the sample with a control;

30 wherein the activation state of the precursor cell is determined by measuring the phosphorylation levels of signaling molecules, and

- 15 -

wherein a difference in the activation state of the isolated precursor cell as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

[0064] The phrase "treat or prevent rheumatoid arthritis" as used herein
5 refers to a medical aid to counteract the disease itself, the symptoms and/or the progression of the disease.

[0065] "Measuring the phosphorylation levels of signaling molecules" as used herein refers to measuring the frequency and/or intensity of phosphorylation of signaling molecules, such as STAT3, STAT5, ERK and/or
10 p38 MAPK.

[0066] A person skilled in the art will appreciate that the control can be a sample from a subject not treated with a substance or treated with a substance that is known not to treat or prevent rheumatoid arthritis. In one embodiment, reduced numbers of the isolated precursor cell in the sample as
15 compared to the control is indicative of a substance for the treatment or prevention of rheumatoid arthritis. In another embodiment, a reduced activation state of the isolated precursor cell in the sample as compared to the control is indicative of a substance for the treatment or prevention of rheumatoid arthritis. In addition, the control can be a sample from the same
20 subject, but before treatment with the substance to be tested or samples from the subject taken at different points of time during treatment with the substance to be tested.

[0067] Substances for the treatment or prevention of rheumatoid arthritis can also be identified using cells or cell lines. For example, individual
25 precursor cells or cell lines derived from the precursor cell of the invention can be contacted with a substance and then the activation state of the cells can be compared to a control.

[0068] The inventors have also studied the activation status of circulating CD3+ cells from rheumatoid arthritis patients at different stages of
30 disease. They discovered that there are progressive increases in the phosphorylation of signaling molecules, such as STAT3 and p38 MAPK, in CD3+ cells, which correlate with disease progression.

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[0069] Accordingly, the invention includes method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

(a) determining the activation state of a CD3+ cell from a sample from the subject; and

5 (a) comparing the activation state of the CD3+ cell from the sample with a control;

wherein, the activation state of the CD3+ cell is determined by measuring the phosphorylation levels of signaling molecules, such as STAT3 and/or p38 MAPK, and

10 wherein a difference in the activation state of the CD3+ cell as compared to the control is indicative of rheumatoid arthritis.

[0070] The "activation state of the CD3+ cell" can be determined by measuring the activation status of signaling molecules within CD3+ cell. For example, the activation status of signaling molecules can be determined by
15 measuring the phosphorylation levels of signaling molecules, such as STAT3 and/or p38 MAPK.

[0071] The phrase "difference in the activation state of the CD3+ cell as compared to the control" refers to a difference in the frequency or levels of phosphorylation of signaling molecules in the CD3+ cell, including STAT3
20 and/or p38 MAPK, as compared to the control.

[0072] The term "sample" as used here refers to any fluid, cell or tissue sample from an individual which includes a CD3+ cell.

[0073] The invention also includes the use of a CD3+ cell to diagnose or monitor rheumatoid arthritis in a subject.

25 **[0074]** The findings of the inventors can also be used in methods of drug discovery. Accordingly, the invention includes method of identifying a substance to treat or prevent rheumatoid arthritis comprising the steps:

(a) determining the activation state of a CD3+ cell from a sample from a subject treated with a substance; and

30 (b) comparing the activation state of the CD3+ cell from the sample with a control;

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wherein the activation state of the CD3+ cell is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the CD3+ cell as compared to the control is indicative of a substance to treat or prevent
5 rheumatoid arthritis.

[0075] The invention also includes the use of a CD3+ cell to identify a substance to treat or prevent rheumatoid arthritis.

[0076] The inventors have also analyzed and characterized the gene expression and protein expression profiles of synovial tissue fibroblast-like
10 synovial cells from subjects with rheumatoid arthritis and osteoarthritis. The inventors have discovered that there are different gene expression and protein expression profiles, and protein phosphorylation profiles in synovial tissue fibroblast-like synovial cells from subjects with rheumatoid arthritis, osteoarthritis and healthy individuals.

15 **[0077]** The inventors discovered a number of rheumatoid arthritis specific genes that can be used to characterize the gene expression profile in the method of the invention. These genes include transport, apoptosis regulatory, cell adhesion, cell surface signaling receptors, intracellular signaling, secreted stimulatory and immunomodulatory genes. In addition, the
20 inventors discovered a significant differential expression of 154 genes in fibroblast-like synovial cells in subjects with osteoarthritis or rheumatoid arthritis. See Tables 1 and 2.

[0078] Accordingly, the invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- 25 (a) determining the gene expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
(b) comparing the gene expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

wherein a difference in the gene expression profile of the synovial
30 tissue fibroblast-like synovial cell as compared to the control is indicative of rheumatoid arthritis.

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[0079] In one embodiment, the gene expression profile that characterizes subjects with rheumatoid arthritis includes enhanced gene expression of one or more of the genes listed in Table 1.

[0080] In another embodiment, the gene expression profile that characterizes subjects with rheumatoid arthritis includes enhanced gene expression of genes encoding immunoglobulin constant regions, CD53, CD11b, CD18, CD86, CD206, CD163, mannose receptor, DC-SIGN, C3AR1, Fc-receptors, complement receptors, and/or MHC class II molecules as compared to the control.

[0081] The invention also includes a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

(a) determining the gene expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and

(b) comparing the gene expression profile of the synovial tissue

fibroblast-like synovial cell from the sample with a control;

wherein a difference in the gene expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of osteoarthritis.

[0082] The term "control" as used here refers to a sample from a subject or group of subjects who are either known as having osteoarthritis or not, or who are known as having a particular severity or degree of osteoarthritis or not.

[0083] In one embodiment, the gene expression profile that characterizes subjects with osteoarthritis includes enhanced gene expression of one or more of the genes listed in Table 2.

[0084] The term "sample" as used here refers to any fluid, cell or tissue sample from an individual which includes a synovial tissue fibroblast-like synovial cell.

[0085] The term "gene expression profile" as used herein refers to the level of RNA expressed from one or more gene in the synovial tissue fibroblast-like synovial cell from a sample from the subject.

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[0086] The term "difference in gene expression profile" as used here refers to an increase or decrease in the measurable expression of RNA of a particular gene or group of genes as compared to the measurable expression of RNA of the same gene or group of genes in a second sample. The comparison can be made between individual samples or populations of samples. In one embodiment, the differential expression can be compared using the ratio of the level of expression of the gene as compared with the expression level of the gene of a control, wherein the ratio is not equal to 1.0. For example, an RNA is differentially expressed if the ratio of the level of expression in a first sample as compared with a second sample is greater than or less than 1.0. For example, a ratio of greater than 1, 1.2, 1.5, 1.7, 2, 3, 3, 5, 10, 15, 20 or more, or a ratio less than 1, 0.8, 0.6, 0.4, 0.2, 0.1, 0.05, 0.001 or less. In another embodiment the differential expression is measured using p-value. For instance, when using p-value, a gene is identified as being differentially expressed as between a first and second population when the p-value is less than 0.1, preferably less than 0.05, more preferably less than 0.01, even more preferably less than 0.005, the most preferably less than 0.001.

[0087] In addition to measuring the gene expression profile, a person skilled in the art will appreciate that the protein expression profile of a synovial tissue fibroblast-like synovial cell can be measured.

[0088] The term "protein expression profile" as used herein refers to the level of one or more proteins expressed in the synovial tissue fibroblast-like synovial cell from a sample from the subject. The protein expression profile can include measurements of the expression of transport, apoptosis regulatory, cell adhesion, cell surface signaling receptors, intracellular signaling, secreted stimulatory and immunomodulatory proteins. This includes measuring the protein expression of immunoglobulin constant regions, CD53, CD11b, CD18, CD86, CD206, CD163, mannose receptor, DC-SIGN, C3AR1, Fc-receptors, complement receptors, and/or MHC class II molecules.

[0089] Accordingly, the invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

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- (a) determining the protein expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- (b) comparing the protein expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

5 wherein a difference in the protein expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of rheumatoid arthritis.

[0090] In one embodiment, the protein expression profile that characterizes subjects with rheumatoid arthritis includes enhanced protein
10 expression of one or more proteins encoded by the genes listed in Table 1.

[0091] The invention also includes a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

- (a) determining the protein expression profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
- 15 (b) comparing the protein expression profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

 wherein a difference in the protein expression profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of osteoarthritis.

20 **[0092]** In one embodiment, the protein expression profile that characterizes subjects with osteoarthritis includes enhanced protein expression of one or more of the proteins encoded by the genes listed in Table 2.

[0093] The term "difference in protein expression profile" as used here
25 refers to an increase or decrease in the measurable expression of a particular protein or group of proteins as compared to the measurable expression of the same protein or group of proteins in a second sample. The comparison can be made between individual samples or populations of samples. In one embodiment, the differential expression can be compared using the ratio of
30 the level of expression of the protein as compared with the expression level of the protein of a control, wherein the ratio is not equal to 1.0. For example, a protein is differentially expressed if the ratio of the level of expression in a first

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sample as compared with a second sample is greater than or less than 1.0. For example, a ratio of greater than 1, 1.2, 1.5, 1.7, 2, 3, 3, 5, 10, 15, 20 or more, or a ratio less than 1, 0.8, 0.6, 0.4, 0.2, 0.1, 0.05, 0.001 or less. In another embodiment the differential expression is measured using p-value.

5 For instance, when using p-value, a protein is identified as being differentially expressed as between a first and second population when the p-value is less than 0.1, preferably less than 0.05, more preferably less than 0.01, even more preferably less than 0.005, the most preferably less than 0.001.

[0094] In addition to gene and protein expression profiles, the inventors
10 also examined protein phosphorylation profiles in synovial tissue fibroblast-like synovial cells.

[0095] Accordingly, the invention includes a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:

- 15 (a) determining the protein phosphorylation profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and
(a) comparing the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

20 wherein a difference in the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of rheumatoid arthritis.

[0096] The term "protein phosphorylation profile" as used herein refers to the level or frequency of phosphorylation of one or more proteins
25 expressed in synovial tissue fibroblast-like synovial cells from a sample from a subject.

[0097] In one embodiment, the difference in the protein phosphorylation profile includes a difference in phosphorylation of AKT, FAK, p38, JNK, cdc-2 and/or PLC-g1 in the synovial tissue fibroblast-like synovial cells in the subject
30 as compared to the control.

[0098] The invention also includes a method of diagnosing or monitoring osteoarthritis in a subject, comprising the steps:

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(a) determining the protein phosphorylation profile of a synovial tissue fibroblast-like synovial cell from a sample from the subject; and

5 (b) comparing the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell from the sample with a control;

wherein a difference in the protein phosphorylation profile of the synovial tissue fibroblast-like synovial cell as compared to the control is indicative of osteoarthritis.

10 **[0099]** The methods of the invention can also be used to identify substances to treat or prevent rheumatoid arthritis or osteoarthritis.

[00100] The inventors also determined that the number of circulating fibrocytes and the activation status of fibrocytes can be used to diagnose or monitor rheumatoid arthritis in a subject.

15 **[00101]** The term "sample" as used here refers to any fluid, cell or tissue sample from an individual which includes circulating fibrocytes. In one embodiment, the sample is from the circulatory system of the individual.

[00102] Accordingly, a further aspect of the invention is a method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the
20 steps:

(a) determining the number of circulating fibrocytes in a sample from the subject; and

(b) comparing the number of fibrocytes from the sample with a control;

25 wherein a difference in the number of fibrocytes in the sample from the subject as compared to the control is indicative of rheumatoid arthritis.

[00103] The phrase "difference in number of fibrocytes in the sample from the subject as compared to the control is indicative of rheumatoid arthritis" refers to the difference in frequency of cells. There are generally
30 greater numbers of the circulating fibrocytes in samples from subjects with rheumatoid arthritis as compared to healthy individuals. In addition, there are greater numbers of circulating fibrocytes in samples from subjects as the

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disease progresses. For example, there are greater numbers of circulating fibrocytes from subjects with late stage rheumatoid arthritis as compared to subjects with early stage rheumatoid arthritis. Thus, if the control is a healthy individual, then there are greater numbers of circulating in the samples from
5 subjects with rheumatoid arthritis as compared to the control. If the control is a subject with early stage rheumatoid arthritis, then there are greater numbers of circulating fibrocytes in samples with late stage rheumatoid arthritis as compared to the control.

[00104] Another aspect of the invention, is a method of diagnosing or
10 monitoring rheumatoid arthritis in a subject, comprising the steps:

(a) determining the activation state of a circulating fibrocyte from a sample from the subject; and

(b) comparing the activation state of the fibrocyte from the sample with a control;

15 wherein the activation state of the fibrocyte is determined by measuring the phosphorylation levels of signaling molecules, and

wherein a difference in the activation state of the fibrocyte as compared to the control is indicative of rheumatoid arthritis.

[00105] The "activation state of the fibrocyte" can be determined by
20 measuring the activation status of signaling molecules within the isolated precursor cell. For example, the activation status of signaling molecules can be determined by measuring the phosphorylation levels of signaling molecules, such as STAT5.

[00106] The phrase "difference in the activation state of the fibrocyte as
25 compared to the control is indicative of rheumatoid arthritis" refers to a difference in the frequency or levels of phosphorylation of signaling molecules in the isolated precursor cell, such as STAT5, as compared to the control. There are more frequent and/or higher levels of phosphorylation of signaling molecules in samples from subjects with rheumatoid arthritis as compared to
30 healthy individuals. There are generally more frequent and/or higher levels of phosphorylation of signaling molecules in samples from subjects as the disease progresses. For example, there are more frequent and/or higher

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levels of phosphorylation of signaling molecules in samples from subjects with late stage rheumatoid arthritis as compared to subjects with early stage rheumatoid arthritis. Thus, if the control is a healthy individual, then there are more frequent and/or higher levels of phosphorylation of signaling molecules
5 in precursor cells in samples from subjects with rheumatoid arthritis as compared to the control. If the control is a subject with early stage rheumatoid arthritis, then there are more frequent and/or higher levels of phosphorylation of signaling molecules in precursor cells in samples from subjects with late stage rheumatoid arthritis as compared to the control.

10 **[00107]** The invention also includes using circulating fibrocytes to diagnose or monitor rheumatoid arthritis.

[00108] An additional aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 15 (a) determining the number of circulating fibrocytes in a sample from a subject treated with a substance; and
(b) comparing the number of fibrocytes from the sample with a control;

wherein a difference in the number of fibrocytes in the sample from the subject as compared to the control is indicative of a substance to treat or
20 prevent rheumatoid arthritis.

[00109] A further aspect of the invention is a method of identifying a substance to treat or prevent rheumatoid arthritis, comprising the steps:

- 25 (a) determining the activation state of circulating fibrocytes from a sample from a subject treated with a substance; and
(b) comparing the activation state of the fibrocyte from the sample with a control;

wherein the activation state of the fibrocyte is determined by measuring the phosphorylation levels of signaling molecules, and

30 wherein a difference in the activation state of the fibrocyte as compared to the control is indicative of a substance to treat or prevent rheumatoid arthritis.

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[00110] In addition, the invention includes the use of circulating fibrocytes to identify a substance to treat or prevent rheumatoid arthritis.

[00111] The following non-limiting examples are illustrative of the present invention:

5 EXAMPLES

Example 1: Characterization of gene and protein expression profiles in RA ST FLS cells.

[00112] The activated phenotype of distinct cell populations in affected RA patients determines disease severity. Suppression of the activated phenotype of cells in early RA synovitis will subdue the disease process. A clear understanding of those factors that contribute to the activated phenotype is required. The objective of the inventors' studies was to determine the signature gene and protein expression profiles in target cell populations in patients diagnosed with RA. The inventors' hypothesized that a signature pattern of activated factors in distinct cell types would identify potential therapeutic targets. Over the past few years, the inventors have initiated a collection of blood, synovial fluid and ST from RA patients, osteoarthritis (OA) patients and trauma patients at the time of joint surgery. Sample collection involves confirmation of the diagnosis of RA/OA using clinical, serologic and radiologic data and informed consent on all study participants. Clinical parameters are recorded at the time of sample collection. Synovial samples are collected by joint aspiration, fine needle biopsy and via arthroscopic or other surgeries. FLS cells from ST from affected RA joints, OA joints and tissue from trauma patients (non-RA, non-OA, surgery) were collected using a negative-selection protocol for cell fractionation, and cultured in DMEM media. Initial studies examined gene expression profiles of RNA from freshly harvested ST, cells that were passaged up to 3X and cells maintained beyond three passages. Affymetrix® microarray analysis (U133 Plus 2.0 microarray representing over 30,000 genes) was performed. RA FLS cells at 3X passage exhibit similar gene expression profiles compared to freshly harvested FLS cells, yet the inventors observed that this characteristic gene expression profile changed with extended time in culture. All subsequent gene expression

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analyses were conducted on RNA extracted from ST FLS cells cultured for <3 passages. Gene expression data were initially analyzed using GeneSpring 6.1 software (Silicon Genetics). Results of gene tree data analysis of ST FLS cells have revealed distinct and reproducible expression profiles, reflective of the different patient populations (trauma patients, OA, RA), that is significant as determined by one-way ANOVA. Gene tree data analysis sorted the RA-specific genes into functional groupings: transport, apoptosis regulatory, cell adhesion, cell surface signaling receptors, intracellular signaling, secreted stimulatory, and immunomodulatory genes. A gene tree based comparison of OA versus RA ST FLS cell expression profiles revealed significant differential expression of 154 genes (one-way ANOVA, $p < 0.01$), including 17 apoptosis regulatory, 17 cell adhesion, 39 cell surface receptors, 25 immunomodulatory and 28 signal transduction genes. To further analyze these data, the Binary Tree-Structured Vector Quantization (BTSVQ) program was used (11). BTSVQ is a computational tool that combines partitive k-means clustering and Self-Organizing Maps (SOM) to analyze and visualize microarray gene expression data with minimal noise and without pre-conceived bias. These analyses confirmed distinct signature patterns of gene expression for FLS cells derived from RA (n=16) and OA (n=20) specimens and further distinguished healthy control (trauma patients, n=6) gene expression patterns from RA and OA expression profiles (Figure 1). Differentially regulated genes in RA FLS cells included cytokines, chemokines and receptors. In agreement with previous studies (12), the inventors also show a transformed phenotype in RA FLS cells, with expression of many genes that are typically not found in fibroblasts. High levels of gene expression for immunoglobulin constant regions: IGKC, IGLC2 and IGHM were seen, typically expressed in B cells. Also, gene expression for many receptors found on antigen presenting cells such as: CD53, CD11b, CD18, CD86, scavenger receptors (CD206, CD163 and the mannose receptor, MRC), DC-SIGN and complement receptor (C3AR1), were observed. The MRC processes molecules for presentation of MHCII and binds to both endogenous and exogenous ligands. Increases in gene expression for Fc- and complement receptor gene expression were

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observed in RA FLS cells and suggest that these cells trap antigens in the form of immune complexes on their cell surface for presentation. Gene expression for HLA-DR, DQ and DP were also upregulated in RA vs. OA or control FLS cells in the array analyses. HLA molecules are expressed on CD68+ synoviocytes following treatment with IFN- γ (13). Notably, gene expression for CD68 was not evident in the isolated FLS cells. Upregulation of HLA molecules would be consistent with the role of synovial fibroblasts in antigen presentation during an autoimmune disease. The likelihood of contaminating leukocytes, e.g. macrophage-like synoviocytes (MLS), in the fibroblast preparations was eliminated since only adherent prolyl-4 hydroxylase (5B5 antibody) positive cells were processed for gene expression analysis, and there was no significant CD2, CD3 or CD5 gene expression observed in the analysis. This suggests that RA FLS cells either upregulate the B cell/macrophage/dendritic cell markers, de-differentiate into this phenotype, or that immature fibroblast-like cells are recruited and differentiate into these cells in affected joints.

[00113] In parallel, protein extracted from the RA, OA and surgical trauma ST FLS cells was analyzed using the BD BioScience PowerBlot™ Western immunoarray technology platform. The full array allows 996 proteins to be interrogated, and the inventors have developed a customized mini-array that specifically interrogates phospho-proteins. In agreement with the data for distinct gene expression, distinct protein expression patterns were observed in the RA FLS cells compared to OA FLS cells (Figure 2). RA FLS cells were activated as determined by higher levels of phospho-AKT, phospho-FAK, phospho-p38, JNK, cdc-2 and PLC- γ 1 proteins (Figure 3). The PI3K/AKT pathway plays an important role in balancing apoptosis and survival (14) and is involved in cell cycle progression, glucose metabolism and chemotaxis (15). RA fibroblasts show enhanced survival in response to TNF- α (16) and TGF- β (17) through an AKT-dependent pathway (17). Additionally, this pathway has also been implicated in TRAIL induced proliferation in RA fibroblasts (18). Activation of the insulin-like growth factor-1 receptor (IGF-1R)

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(19), IL-17 (20) and the IL-18 receptor (21) also effect signal transduction in an AKT-dependent manner to induce cytokine/chemokine or adhesion molecule synthesis in RA fibroblasts. Focal adhesion kinase (FAK) regulates anti-apoptotic pathways through PI3K-dependent and -independent pathways.

5 FAK is a widely expressed cytoplasmic protein tyrosine kinase involved in integrin mediated signal transduction. B1 integrin signaling through FAK upregulates ICAM-1 and Fas in RA FLS cells (22). The JNK and p38 pathways are preferentially activated by stress, inflammatory cytokines and growth factors. TNF can signal through both JNK and p38 to activate AP-1

10 and NF-kB (23) and IL-1 upregulates MMP13 (24) and collagenase 1 (25) via the JNK pathway in RA FLS cells. The entry of all cells into mitosis is regulated by cdc2 and increased cdc2 phosphorylation has been reported in RA fibroblasts and may be involved in aberrant mitosis (26). Viewed altogether, the data confirms that multiple genes and signaling pathways are

15 activated in RA FLS cells contributing to the distinct phenotype of these cells.

Example 2: Fibrocytes in RA.

[00114] RA is a complex heterogeneous disease. Hyperproliferation of FLS cells is considered to be a major contributor to pannus formation;

20 however, little direct evidence supports hyperproliferation of these cells *in vivo*. Few mitotic figures are observed, thymidine uptake only occurs in a percentage of the cells (27) and FLS cells divide very slowly in culture (28). Decreased senescence in FLS cells may occur and RA FLS cells have been shown to retain telomerase activity (29), but these cells are not immortalized

25 *in vitro* (29) (30). The outgrowth of FLS cells in the ST of affected RA joints is, therefore an enigma, and one possible explanation might be that FLS cells are recruited from the circulation. Many years ago, a circulating population of fibroblasts-like cells, was identified (31). More recently, these cells have been characterized further, designated as fibrocytes, and implicated in influencing

30 disease development in tumor biology, scleroderma, asthma and pulmonary fibrosis (32) (33) (34) (35).

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[00115] Fibrocytes are unique circulating cells that are relatively rare in the circulation, comprising only 0.1-1% of the white blood cells. Characterization of these cells has been predominantly by FACS staining of cells cultured for up to two weeks *ex vivo* and relatively little work has been performed *in vivo*. *In vitro*, fibrocytes have a unique phenotype and express markers of both stromal cells and hematopoietic cells, including: fibronectin, collagen, prolyl 4-hydroxylase, CD11a, CD11b, CD13, CD18, CD45RO, ICAM1, CD80, CD86, CXCR4, CCR7 and CCR5 (32) (36). Fibrocytes originate from the bone marrow (37) and arise from a CD14+ve pool of cells in the circulation, but fibrocytes themselves become CD14- (38). At the time of culture, these cells express CD34 and CD45 (33). When cultured *ex vivo*, these cells become adherent and develop a spindle-shaped morphology (33) (39) and downregulate CD45 and CD34. Three weeks after culture these cells express the myofibroblast marker, α -smooth muscle actin (SMA) (33), and have the ability to contract collagen gels *in vitro* (38). *Ex vivo* cultured fibrocytes differentiated into α -SMA expressing cells when directly co-cultured with T cells or upon TGF- β stimulation (38). Fibrocyte differentiation is inhibited by serum amyloid P (SAP) (36). Recently, *in vivo* evidence indicates that the fibrocyte population contributes to the myofibroblast population in a murine wound healing model (37). Fibrocytes secrete collagen and fibronectin, thereby contributing to granulation formation, and they are contractile, enhancing wound contraction and healing. They have also been shown to present antigen (40) and can secrete chemokines, cytokines and angiogenic factors (32), suggesting that fibrocytes contribute to both inflammation and its resolution.

[00116] Increased myofibroblast-like cells in the joint are observed in RA and correlate with the degree of inflammatory synovitis. It has been suggested that RA myofibroblasts originate from the circulating fibrocyte population (41) (42). The percentage of α -SMA expressing cells in RA patients varies from 1-30% (43) and the inventors have observed upregulated α -SMA gene expression in RA FLS cells (Figure 1). Whether these myofibroblasts were derived locally, or were recruited from the circulating pool, is unclear.

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Certainly, circulating endothelial progenitor cells are increased during the onset of collagen induced arthritis, likely contributing to neoangiogenesis in affected tissues (Kurosaka et al 2005). Endothelial precursors are recruited in RA (44) and increased circulating endothelial precursors are observed in 5 murine CIA (45) and in patients with RA (46). The inference is that circulating endothelial precursors will traffic to affected RA joints to promote the neoangiogenesis. Given that fibrocytes express CCR3, CCR5 and CCR7, and the cognate ligands for these receptors are found in synovial fluid, it is likely that fibrocytes will also traffic to the inflamed RA joint. Indeed, RA FLS cells 10 expressed higher levels of some fibrocyte markers including: CCR5, CXCR4, CD54, CD18, CD11b and CD45 (Figure 1). Fibrocytes and fibroblasts can differentiate into α -SMA expressing myofibroblasts upon stimulation with TGF- β . Notably, increased levels of TGF- β are present in RA STs. Myofibroblast transformation involves activation of adhesion and integrin signaling through 15 FAK and AKT pathways (47). TGF- β promotes AKT-dependent survival of mesenchymal cells through p38 MAPK-induced growth factor secretion (48). Constitutive phosphorylation of FAK is involved in myofibroblast differentiation in scleroderma (49). Apparently, many of the pathways the inventors have identified as potentially activated in the RA FLS cells have been implicated in 20 fibrocyte differentiation.

Example 3: Signal taxonomy in defined RA cell populations.

[00117] Changes in intracellular protein levels, subcellular localization, or activation state are considered to be reflective of a cell's capabilities or 25 functions. Some of these events are relatively transitory – such as some phosphorylation of proteins in cell signaling cascades. Some of the relevant cell populations are so rare as to make their isolation for standard biochemical analysis nearly impossible. Remodeling of such cell signaling mechanisms drives disease pathogenesis contributing to immune cell dysregulation despite 30 intense therapy regimens. Therefore, to understand how signaling networks are remodeled in RA there is a need to measure complex populations of

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immune system cells and phenotype them not only for their cell lineage status, but also for their relative activation state.

[00118] Studies in human myeloid leukemia have shown that signaling can be mapped at the individual cell level by flow cytometry and have
5 demonstrated links between oncogene mutations and patterns of proliferative signaling in tumors (50). Furthermore, this work suggested that a tumor could be described by its signal transduction potential and that this status stratified patient risk of relapse following chemotherapy. Since RA is a systemic and chronic inflammatory autoimmune disease that targets synovial joints, disease
10 pathogenesis is multifactorial and extends beyond T or FLS cell mediated destruction of cartilage. Production of pro-inflammatory cytokines such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$ by activated monocytes and macrophages contribute to tissue destruction by activation of chondrocytes and fibroblasts that release metalloproteinases and collagenases into the synovial cavity. Cartilage loss
15 and bone erosion are physical manifestations of disease progression. Additional blood borne compartments, such as B cells, contribute to production of autoantibodies and rheumatoid factor and have been regarded as playing important roles. Both T and B cell lymphocyte deregulation, as well as the involvement of chondrocytes and fibroblasts suggest a dynamic
20 interaction of cell-to-cell communications contribute to disease pathogenesis of RA.

[00119] The nature of the intracellular pathways activated with most primary immune cell interactions is not well understood *in vivo* and less clear in disease states. In many cases it is only understood using derived cell lines,
25 *in vitro*, and at best is often accomplished by lysis of cells and western immunoblots of total cellular material. Therefore significant information on population variations that exist is missed and advances in genomics and proteomic technologies that rely on lysate material do not access the heterogeneous subsets that exist in the immune system.

30 **[00120]** Multiparameter flow cytometric analysis allows for small subpopulations to be discerned using cell surface markers - representing different cellular subsets, differentiation or activation states.

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[00121] The inventors developed a series of assay systems for flow cytometric based biochemical analysis at the single cell level for kinase and phospho-protein profiling. Measurement of up to 12 simultaneous protein or kinase events per cell for studying signaling events in primary cells are possible with these systems (51) (52) (53) (54). This allows for unprecedented study of signaling in autoimmune diseases as immunocytes are particularly amenable to these techniques.

[00122] Underlying the gross dysfunctionality of autoimmunity are the signaling systems that drive their actions. The last two decades of research have uncovered numerous pathways leading from surface receptors to gene regulation. Many of these pathways, if not all, at one point or another pass signals through phosphorylation or dephosphorylation events on proteins or lipids. Integration of signaling events leads to relocalization of proteins within cells, such as with translocation of proteins to the nucleus. Until recently, measurement of such events has been limited to cell lines or bulk lysis assays. Interpretation of such assays is considered a pale rendition of what we know is the intricacy of complex population primary cell events. Therefore a true understanding of the nature of signaling dysfunctions during disease processes in heterogeneous patient samples or animal model systems has been beyond reach.

[00123] It can be hypothesized that the activation profiles of proteins, such as phospho-proteins that drive proliferation and activation signaling cascades will differ, in disease states, both from a "normal" profile of a non-disease presence and from other samples with significantly different pathology. During disease pathogenesis, cells are accessing different environmental cues, or ignoring those that might be attempting to block their replication (or induce their apoptosis). As such, it would be expected that there would be underlying differences in the activation profiles of certain phospho-proteins across immune and non-immune cells in RA pathogenesis.

[00124] Therefore, with sufficient understanding of relationships between cell signaling and immunopathology, activation profiles of phospho-proteins could indicate the presence of individual aggressive cell subsets within a

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complex population of cells. Since it is hard to predict which kinases might be relevant in different cell subsets, this hypothesis has limited utility in the absence of a high throughput manner to measure many kinases. However, if one could measure dozens of kinase activation profiles—or their target
5 proteins—simultaneously—there is the opportunity to generate invaluable information about the role of signaling events in rheumatologic disease, test hypotheses of signaling systems in response to various therapies, as well as develop diagnostic indicators based on kinase profiles. Finally, it might be possible to reveal signaling states that are hidden from obvious view if one
10 were only looking at basal phosphorylation states.

[00125] Knowledge of intracellular signaling differences among arthritic immune cells could therefore provide the basis for an improved autoimmune classification system. Importantly, such a classification system would go beyond a simple signature, but could be used to infer mechanism associated
15 with the signature.

[00126] In the present studies the inventors have shown that by surveying phospho-protein/basal phosphorylation states, the underlying dysregulated signaling nodes in primary human RA samples can be revealed and the identification of signaling pathology profiles can be enabled.
20 Specifically, based on our gene and protein expression data elaborating an emerging phenotype for the RA FLS, the inventors examined peripheral blood mononuclear cells (PBMC) for a fibrocyte population with similar properties. At the outset, PBMC from healthy individuals were analyzed by multiparameter flow cytometry to identify the fibrocyte population. The data in Figure 4
25 indicate that immunostaining for collagen, CD34, CD45, prolyl 4-hydroxylase and CD14 identifies this precursor fibrocyte population. In subsequent experiments, multiparametric staining using both surface and intracellular stains was employed to determine the activation status of the circulating fibrocytes in the PBMC of healthy individuals, patients with early RA and later
30 stage disease. Early RA was defined as patients within the first year of onset of symptoms with 3 swollen joints. Changes in the signaling status that occurs during the functional activation of this fibrocyte population might include

- 34 -

phosphorylation-activation of STATs, Erk and MAP kinases. Accordingly, using polychromatic analyses the inventors examined the frequency of activated fibrocytes, focusing on STAT3, STAT5, Erk and p38 MAPK. CD3-CD45+collagen+ fibrocytes were stained for phospho-STAT3 (Figure 5),
5 phospho-STAT5 (Figure 6), phospho-Erk (Figure 7) and phospho-p38 MAPK (Figure 8) and the frequency of staining determined in each patient population: healthy individuals (n=20), early RA patients (n=8), late stage disease RA patients (n=4). These data indicate that the frequency of phospho-staining for these signaling effectors in the RA patient fibrocytes is
10 significantly higher (panels B) than that seen in fibrocytes from healthy individuals.

Example 4: Collagen-induced arthritis model

[00127] Collagen-induced arthritis (CIA) is a widely used model of
15 rheumatoid arthritis (55) (56). Mice with CIA exhibit obvious swelling of paws and joints as compared to control animals (Figure 12A). The mice were given a clinical disease score based on the severity of the disease (Figure 12B). Figure 12C shows immunohistochemistry staining of the joint.

[00128] The inventors collected PBMC by cardiac puncture at different
20 stages of disease and analyzed the cells by FACS for positive staining to α -SMA and collagen. As can be seen in Figures 12D and E, the number of circulating fibrocytes is higher in mice with higher disease scores.

[00129] The circulating fibrocytes also showed increased p-STAT5 in the animals with CIA as compared to the control animals (Figure 13).

25 **[00130]** Figures 14 and 15 show the results of immunohistochemistry of samples from mice with CIA as compared to controls.

[00131] The scope of the claims should not be limited by the preferred
embodiments and examples, but should be given the broadest interpretation
30 consistent with the description as a whole.

Table 1

Probe set ID number	Public ID number (NCBI)	Target description	Chromosomal location	Unigene ID	Gene Title	Gene Symbol
209765_at	Y13786	gb:Y13786.2 /DB_XREF=gi:12053590 /FEA=FLmRNA /CNT=58 /TID=Hs.278679.1 /TIER=Stack /STK=24 /UG=Hs.278679 /LL=8728 /UG_GENE=ADAM19 /DEF=Homo sapiens mRNA for meltrin-betaADAM 19 homologue. /PROD=meltrin-betaADAM 19 homologue /FL=gb:AF311317.1	chr5q32-q33	Hs.289368	ADAM metalloproteinase domain 19 (meltrin beta)	ADAM19
206134_at	NM_014479	gb:NM_014479.1 /DB_XREF=gi:7657318 /GEN=M12.219 /FEA=FLmRNA /CNT=21 /TID=Hs.145296.0 /TIER=FL+Stack /STK=14 /UG=Hs.145296 /LL=27299 /DEF=Homo sapiens disintegrin protease (M12.219), mRNA. /PROD=disintegrin protease /FL=gb:NM_014479.1	chr8p21.2	Hs.145296	ADAM-like, decysin 1	ADAMDEC1
206513_at	NM_004833	gb:NM_004833.1 /DB_XREF=gi:4757733 /GEN=AIM2 /FEA=FLmRNA /CNT=15 /TID=Hs.105115.0 /TIER=FL /STK=7 /UG=Hs.105115 /LL=9447 /DEF=Homo sapiens absent in melanoma 2 (AIM2), mRNA. /PROD=absent in melanoma 2 /FL=gb:AF024714.1 gb:NM_004833.1	chr1q22	Hs.105115	absent in melanoma 2	AIM2
218332_at	NM_018476	gb:NM_018476.1 /DB_XREF=gi:8923715 /GEN=HBEX2 /FEA=FLmRNA /CNT=116 /TID=Hs.283719.0 /TIER=FL+Stack /STK=54 /UG=Hs.283719 /LL=55859 /DEF=Homo sapiens uncharacterized hypothalamus protein HBEX2 (HBEX2), mRNA. /PROD=uncharacterized hypothalamus protein HBEX2	chrXq21-q23	Hs.334370	brain expressed, X-linked 1	BEX1
205715_at	NM_004334	gb:NM_004334.1 /DB_XREF=gi:4757873 /GEN=BST1 /FEA=FLmRNA /CNT=43 /TID=Hs.169998.0 /TIER=FL+Stack /STK=21 /UG=Hs.169998 /LL=683 /DEF=Homo sapiens bone marrow stromal cell antigen 1 (BST1), mRNA. /PROD=bone marrow stromal cell antigen 1 precursor /FL=gb:D21	chr4p15	Hs.169998	bone marrow stromal cell antigen 1	BST1
202953_at	NM_000491	gb:NM_000491.2 /DB_XREF=gi:11038661 /GEN=C1QB /FEA=FLmRNA /CNT=135 /TID=Hs.8986.0 /TIER=FL+Stack /STK=16 /UG=Hs.8986 /LL=713 /DEF=Homo sapiens complement component 1, q subcomponent, beta polypeptide (C1QB), mRNA. /PROD=complement component 1, q subcompon	chr1p36.3-p34.1	Hs.8986	complement component 1, q subcomponent, beta polypeptide	C1QB
209906_at	U62027	gb:U62027.1 /DB_XREF=gi:1511643 /GEN=HNFA09 /FEA=FLmRNA /CNT=43 /TID=Hs.155935.0 /TIER=FL+Stack /STK=19 /UG=Hs.155935 /LL=719 /DEF=Human anaphylatoxin C3a receptor (HNFA09) mRNA, complete cds. /PROD=anaphylatoxin C3a receptor /FL=gb:U62027.1 gb:U28488.1	chr12p13.31	Hs.155935	complement component 3a receptor 1	C3AR1
229824_at	AL133706	gb:AL133706 /DB_XREF=gi:6601894 /DB_XREF=DKFZp76100410_s1 /CLONE=DKFZp76100410 /FEA=EST /CNT=29 /TID=Hs.4257.0 /TIER=Stack /STK=28 /UG=Hs.4257 /UG_TITLE=EST	chr9q22.1-q22.2	Hs.4257	Endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	C9orf47

Table 1 (continuation)

206407_s_at	NM_005408	gb:NM_005408.1 /DB_XREF=gi:4885586 /GEN=SCYA13 /FEA=FLmRNA /CNT=19 /TID=Hs.11383.0 /TIER=FL /STK=6 /UG=Hs.11383 /LL=6357 /DEF=Homo sapiens small inducible cytokine subfamily A (Cys-Cys), member 13 (SCYA13), mRNA. /PROD=small inducible cytokine subfamily A	chr17q11.2	Hs.414629	chemokine (C-C motif) ligand 13	CCL13
209924_at	AB000221	gb:AB000221.1 /DB_XREF=gi:2289718 /GEN=PARC /FEA=FLmRNA /CNT=50 /TID=Hs.16530.0 /TIER=FL+Stack /STK=21 /UG=Hs.16530 /LL=6362 /DEF=Homo sapiens mRNA for CC chemokine, complete cds. /PROD=CC chemokine /FL=gb:AB000221.1 gb:NM_002988.1	chr17q11.2	Hs.16530	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	CCL18
216598_s_at	S69738	gb:S69738.1 /DB_XREF=gi:545464 /GEN=MCP-1 /FEA=mRNA /CNT=1 /TID=Hs.303649.1 /TIER=ConsEnd /STK=0 /UG=Hs.303649 /LL=6347 /DEF=MCP-1=monocyte chemotactic protein (human, aortic endothelial cells, mRNA, 661 nt). /PROD=MCP-1	chr17q11.2-q21.1	Hs.303649	chemokine (C-C motif) ligand 2	CCL2
205114_s_at	NM_002983	gb:NM_002983.1 /DB_XREF=gi:4506842 /GEN=SCYA3 /FEA=FLmRNA /CNT=78 /TID=Hs.73817.0 /TIER=FL+Stack /STK=30 /UG=Hs.73817 /LL=6348 /DEF=Homo sapiens small inducible cytokine A3 (homologous to mouse Mip-1a) (SCYA3), mRNA. /PROD=small inducible cytokine A3 (hom	chr17q21.1	Hs.512304	chemokine (C-C motif) ligand 3 /// chemokine (C-C motif) ligand 3-like 1 /// chemokine (C-C motif) ligand 3-like 3	CCL3 /// CCL3L1 /// CCL3L3
214038_at	AI984980	gb:AI984980 /DB_XREF=gi:5812257 /DB_XREF=wr88g11.x1 /CLONE=IMAGE:2494820 /FEA=FLmRNA /CNT=29 /TID=Hs.271387.0 /TIER=Stack /STK=16 /UG=Hs.271387 /LL=6355 /UG_GENE=SCYA8 /UG_TITLE=small inducible cytokine subfamily A (Cys-Cys), member 8 (monocyte chemotacti	chr17q11.2	Hs.271387	chemokine (C-C motif) ligand 8	CCL8
209583_s_at	AF063591	gb:AF063591.1 /DB_XREF=gi:12002013 /FEA=FLmRNA /CNT=108 /TID=Hs.79015.0 /TIER=FL+Stack /STK=37 /UG=Hs.79015 /LL=4345 /UG_GENE=MOX2 /DEF=Homo sapiens brain my033 protein mRNA, complete cds. /PROD=brain my033 protein /FL=gb:AF063591.1	chr3q12-q13	Hs.79015	CD200 antigen	CD200
207277_at	AF290886	gb:AF290886.1 /DB_XREF=gi:13383467 /FEA=FLmRNA /CNT=8 /TID=Hs.278694.0 /TIER=FL /STK=0 /UG=Hs.278694 /LL=30835 /UG_GENE=CD209 /DEF=Homo sapiens DC-SIGN mRNA, complete cds. /PROD=DC-SIGN /FL=gb:AF290886.1 gb:M98457.1 gb:NM_021155.1	chr19p13	Hs.278694	CD209 antigen	CD209
203416_at	NM_000560	gb:NM_000560.1 /DB_XREF=gi:10834971 /GEN=CD53 /FEA=FLmRNA /CNT=137 /TID=Hs.82212.0 /TIER=FL+Stack /STK=64 /UG=Hs.82212 /LL=963 /DEF=Homo sapiens CD53 antigen (CD53), mRNA. /PROD=CD53 antigen /FL=gb:NM_000560.1 gb:M60871.1 gb:M37033.1	chr1p13	Hs.443057	CD53 antigen	CD53
218451_at	NM_022842	gb:NM_022842.1 /DB_XREF=gi:12383093 /GEN=FLJ22969 /FEA=FLmRNA /CNT=97 /TID=Hs.146170.0 /TIER=FL+Stack /STK=16 /UG=Hs.146170 /LL=64866 /DEF=Homo sapiens hypothetical protein FLJ22969 (FLJ22969), mRNA. /PROD=hypothetical protein FLJ22969 /FL=gb:NM_022842.1	chr3p21.31	Hs.146170	CUB domain containing protein 1	CDCP1

Table 1 (continuation)

217428_s_at	X98568	gb:X98568 /DB_XREF=gi:1405722 /FEA=DNA /CNT=2 /TID=Hs.179729.1 /TIER=ConsEnd /STK=0 /UG=Hs.179729 /LL=1300 /UG_GENE=COL10A1 /UG_TITLE=collagen, type X, alpha 1 (Schmid metaphyseal chondrodysplasia) /DEF=H.sapiens type X collagen gene	chr6q21-q22	Hs.179729	collagen, type X, alpha 1 (Schmid metaphyseal chondrodysplasia)	COL10A1
205159_at	AV756141	gb:AV756141 /DB_XREF=gi:10913989 /DB_XREF=AV756141 /CLONE=BMFAKF10 /FEA=FLmRNA /CNT=51 /TID=Hs.285401.0 /TIER=Stack /STK=20 /UG=Hs.285401 /LL=1439 /UG_GENE=CSF2RB /UG_TITLE=colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	chr22q13.1	Hs.285401	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage) /// colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	CSF2RB
201487_at	NM_001814	gb:NM_001814.1 /DB_XREF=gi:4503140 /GEN=CTSC /FEA=FLmRNA /CNT=257 /TID=Hs.10029.0 /TIER=FL+Stack /STK=125 /UG=Hs.10029 /LL=1075 /DEF=Homo sapiens cathepsin C (CTSC), mRNA. /PROD=cathepsin C /FL=gb:NM_001814.1	chr11q14.1-q14.3	Hs.128065	cathepsin C	CTSC
203666_at	NM_000609	gb:NM_000609.1 /DB_XREF=gi:10834987 /GEN=SDF1 /FEA=FLmRNA /CNT=114 /TID=Hs.237356.0 /TIER=FL+Stack /STK=60 /UG=Hs.237356 /LL=6387 /DEF=Homo sapiens stromal cell-derived factor 1 (SDF1), mRNA. /PROD=stromal cell-derived factor 1 /FL=gb:L36033.1 gb:NM_000609	chr10q11.1	Hs.436042	chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	CXCL12
223553_s_at	BC004564	gb:BC004564.1 /DB_XREF=gi:13528734 /FEA=FLmRNA /CNT=30 /TID=Hs.122559.1 /TIER=FL+Stack /STK=12 /UG=Hs.122559 /DEF=Homo sapiens, Similar to hypothetical protein FLJ22570, clone MGC:10476, mRNA, complete cds. /PROD=Similar to hypothetical protein FLJ22570 /	chr5q35.3	Hs.122559	docking protein 3	DOK3
219454_at	NM_015507	gb:NM_015507.2 /DB_XREF=gi:13124887 /GEN=EGFL6 /FEA=FLmRNA /CNT=163 /TID=Hs.12844.0 /TIER=FL+Stack /STK=40 /UG=Hs.12844 /LL=25975 /DEF=Homo sapiens EGF-like domain, multiple 6 (EGFL6), mRNA. /PROD=epidermal growth factor-like protein 6precursor /FL=gb:NM_015507	chrp22	Hs.12844	EGF-like domain, multiple 6	EGFL6
1554899_s_at	BC020763	gb:BC020763.1 /DB_XREF=gi:1808866 /TID=Hs.433300.2 /CNT=3 /FEA=FLmRNA /TIER=FL /STK=1 /LL=2207 /UG_GENE=FCER1G /UG=Hs.433300 /DEF=Homo sapiens, Similar to Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide, clone MGC:22620 IMAGE:470442	chr1q23	Hs.433300	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	FCER1G
203561_at	NM_021642	gb:NM_021642.1 /DB_XREF=gi:11056051 /GEN=FCGR2A /FEA=FLmRNA /CNT=142 /TID=Hs.78864.0 /TIER=FL+Stack /STK=8 /UG=Hs.78864 /LL=2212 /DEF=Homo sapiens Fc fragment of IgG, low affinity IIa, receptor for (CD32) (FCGR2A), mRNA. /PROD=Fc fragment of IgG, low affi	chr1q23	Hs.352642	Fc fragment of IgG, low affinity IIa, receptor (CD32)	FCGR2A
218468_s_at	AF154054	gb:AF154054.1 /DB_XREF=gi:10863087 /GEN=DRM /FEA=FLmRNA /CNT=228 /TID=Hs.40098.0 /TIER=FL+Stack /STK=20 /UG=Hs.40098 /LL=26585 /DEF=Homo sapiens DRM (DRM), mRNA, complete cds. /PROD=DRM /FL=gb:NM_013372.1 gb:AF110137.2 gb:AF045800.1 gb:AF154054.1	chr15q13-q15	Hs.40098	gremlin 1, cysteine knot superfamily, homolog (Xenopus laevis)	GREM1

Table 1 (continuation)

217478_s_at	X76775	gb:X76775/DB_XREF=gi:512468/FEA=DNA_1/CNT=1/TID=Hs.77522.1/TIER=ConsEnd/STK=0/UG=Hs.77522/LL=3108/UG_GENE=HLA-DMA/UG_TITLE=major histocompatibility complex, class II, DM alpha/DEF=H.sapiens HLA-DMA gene	chr6p21.3	Hs.351279	major histocompatibility complex, class II, DM alpha	HLA-DMA
203932_at	NM_002118	gb:NM_002118.1/DB_XREF=gi:4504398/GEN=HLA-DMB/FEA=FLmRNA/CNT=91/TID=Hs.1162.0/TIER=FL+Stack/STK=49/UG=Hs.1162/LL=3109/DEF=Homo sapiens major histocompatibility complex, class II, DM beta (HLA-DMB), mRNA./PROD=major histocompatibility complex, c	chr6p21.3	Hs.1162	major histocompatibility complex, class II, DM beta /// major histocompatibility complex, class II, DM beta	HLA-DMB
211991_s_at	M27487	gb:M27487.1/DB_XREF=gi:703088/GEN=HLA-DPA1/FEA=FLmRNA/CNT=358/TID=Hs.914.0/TIER=FL+Stack/STK=139/UG=Hs.914/DEF=Homo sapiens MHC class II DPw3-alpha-1 chain mRNA, complete cds./PROD=MHC class II DP3-alpha /FL=gb:M27487.1	chr6p21.3	Hs.914	major histocompatibility complex, class II, DP alpha 1	HLA-DPA1
212671_s_at	BG397856	gb:BG397856/DB_XREF=gi:13291304/DB_XREF=602438950F1/CLONE=IMAGE:4564956/FEA=mRNA/CNT=167/TID=Hs.198253.2/TIER=Stack/STK=59/UG=Hs.198253/LL=3117/UG_GENE=HLA-DQA1/UG_TITLE=major histocompatibility complex, class II, DQ alpha 1	chr6p21.3	Hs.387679	major histocompatibility complex, class II, DQ alpha 1 /// major histocompatibility complex, class II, DQ alpha 2	HLA-DQA1 /// HLA-DQA2
208894_at	M60334	gb:M60334.1/DB_XREF=gi:188255/GEN=HLA-DRA/FEA=FLmRNA/CNT=470/TID=Hs.76807.0/TIER=FL/STK=0/UG=Hs.76807/LL=3122/DEF=Human MHC class II HLA-DR-alpha mRNA, complete cds./PROD=cell surface glycoprotein /FL=gb:M60334.1 gb:NM_019111.1	chr6p21.3	Hs.409805	major histocompatibility complex, class II, DR alpha /// major histocompatibility complex, class II, DR alpha	HLA-DRA
204670_x_at	NM_002125	gb:NM_002125.1/DB_XREF=gi:4504412/GEN=HLA-DRB5/FEA=FLmRNA/CNT=62/TID=Hs.308026.0/TIER=FL/STK=1/UG=Hs.308026/LL=3127/DEF=Homo sapiens major histocompatibility complex, class II, DR beta 5 (HLA-DRB5), mRNA./PROD=major histocompatibility complex,	chr6p21.3	Hs.308026	major histocompatibility complex, class II, DR beta 1	HLA-DRB1
209312_x_at	U65585	gb:U65585.1/DB_XREF=gi:5478215/GEN=HLA-DRB1/FEA=FLmRNA/CNT=126/TID=Hs.180255.0/TIER=FL/STK=0/UG=Hs.180255/LL=3123/DEF=Homo sapiens MHC class II antigen (HLA-DRB1) mRNA, HLA-DRB1*PBL allele, complete cds./PROD=MHC class II antigen/FL=gb:NM_0021			major histocompatibility complex, class II, DR beta 1 /// major histocompatibility complex, class II, DR beta 1	HLA-DRB1
208306_x_at	NM_021983	gb:NM_021983.2/DB_XREF=gi:11875206/GEN=HLA-DRB4/FEA=FLmRNA/CNT=2/TID=Hs.293934.0/TIER=FL/STK=0/UG=Hs.293934/LL=3126/DEF=Homo sapiens major histocompatibility complex, class II, DR beta 4 (HLA-DRB4), mRNA./PROD=major histocompatibility complex,	chr6p21.3	Hs.308026	Major histocompatibility complex, class II, DR beta 3	HLA-DRB3
217362_x_at	AF005487	gb:AF005487.1/DB_XREF=gi:5915893/FEA=mRNA/CNT=2/TID=Hs.167385.0/TIER=ConsEnd/STK=0/UG=Hs.167385/UG_TITLE=Homo sapiens MHC class II antigen HLA-DRB6 mRNA, partial cds/DEF=Homo sapiens MHC class II antigen (DRB6) mRNA, HLA-DRB6*0201 allele, sequenc	chr6p21.3		major histocompatibility complex, class II, DR beta 6 (pseudogene)	HLA-DRB6

Table 1 (continuation)

229400_at	AW299531	gb:AW299531 /DB_XREF=gi:6709208 /DB_XREF=xs51a03.x1 /CLONE=IMAGE:2773132 /FEA=EST /CNT=17 /TID=Hs.188023.0 /TIER=Stack /STK=10 /UG=Hs.188023 /UG_TITLE=ESTs	chr2q31.1	Hs.123070	homeo box D10	HOXD10
209374_s_at	BC001872	gb:BC001872.1 /DB_XREF=gi:12804852 /FEA=FLmRNA /CNT=302 /TID=Hs.302063.0 /TIER=FL+Stack /STK=207 /UG=Hs.302063 /LL=3507 /UG_GENE=IGHM /DEF=Homo sapiens, clone MGC:1228, mRNA, complete cds. /PROD=Unknown (protein for MGC:1228) /FL=gb:BC002963.1 gb:BC001872	chr14q32.33	Hs.439852	immunoglobulin heavy constant mu	IGHM
214669_x_at	BG485135	gb:BG485135 /DB_XREF=gi:13417414 /DB_XREF=602503756F1 /CLONE=IMAGE:4617445 /FEA=mRNA /CNT=101 /TID=Hs.325722.1 /TIER=ConsEnd /STK=0 /UG=Hs.325722 /LL=28875 /UG_GENE=IGKV3D-15 /UG_TITLE=immunoglobulin kappa variable 3D-15	chr2p12	Hs.377975 /// Hs.449606 /// Hs.494060 /// Hs.512126 /// Hs.534005	Immunoglobulin kappa variable 1-5	IGKC
226218_at	BE217880	gb:BE217880 /DB_XREF=gi:8905198 /DB_XREF=lv31a11.x1 /CLONE=IMAGE:3175004 /FEA=EST /CNT=52 /TID=Hs.237868.1 /TIER=Stack /STK=24 /UG=Hs.237868 /LL=3575 /UG_GENE=IL7R /UG_TITLE=interleukin 7 receptor	chr5p13	Hs.362807	Interleukin 7 receptor	IL7R
205786_s_at	NM_000632	gb:NM_000632.2 /DB_XREF=gi:6006013 /GEN=ITGAM /FEA=FLmRNA /CNT=40 /TID=Hs.172631.0 /TIER=FL /STK=1 /UG=Hs.172631 /LL=3684 /DEF=Homo sapiens integrin, alpha M (complement component receptor 3, alpha; also known as CD11b (p170), macrophage antigen alpha pol	chr16p11.2	Hs.172631	integrin, alpha M (complement component receptor 3, alpha; also known as CD11b (p170), macrophage antigen alpha polypeptide) /// integrin, alpha M (complement component receptor 3, alpha; also known as CD11b (p170), macrophage antigen alpha polypeptide)	ITGAM
202803_s_at	NM_000211	gb:NM_000211.1 /DB_XREF=gi:4557885 /GEN=ITGB2 /FEA=FLmRNA /CNT=176 /TID=Hs.83968.0 /TIER=FL+Stack /STK=80 /UG=Hs.83968 /LL=3689 /DEF=Homo sapiens integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1)	chr21q22.3	Hs.375957	integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1) beta subunit)	ITGB2
228167_at	AW574798	gb:AW574798 /DB_XREF=gi:7246337 /DB_XREF=UI-HF-BKO-abh-e-04-0-UI.s1 /CLONE=IMAGE:3056335 /FEA=mRNA /CNT=35 /TID=Hs.43616.0 /TIER=Stack /STK=18 /UG=Hs.43616 /UG_TITLE=Homo sapiens mRNA for FLJ00029 protein, partial cds	chr3q27.3	Hs.439354	kelch-like 6 (Drosophila)	KLHL6

Table 1 (continuation)

205306_x_at	A1074145	gb:A1074145 /DB_XREF=gi:3400789 /DB_XREF=ov13a06.x1 /CLONE=IMAGE:1637170 /FEA=FLmRNA /CNT=48 /TID=Hs.107318.0 /TIER=Stack /STK=10 /UG=Hs.107318 /LL=8564 /UG_GENE=KMO /UG_TITLE=kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) /FL=gb:NM_003679.1 gb:AF0	chr1q42-q44	Hs.409081	kynurenine 3-monooxygenase (kynurenine 3-hydroxylase)	KMO
201720_s_at	A1589086	gb:A1589086 /DB_XREF=gi:4598134 /DB_XREF=tf80g10.x1 /CLONE=IMAGE:2105634 /FEA=FLmRNA /CNT=274 /TID=Hs.79356.0 /TIER=Stack /STK=22 /UG=Hs.79356 /LL=7805 /UG_GENE=LAPTM5 /UG_TITLE=Lysosomal-associated multispinning membrane protein-5 /FL=gb:NM_006762.1 gb:U	chr1p34	Hs.436200	lysosomal associated multispinning membrane protein 5	LAPTM5
206140_at	NM_004789	gb:NM_004789.1 /DB_XREF=gi:4758673 /GEN=LHX2 /FEA=FLmRNA /CNT=18 /TID=Hs.1569.0 /TIER=FL /STK=1 /UG=Hs.1569 /LL=9355 /DEF=Homo sapiens LIM homeobox protein 2 (LHX2), mRNA /PROD=LIM homeobox protein 2 /FL=gb:NM_004789.1 gb:AF124735.1	chr9q33-q34.1	Hs.1569	LIM homeobox 2	LHX2
213909_at	AU147799	gb:AU147799 /DB_XREF=gi:11009320 /DB_XREF=AU147799 /CLONE=MAMMA1001744 /FEA=mRNA /CNT=43 /TID=Hs.288467.0 /TIER=Stack /STK=20 /UG=Hs.288467 /UG_TITLE=Homo sapiens cDNA FLJ12280 fis, clone MAMMA1001744	chr3q29	Hs.288467	leucine rich repeat containing 15	LRRRC15
213975_s_at	AV711904	gb:AV711904 /DB_XREF=gi:10731210 /DB_XREF=AV711904 /CLONE=DCAAIE08 /FEA=mRNA /CNT=21 /TID=Hs.277431.0 /TIER=Stack /STK=8 /UG=Hs.277431 /UG_TITLE=Homo sapiens cDNA: FLJ23356 fis, clone HEP14919	chr19q13.4 /// chr12q15	Hs.149924	lysozyme (renal amyloidosis) /// leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	LYZ /// LILRB1
203435_s_at	NM_007287	gb:NM_007287.1 /DB_XREF=gi:6042199 /GEN=MME /FEA=FLmRNA /CNT=219 /TID=Hs.1298.2 /TIER=FL+Stack /STK=59 /UG=Hs.1298 /LL=4311 /DEF=Homo sapiens membrane metallo-endopeptidase (neutral endopeptidase, enkephalinase, CALLA, CD10) (MME), transcript variant 1 bis	chr3q25.1-q25.2	Hs.307734	membrane metallo-endopeptidase (neutral endopeptidase, enkephalinase, CALLA, CD10)	MME
204580_at	NM_002426	gb:NM_002426.1 /DB_XREF=gi:4505206 /GEN=MMP12 /FEA=FLmRNA /CNT=72 /TID=Hs.1695.0 /TIER=FL+Stack /STK=18 /UG=Hs.1695 /LL=4321 /DEF=Homo sapiens matrix metalloproteinase 12 (macrophage elastase) (MMP12), mRNA /PROD=matrix metalloproteinase 12 preproprotein	chr11q22.3	Hs.1695	matrix metalloproteinase 12 (macrophage elastase)	MMP12
226844_at	A1375115	gb:A1375115 /DB_XREF=gi:4175105 /DB_XREF=tc09e10.x1 /CLONE=IMAGE:2063370 /FEA=EST /CNT=43 /TID=Hs.293849.0 /TIER=Stack /STK=27 /UG=Hs.293849 /UG_TITLE=ESTs	chr9p21.2	Hs.128905	MOB1, Mps One Binder kinase activator-like 2B (yeast)	MOBK12B
226818_at	T64884	gb:T64884 /DB_XREF=gi:673929 /DB_XREF=yd10b06.s1 /CLONE=IMAGE:66707 /FEA=mRNA /CNT=72 /TID=Hs.288581.0 /TIER=Stack /STK=8 /UG=Hs.288581 /UG_TITLE=Homo sapiens cDNA FLJ14296 fis, clone PLACE1008455	chr11q12.1	Hs.62264	macrophage expressed gene 1	MPEG1

Table 1 (continuation)

204438_at	NM_002438	gb:NM_002438.1 /DB_XREF=gi:4505244 /GEN=MRC1 /FEA=FLmRNA /CNT=64 /TID=Hs.75182.0 /TIER=FL+Stack /STK=25 /UG=Hs.75182 /LL=4360 /DEF=Homo sapiens mannose receptor, C type 1 (MRC1), mRNA. /PROD=mannose receptor, C type 1 /FL=gb:NM_002438.1 gb:J05550.1	chr10p13	Hs.75182	mannose receptor, C type 1 /// mannose receptor, C type 1-like 1	MRC1 /// MRC1L1
155728_a_at	AF354928	gb:AF354928.1 /DB_XREF=gi:15808758 /TID=Hs.325960.4 /CNT=1 /FEA=FLmRNA /TIER=FL /STK=1 /LL=51338 /UG_GENE=MS4A4A /UG=Hs.325960 /DEF=Homo sapiens MS4A4A protein mRNA, complete cds, alternatively spliced. /PROD=MS4A4A protein /FL=gb:AF354928.1	chr11q12	Hs.325960	membrane-spanning 4-domains, subfamily A, member 4	MS4A4A
209949_at	BC001606	gb:BC001606.1 /DB_XREF=gi:12804408 /FEA=FLmRNA /CNT=31 /TID=Hs.949.0 /TIER=FL /STK=4 /UG=Hs.949 /LL=4688 /UG_GENE=NCF2 /DEF=Homo sapiens, Similar to neutrophil cytosolic factor 2 (65kD, chronic granulomatous disease, autosomal 2), clone MGC:2275, mRNA, co	chr1q25	Hs.949	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)	NCF2
221210_s_at	NM_030769	gb:NM_030769.1 /DB_XREF=gi:13540532 /GEN=C1ORF13 /FEA=FLmRNA /CNT=1 /TID=HsAffx:900046.172 /TIER=FL /STK=0 /DEF=Homo sapiens hypothetical protein similar to swine acylneuraminase (C1ORF13), mRNA. /PROD=hypothetical protein similar to swineacyneuram	chr1q25	Hs.64896	N-acetylneuraminase pyruvate lyase (dihydrodipicolinate synthase) /// N-acetylneuraminase pyruvate lyase (dihydrodipicolinate synthase)	NPL
218625_at	NM_016588	gb:NM_016588.1 /DB_XREF=gi:7706122 /GEN=LOC51299 /FEA=FLmRNA /CNT=106 /TID=Hs.103291.0 /TIER=FL+Stack /STK=36 /UG=Hs.103291 /LL=51299 /DEF=Homo sapiens neuritin (LOC51299), mRNA. /PROD=neuritin /FL=gb:NM_016588.1 gb:BC002683.1 gb:AF136631.1	chr6p25.1	Hs.103291	neuritin 1	NRN1
231867_at	AB032953	gb:AB032953.1 /DB_XREF=gi:6329762 /GEN=KIAA1127 /FEA=mRNA /CNT=32 /TID=Hs.173560.0 /TIER=ConsEnd /STK=2 /UG=Hs.173560 /LL=57451 /DEF=Homo sapiens mRNA for KIAA1127 protein, partial cds. /PROD=KIAA1127 protein	chr5q34	Hs.173560	odz, odd Oz/ten-m homolog 2 (Drosophila)	ODZ2
226459_at	AW575754	gb:AW575754 /DB_XREF=gi:7247293 /DB_XREF=UI-HF-BM0-adw-c-06-0-UI.s1 /CLONE=IMAGE:3063154 /FEA=EST /CNT=60 /TID=Hs.86437.0 /TIER=Stack /STK=35 /UG=Hs.86437 /UG_TITLE=ESTs, Highly similar to AF219140 1 gastric cancer-related protein GCYS-20 (H.sapiens)	chr10q24.1	Hs.374836	phosphoinositide-3-kinase adaptor protein 1	PIK3AP1
206214_at	NM_005084	gb:NM_005084.1 /DB_XREF=gi:4826883 /GEN=PLA2G7 /FEA=FLmRNA /CNT=21 /TID=Hs.93304.0 /TIER=FL+Stack /STK=8 /UG=Hs.93304 /LL=7941 /DEF=Homo sapiens phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma) (PLA2G7), mRNA. /PROD=phospho	chr6p21.2-p12	Hs.93304	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma) /// phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	PLA2G7

Table 1 (continuation)

212588_at	Y00062	gb:Y00062.1 /DB_XREF=gi:34275 /FEA=mRNA /CNT=145 /TID=Hs.170121.1 /TIER=Stack /STK=18 /UG=Hs.170121 /LL=5788 /UG_GENE=PTPRC /UG_TITLE=protein tyrosine phosphatase, receptor type, C /DEF=Human mRNA for T200 leukocyte common antigen (CD45, LC-A).	chr1q31-q32	Hs.444324	protein tyrosine phosphatase, receptor type, C	PTPRC
37793_r_at	AF034956	Cluster Incl. AF034956: Homo sapiens RAD51D mRNA, complete cds /cds=(124,993) /gb=AF034956 /gi=2920581 /ug=Hs.125244 /len=1564	chr17q11	Hs.125244	RAD51-like 3 (S. cerevisiae)	RAD51L3
203185_at	NM_014737	gb:NM_014737.1 /DB_XREF=gi:7661963 /GEN=RASSF2 /FEA=FLmRNA /CNT=152 /TID=Hs.80905.0 /TIER=FL+Stack /STK=30 /UG=Hs.80905 /LL=9770 /DEF=Homo sapiens Ras association (RalGDS/AF-6) domain family 2 (RASSF2), mRNA. /PROD=Ras association (RalGDS/AF-6) domain famil	chr20pter-p12.1	Hs.80905	Ras association (RalGDS/AF-6) domain family 2	RASSF2
225763_at	A1659418	gb:A1659418 /DB_XREF=gi:4762988 /DB_XREF=tu30a07.x1 /CLONE=IMAGE:2252532 /FEA=mRNA /CNT=77 /TID=Hs.14040.0 /TIER=Stack /STK=23 /UG=Hs.14040 /UG_TITLE=Homo sapiens cDNA: FLJ21772 fis, clone COLF7808	chr1q22-q24	Hs.233125	RCSD domain containing 1	RCSD1
213566_at	NM_005615	gb:NM_005615.1 /DB_XREF=gi:5032044 /GEN=RNASE6 /FEA=FLmRNA /CNT=53 /TID=Hs.23262.0 /TIER=FL+Stack /STK=30 /UG=Hs.23262 /LL=6039 /DEF=Homo sapiens ribonuclease, RNase A family, k6 (RNASE6), mRNA. /PROD=ribonuclease, RNase A family, k6 /FL=gb:NM_005615.1	chr14q11.2	Hs.23262	ribonuclease, RNase A family, k6 /// ribonuclease, RNase A family, k6	RNASE6
219385_at	NM_020125	gb:NM_020125.1 /DB_XREF=gi:9910341 /GEN=SBB142 /FEA=FLmRNA /CNT=37 /TID=Hs.20450.0 /TIER=FL /STK=0 /UG=Hs.20450 /LL=56833 /DEF=Homo sapiens BCM-like membrane protein precursor (SBB142), mRNA. /PROD=BCM-like membrane protein precursor /FL=gb:NM_020125.1 gb	chr1q23.2	Hs.438683	SLAM family member 8	SLAMF8
203473_at	NM_007256	gb:NM_007256.1 /DB_XREF=gi:6005819 /GEN=SLC21A9 /FEA=FLmRNA /CNT=120 /TID=Hs.7884.0 /TIER=FL+Stack /STK=25 /UG=Hs.7884 /LL=11309 /DEF=Homo sapiens solute carrier family 21 (organic anion transporter), member 9 (SLC21A9), mRNA. /PROD=solute carrier family	chr11q13	Hs.7884	solute carrier organic anion transporter family, member 2B1	SLCO2B1
240715_at	AW269421	gb:AW269421 /DB_XREF=gi:6656451 /DB_XREF=xv42e03.x1 /CLONE=IMAGE:2815804 /FEA=EST /CNT=4 /TID=Hs.128093.0 /TIER=ConsEnd /STK=4 /UG=Hs.128093 /UG_TITLE=ESTs	chr12q24.1	Hs.381715	T-box 5	TBX5
205844_at	NM_004666	gb:NM_004666.1 /DB_XREF=gi:4759311 /GEN=VNN1 /FEA=FLmRNA /CNT=36 /TID=Hs.12114.0 /TIER=FL+Stack /STK=13 /UG=Hs.12114 /LL=8876 /DEF=Homo sapiens vanin 1 (VNN1), mRNA. /PROD=vanin 1 /FL=gb:U39664.1 gb:NM_004666.1	chr6q23-q24	Hs.12114	vanin 1 /// vanin 1	VNN1
205922_at	NM_004665	gb:NM_004665.1 /DB_XREF=gi:4759313 /GEN=VNN2 /FEA=FLmRNA /CNT=24 /TID=Hs.121102.0 /TIER=FL+Stack /STK=13 /UG=Hs.121102 /LL=8875 /DEF=Homo sapiens vanin 2 (VNN2), mRNA. /PROD=vanin 2 /FL=gb:D89974.1 gb:NM_004665.1			vanin 2 /// vanin 2	VNN2

Table 1 (continuation)

227346_at	AI741188	gb:AI741188 /DB_XREF=gi:5109476 /DB_XREF=wg26a11.x1 /CLONE=IMAGE:2366204 /FEA=EST /CNT=36 /TID=Hs.121587.0 /TIER=Stack /STK=12 /UG=Hs.121587 /UG_TITLE=ESTs			Zinc finger protein, subfamily 1A, 1 (Ikaros)	ZNFN1A1
214836_x_at	BG536224	gb:BG536224 /DB_XREF=gi:13527769 /DB_XREF=602565445F1 /CLONE=IMAGE:4690258 /FEA=DNA /CNT=36 /TID=Hs.123030.0 /TIER=ConsEnd /STK=0 /UG=Hs.123030 /UG_TITLE=Human kappa-immunoglobulin germline pseudogene (Chr22.4) variable region (subgroup V kappa II)		Hs.469271 /// Hs.525895 /// Hs.534006	Immunoglobulin kappa light chain VJ region (ID POM010) /// Immunoglobulin kappa light chain VJ region (ID POM022) /// (clone TR1.6VL) anti-thyroid peroxidase monoclonal antibody IgK chain, V region	---
219947_at	NM_016184	gb:NM_016184.1 /DB_XREF=gi:7705337 /GEN=CLECSF6 /FEA=FLmRNA /CNT=15 /TID=Hs.115515.0 /TIER=FL /STK=7 /UG=Hs.115515 /LL=50856 /DEF=Homo sapiens C-type (calcium dependent, carbohydrate-recognition domain) lectin, superfamily member 6 (CLECSF6), mRNA. /PROD=	chr12p13	Hs.115515	C-type (calcium dependent, carbohydrate-recognition domain) lectin, superfamily member 6	CLECSF6
					endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	EDG3
					immunoglobulin heavy constant alpha 1 /// immunoglobulin heavy constant alpha 2 (A2m marker) /// hypothetical protein MGC27165	IGHA1; IGH2; MGC27165
					mast cell-expressed membrane protein 1	MCEMP1
					protein kinase substrate MK2S4	MK2S4

Table 2

Probe set ID number	Public ID number (NCBI)	Target description	Chromosomal location	Unigene ID	Gene Title	Gene Symbol
206046_at	NM_003812	gb:NM_003812.1 /DB_XREF=gi:4501912 /GEN=ADAM23 /FEA=FLmRNA /CNT=26 /TID=Hs.7164.0 /TIER=FL+Stack /STK=11 /UG=Hs.7164 /LL=8745 /DEF=Homo sapiens a disintegrin and metalloproteinase domain 23 (ADAM23), mRNA. /PROD=a disintegrin and metalloproteinase domain	chr2q33	Hs.432317	ADAM metalloproteinase domain 23	ADAM23
206170_at	NM_000024	gb:NM_000024.2 /DB_XREF=gi:13162366 /GEN=ADRB2 /FEA=FLmRNA /CNT=35 /TID=Hs.2551.0 /TIER=FL /STK=0 /UG=Hs.2551 /LL=154 /DEF=Homo sapiens adrenergic, beta-2-, receptor, surface (ADRB2), mRNA. /PROD=adrenergic, beta-2-, receptor, surface /FL=gb:NM_000024.2 g			adrenergic, beta-2-, receptor, surface	ADRB2
205357_s_at	NM_000685	gb:NM_000685.2 /DB_XREF=gi:6715581 /GEN=AGTR1 /FEA=FLmRNA /CNT=61 /TID=Hs.89472.0 /TIER=FL+Stack /STK=18 /UG=Hs.89472 /LL=185 /DEF=Homo sapiens angiotensin receptor 1 (AGTR1), transcript variant 1, mRNA. /PROD=angiotensin receptor 1 /FL=gb:M93394.1 gb:NM_	chr3q21-q25	Hs.89472	angiotensin II receptor, type 1	AGTR1
216594_x_at	S68290	gb:S68290.1 /DB_XREF=gi:544763 /GEN=chlorocone reductase homolog /FEA=mRNA /CNT=1 /TID=Hs.306098.1 /TIER=ConsEnd /STK=0 /UG=Hs.306098 /LL=1645 /UG_TITLE=aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	chr10p15-p14	Hs.201967	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	AKR1C1
209699_x_at	U05598	gb:U05598.1 /DB_XREF=gi:531159 /FEA=FLmRNA /CNT=124 /TID=Hs.201967.0 /TIER=FL+Stack /STK=29 /UG=Hs.201967 /LL=1646 /UG_GENE=AKR1C2 /DEF=Human dihydrodiol dehydrogenase mRNA, complete cds. /PROD=dihydrodiol dehydrogenase /FL=gb:U05598.1 gb:AB031083.1 gb:AB	chr10p15-p14	Hs.201967	aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type II)	AKR1C2
223093_at	T99215	gb:T99215 /DB_XREF=gi:748952 /DB_XREF=y63a06.s1 /CLONE=IMAGE:122386 /FEA=FLmRNA /CNT=174 /TID=Hs.168640.1 /TIER=Stack /STK=13 /UG=Hs.168640 /LL=56172 /UG_GENE=ANKH /UG_TITLE=ankylolysis, progressive (mouse) homolog /FL=gb:AF274753.1	chr5p15.1	Hs.156727	ankylolysis, progressive homolog (mouse)	ANKH
227827_at	AW138143	gb:AW138143 /DB_XREF=gi:6142543 /DB_XREF=UI-H-B11-acy-b-09-0-UI.s1 /CLONE=IMAGE:2715976 /FEA=EST /CNT=32 /TID=Hs.71721.0 /TIER=Stack /STK=16 /UG=Hs.71721 /UG_TITLE=ESTs			Sorbin and SH3 domain containing 2	ARGBP2

Table 2 (continuation)

230309_at	BE876610	gb:BE876610 /DB_XREF=gi:10325386 /DB_XREF=601487767F1 /CLONE=IMAGE:3889936 /FEA=EST /CNT=13 /TID=Hs.172382.1 /TIER=Stack /STK=11 /UG=Hs.172382 /LL=23743 /UG_GENE=BHMT2 /UG_TITLE=betaine-homocysteine methyltransferase 2				Betaine-homocysteine methyltransferase 2	BHMT2
206176_at	NM_001718	gb:NM_001718.2 /DB_XREF=gi:4809281 /GEN=BMP6 /FEA=FLmRNA /CNT=18 /TID=Hs.285671.0 /TIER=FL /STK=0 /UG=Hs.285671 /LL=654 /DEF=Homo sapiens bone morphogenetic protein 6 (BMP6), mRNA. /PROD=bone morphogenetic protein 6 precursor /FL=gb:M60315.1 gb:NM_001718.	chr6p24-p23	Hs.285671		bone morphogenetic protein 6	BMP6
241412_at	A1620677	gb:A1620677 /DB_XREF=gi:4629803 /DB_XREF=tu85e09.x1 /CLONE=IMAGE:2257864 /FEA=EST /CNT=7 /TID=Hs.154191.0 /TIER=ConsEnd /STK=0 /UG=Hs.154191 /UG_TITLE=ESTs	chr4q13-q21	Hs.73105		betacellulin	BTC
224458_at	BC006115	gb:BC006115.1 /DB_XREF=gi:13543948 /FEA=FLmRNA /CNT=1 /TID=HsAfx.900859.640 /TIER=FL /STK=0 /DEF=Homo sapiens, Similar to RIKEN cDNA 2810432L12 gene, clone MGC:12992, mRNA, complete cds. /PROD=Similar to RIKEN cDNA 2810432L12 gene /FL=gb:BC006115.1	chr9q31.1	Hs.431270		chromosome 9 open reading frame 125 // chromosome 9 open reading frame 125	C9orf125
235182_at	A1816793	gb:A1816793 /DB_XREF=gi:5435872 /DB_XREF=wj34b11.x1 /CLONE=IMAGE:2404701 /FEA=EST /CNT=13 /TID=Hs.135100.0 /TIER=ConsEnd /STK=4 /UG=Hs.135100 /UG_TITLE=ESTs	chr20p12.1	Hs.156650		chromosome 20 open reading frame 82	C20orf82
227226_at	AA418816	gb:AA418816 /DB_XREF=gi:2080617 /DB_XREF=zw01a04.s1 /CLONE=IMAGE:767982 /FEA=EST /CNT=34 /TID=Hs.20953.0 /TIER=Stack /STK=24 /UG=Hs.20953 /UG_TITLE=ESTs	chr6q14.3	Hs.425033		chromosome 6 open reading frame 117	C6orf117
209616_s_at	S73751	gb:S73751.1 /DB_XREF=gi:688112 /FEA=FLmRNA /CNT=178 /TID=Hs.76688.0 /TIER=FL /STK=0 /UG=Hs.76688 /LL=1066 /UG_GENE=CES1 /DEF=Homo sapiens acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds. /PROD=acyl coenzyme A:cholesterol acyltransferase /FL	chr16q13-q22.1	Hs.278997		carboxylesterase 1 (monocyte/macrophage serine esterase 1)	CES1
208791_at	M25915	gb:M25915.1 /DB_XREF=gi:180619 /FEA=FLmRNA /CNT=470 /TID=Hs.75106.0 /TIER=FL /STK=3 /UG=Hs.75106 /LL=1191 /UG_GENE=CLU /UG_TITLE=clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)	chr8p21-p12	Hs.436657		clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)	CLU
205713_s_at	NM_000095	gb:NM_000095.1 /DB_XREF=gi:4557482 /GEN=COMP /FEA=FLmRNA /CNT=64 /TID=Hs.1584.0 /TIER=FL+Stack /STK=16 /UG=Hs.1584 /LL=1311 /DEF=Homo sapiens cartilage oligomeric matrix protein (pseudoachondroplasia, epiphyseal dysplasia 1, multiple) (COMP), mRNA. /PROD=	chr19p13.1	Hs.1584		cartilage oligomeric matrix protein	COMP

Table 2 (continuation)

206315_at	NM_004750	gb:NM_004750.1 /DB_XREF=gi:4758061 /GEN=CRLF1 /FEA=FLmRNA /CNT=20 /TID=Hs.114948.0 /TIER=FL+Stack /STK=13 /UG=Hs.114948 /LL=9244 /DEF=Homo sapiens cytokine receptor-like factor 1 (CRLF1), mRNA. /PROD=cytokine receptor-like factor 1 /FL=gb:AF073515.1 gb:NM	chr19p12	Hs.114948	cytokine receptor-like factor 1	CRLF1
208350_at	NM_001890	gb:NM_001890.1 /DB_XREF=gi:4503084 /GEN=CSN1 /FEA=FLmRNA /CNT=4 /TID=Hs.3155.0 /TIER=FL /STK=0 /UG=Hs.3155 /LL=1446 /DEF=Homo sapiens casein, alpha (CSN1), mRNA. /PROD=casein, alpha /FL=gb:NM_001890.1 gb:U23157.1	chr4q21.1	Hs.3155	casein alpha s1	CSN1S1
202435_s_at	AU154504	gb:AU154504 /DB_XREF=gi:11016025 /DB_XREF=AU154504 /CLONE=NT2RP4001328 /FEA=FLmRNA /CNT=212 /TID=Hs.154654.0 /TIER=Stack /STK=20 /UG=Hs.154654 /LL=1545 /UG_GENE=CYP1B1 /UG_TITLE=cytochrome P450, subfamily B, polypeptide 1 (glaucoma 3, p	chr2p21	Hs.154654	cytochrome P450, family 1, subfamily B, polypeptide 1	CYP1B1
205818_at	NM_014618	gb:NM_014618.1 /DB_XREF=gi:7657008 /GEN=DBCCR1 /FEA=FLmRNA /CNT=33 /TID=Hs.6090.0 /TIER=FL+Stack /STK=8 /UG=Hs.6090 /LL=1620 /DEF=Homo sapiens deleted in bladder cancer chromosome region candidate 1 (DBCCR1), mRNA. /PROD=deleted in bladder cancer chromosome	chr9q32-q33	Hs.6090	deleted in bladder cancer 1	DBC1
210397_at	U73945	gb:U73945.1 /DB_XREF=gi:1755147 /FEA=FLmRNA /CNT=26 /TID=Hs.32949.0 /TIER=FL /STK=0 /UG=Hs.32949 /LL=1672 /UG_GENE=DEFB1 /DEF=Human beta-defensin-1 mRNA, complete cds. /PROD=beta-defensin-1 /FL=gb:U73945.1 gb:NM_005218.2	chr8p23.2-p23.1	Hs.32949	defensin, beta 1	DEFB1
205554_s_at	NM_004944	gb:NM_004944.1 /DB_XREF=gi:4826697 /GEN=DNASE1L3 /FEA=FLmRNA /CNT=51 /TID=Hs.88646.0 /TIER=FL /STK=0 /UG=Hs.88646 /LL=1776 /DEF=Homo sapiens deoxyribonuclease I-like 3 (DNASE1L3), mRNA. /PROD=deoxyribonuclease I-like 3 /FL=gb:U56814.1 gb:AF047354.1 gb:NM	chr3p21.1-3p14.3	Hs.88646	deoxyribonuclease I-like 3	DNASE1L3
204014_at	NM_001394	gb:NM_001394.2 /DB_XREF=gi:12707552 /GEN=DUSP4 /FEA=FLmRNA /CNT=105 /TID=Hs.2359.0 /TIER=FL /STK=4 /UG=Hs.2359 /LL=1846 /DEF=Homo sapiens dual specificity phosphatase 4 (DUSP4), mRNA. /PROD=dual specificity phosphatase 4 /FL=gb:NM_001394.2 gb:BC002671.1	chr8p12-p11	Hs.417962	dual specificity phosphatase 4	DUSP4
204271_s_at	M74921	gb:M74921.1 /DB_XREF=gi:182275 /GEN=ETs /FEA=FLmRNA /CNT=130 /TID=Hs.82002.0 /TIER=FL /STK=6 /UG=Hs.82002 /LL=1910 /DEF=Human endothelin receptor mRNA, complete cds. /PROD=endothelin receptor /FL=gb:D90402.1 gb:NM_000115.1 gb:M74921.1	chr13q22	Hs.82002	endothelin receptor type B	EDNRB
206070_s_at	AF213459	gb:AF213459.1 /DB_XREF=gi:12003434 /GEN=EPHA3 /FEA=FLmRNA /CNT=20 /TID=Hs.123642.0 /TIER=FL /STK=0 /UG=Hs.123642 /LL=2042 /DEF=Homo sapiens ephrin receptor EPHA3 complete form (EPHA3) mRNA, complete cds. /PROD=ephrin receptor EPHA3 complete form /FL=gb:NM	chr3p11.2	Hs.123642	EPH receptor A3	EPHA3

Table 2 (continuation)

221884_at	BE466525	gb:BE466525/DB_XREF=gi:9512223/DB_XREF=hx94b10.x1 /CLONE=IMAGE:3195451/FEA=mRNA/CNT=52/TID=Hs.234773.0 /TIER=Stack/STK=13/UG=Hs.234773/UG_TITLE=Homo sapiens cDNA: FLJ22281 fis, clone HRC03849, highly similar to S69002 human mRNA for AML1-EVI-1	chr3q24-q28	Hs.436019	ecotropic viral integration site 1	EVI1
238877_at	BE674583	gb:BE674583/DB_XREF=gi:10035124/DB_XREF=7e02h07.x1 /CLONE=IMAGE:3281341/FEA=EST/CNT=7/TID=Hs.102408.0 /TIER=ConsEnd/STK=4/UG=Hs.102408/UG_TITLE=ESTs			Eyes absent homolog 4 (Drosophila)	EYA4
202771_at	NM_014745	gb:NM_014745.1/DB_XREF=gi:7662013/GEN=KIAA0233/FEA=FLmRNA /CNT=124/TID=Hs.79077.0/TIER=FL+Stack/STK=53/UG=Hs.79077 /LL=9780/DEF=Homo sapiens KIAA0233 gene product (KIAA0233), mRNA. /PROD=KIAA0233 gene product /FL=gb:D87071.1 gb:NM_014745.1	chr16q24.3	Hs.79077	family with sequence similarity 38, member A	FAM38A
227475_at	AI676059	gb:AI676059/DB_XREF=gi:4876539/DB_XREF=wc04g08.x1 /CLONE=IMAGE:2314238/FEA=EST/CNT=31/TID=Hs.163900.0 /TIER=Stack/STK=23/UG=Hs.163900/UG_TITLE=ESTs	chr6p25	Hs.297452	forkhead box Q1	FOXQ1
219764_at	NM_007197	gb:NM_007197.1/DB_XREF=gi:6005761/GEN=FZD10/FEA=FLmRNA /CNT=27/TID=Hs.31664.0/TIER=FL+Stack/STK=16/UG=Hs.31664 /LL=11211/DEF=Homo sapiens frizzled (Drosophila) homolog 10 (FZD10), mRNA. /PROD=frizzled (Drosophila) homolog 10 /FL=gb:AB027464.1 gb:N	chr12q24.33	Hs.31664	frizzled homolog 10 (Drosophila)	FZD10
227405_s_at	AW340311	gb:AW340311/DB_XREF=gi:6836937/DB_XREF=hc95f03.x1 /CLONE=IMAGE:2907773/FEA=EST/CNT=38/TID=Hs.32659.0 /TIER=Stack/STK=24/UG=Hs.32659/UG_TITLE=ESTs	chr10p11.21	Hs.302634	frizzled homolog 8 (Drosophila)	FZD8
208463_at	NM_000809	gb:NM_000809.1/DB_XREF=gi:4557604/GEN=GABRA4/FEA=FLmRNA /CNT=8/TID=Hs.248112.0/TIER=FL/STK=0/UG=Hs.248112/LL=2557 /DEF=Homo sapiens gamma-aminobutyric acid (GABA) A receptor, alpha 4 (GABRA4), mRNA. /PROD=gamma-aminobutyric acid A receptor, alpha	chr4p12	Hs.248112	gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4
218885_s_at	NM_024642	gb:NM_024642.1/DB_XREF=gi:13375880/GEN=FLJ21212 /FEA=FLmRNA/CNT=70/TID=Hs.47099.0/TIER=FL/STK=0/UG=Hs.47099 /LL=79695/DEF=Homo sapiens hypothetical protein FLJ21212 (FLJ21212), mRNA. /PROD=hypothetical protein FLJ21212 /FL=gb:NM_024642.1	chr9q22.33	Hs.47099	UDP-N-acetyl-alpha-D- galactosamine:polypeptide N- acetylgalactosaminyltransferase 12 (GalNAc-T12)	GALNT12
230360_at	AW006648	gb:AW006648/DB_XREF=gi:5855426/DB_XREF=w106e01.x1 /CLONE=IMAGE:2506680/FEA=EST/CNT=10/TID=Hs.30484.0 /TIER=Stack/STK=8/UG=Hs.30484/UG_TITLE=ESTs	chr15q21.2	Hs.30484	gliomedin	GLDN
206355_at	R20102	gb:R20102/DB_XREF=gi:774736/DB_XREF=yg39h06.r1 /CLONE=IMAGE:35031/FEA=FLmRNA/CNT=20/TID=Hs.288642.0 /TIER=ConsEnd/STK=0/UG=Hs.288642/LL=2774/UG_GENE=GNAL /UG_TITLE=guanine nucleotide binding protein (G protein), alpha activating activity polypept	chr18p11.22- p11.21	Hs.136295	guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type	GNAL

Table 2 (continuation)

227769_at	AI703476	gb:AI703476 /DB_XREF=gi:4991376 /DB_XREF=we24f08.x1 /CLONE=IMAGE:2342055 /FEA=EST /CNT=30 /TID=Hs.250899.1 /TIER=Stack /STK=17 /UG=Hs.250899 /LL=3281 /UG_GENE=HSPB1 /UG_TITLE=heat shock factor binding protein 1			G protein-coupled receptor 27	GPR27
206002_at	NM_005756	gb:NM_005756.1 /DB_XREF=gi:5031732 /GEN=GPR64 /FEA=FLmRNA /CNT=24 /TID=Hs.184942.0 /TIER=FL+Stack /STK=9 /UG=Hs.184942 /LL=10149 /DEF=Homo sapiens G protein-coupled receptor 64 (GPR64), mRNA. /PROD=G protein-coupled receptor 64 /FL=gb:NM_005756.1	chrp22.13	Hs.421137	G protein-coupled receptor 64	GPR64
201348_at	NM_002084	gb:NM_002084.2 /DB_XREF=gi:6006000 /GEN=GPX3 /FEA=FLmRNA /CNT=468 /TID=Hs.172153.0 /TIER=FL+Stack /STK=256 /UG=Hs.172153 /LL=2878 /DEF=Homo sapiens glutathione peroxidase 3 (plasma) (GPX3), mRNA. /PROD=plasma glutathione peroxidase 3 precursor /FL=gb:NM_0	chr5q23	Hs.386793	glutathione peroxidase 3 (plasma)	GPX3
218959_at	NM_017409	gb:NM_017409.1 /DB_XREF=gi:8393550 /GEN=HOXC10 /FEA=FLmRNA /CNT=63 /TID=Hs.44276.0 /TIER=FL+Stack /STK=18 /UG=Hs.44276 /LL=3226 /DEF=Homo sapiens homeo box C10 (HOXC10), mRNA. /PROD=homeo box C10 /FL=gb:BC001293.1 gb:NM_017409.1 gb:AF255675.1	chr12q13.3	Hs.44276	homeo box C10	HOXC10
208937_s_at	D13889	gb:D13889.1 /DB_XREF=gi:464181 /GEN=Id-1H /FEA=FLmRNA /CNT=355 /TID=Hs.75424.1 /TIER=FL /STK=0 /UG=Hs.75424 /LL=3397 /DEF=Human mRNA for Id-1H, complete cds. /PROD=Id-1H /FL=gb:NM_002165.1 gb:BC000613.1 gb:D13889.1	chr20q11	Hs.410900	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	ID1
211430_s_at	M87789	gb:M87789.1 /DB_XREF=gi:185361 /FEA=FLmRNA /CNT=1 /TID=Hs.300697.0 /TIER=FL /STK=0 /UG=Hs.300697 /LL=3502 /UG_GENE=IGHG3 /DEF=Human (hybridoma H210) anti-hepatitis A IgG variable region, constant region, complementarity-determining regions mRNA, complete	chr14q32.33	Hs.413826	immunoglobulin heavy locus /// immunoglobulin heavy constant gamma 1 (G1m marker) /// immunoglobulin heavy constant gamma 2 (G2m marker) /// immunoglobulin heavy constant gamma 3 (G3m marker) /// immunoglobulin heavy constant mu	IGH@ /// IGHG1 /// IGHG2 /// IGHG3 /// IGHM
212592_at	AV733266	gb:AV733266 /DB_XREF=gi:10850811 /DB_XREF=AV733266 /CLONE=cdAAJG04 /FEA=EST /CNT=270 /TID=Hs.76325.1 /TIER=Stack /STK=67 /UG=Hs.76325 /LL=10569 /UG_GENE=SLU7 /UG_TITLE=step II splicing factor SLU7	chr4q21	Hs.381568	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	IGJ
209138_x_at	M87790	gb:M87790.1 /DB_XREF=gi:185363 /FEA=FLmRNA /CNT=660 /TID=Hs.181125.0 /TIER=FL+Stack /STK=584 /UG=Hs.181125 /LL=3535 /UG_GENE=IGL@ /DEF=Human (hybridoma H210) anti-hepatitis A immunoglobulin lambda chain variable region, constant region, complementarity-de	chr22q11.2	Hs.458262	Immunoglobulin lambda joining 3	IGLC2

Table 2 (continuation)

206766_at	AF112345	gb:AF112345.1 /DB_XREF=gi:6650627 /GEN=ITGA10 /FEA=FLmRNA /CNT=13 /TID=Hs.158237.0 /TIER=FL /STK=0 /UG=Hs.158237 /LL=8515 /DEF=Homo sapiens integrin alpha 10 subunit (ITGA10) mRNA, complete cds. /PROD=integrin alpha 10 subunit /FL=gb:AF112345.1 gb:NM_0036	chr1q21	Hs.158237	integrin, alpha 10	ITGA10
214927_at	AL359052	gb:AL359052.1 /DB_XREF=gi:8518175 /FEA=mRNA /CNT=13 /TID=Hs.311054.0 /TIER=ConsEnd /STK=5 /UG=Hs.311054 /DEF=Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422. /PROD=ITGBL1, integrin beta-like 1			Integrin, beta-like 1 (with EGF-like repeat domains)	ITGBL1
221841_s_at	BF514079	gb:BF514079 /DB_XREF=gi:11599258 /DB_XREF=UI-H-BW1-amw-b-08-0-UI.s1 /CLONE=IMAGE:3071198 /FEA=EST /CNT=61 /TID=Hs.7934.1 /TIER=Stack /STK=11 /UG=Hs.7934 /LL=9314 /UG_GENE=KLF4 /UG_TITLE=Kruppel-like factor 4 (gut)	chr9q31	Hs.376206	Kruppel-like factor 4 (gut)	KLF4
204249_s_at	NM_005574	gb:NM_005574.2 /DB_XREF=gi:6633806 /GEN=LMO2 /FEA=FLmRNA /CNT=93 /TID=Hs.184585.0 /TIER=FL+Stack /STK=42 /UG=Hs.184585 /LL=4005 /DEF=Homo sapiens LIM domain only 2 (rhombotin-like 1) (LMO2), mRNA. /PROD=LIM domain only 2 /FL=gb:NM_005574.2	chr11p13	Hs.283063	LIM domain only 2 (rhombotin-like 1)	LMO2
228653_at	A1700341	gb:A1700341 /DB_XREF=gi:4988241 /DB_XREF=wd06e10.x1 /CLONE=IMAGE:2327370 /FEA=EST /CNT=23 /TID=Hs.110406.0 /TIER=Stack /STK=14 /UG=Hs.110406 /UG_TITLE=ESTs			SAM domain containing 1	LOC389432
206953_s_at	NM_012302	gb:NM_012302.1 /DB_XREF=gi:6912463 /GEN=KIAA0786 /FEA=FLmRNA /CNT=8 /TID=Hs.24212.0 /TIER=FL /STK=0 /UG=Hs.24212 /LL=23266 /DEF=Homo sapiens latrophilin (KIAA0786), mRNA. /PROD=latrophilin /FL=gb:NM_012302.1 gb:AF104939.1	chr1p31.1	Hs.24212	latrophilin 2	LPHN2
231781_s_at	AK021919	gb:AK021919.1 /DB_XREF=gi:10433216 /FEA=FLmRNA /CNT=13 /TID=Hs.125790.2 /TIER=ConsEnd /STK=0 /UG=Hs.125790 /LL=79442 /UG_GENE=LRRC2 /UG_TITLE=leucine-rich repeat-containing 2 /DEF=Homo sapiens cDNA FLJ11857 fis, clone HEMBA1006807, moderately similar to H	chr3p21.31	Hs.380055	leucine rich repeat containing 2	LRRC2
210302_s_at	AF262032	gb:AF262032.1 /DB_XREF=gi:9964006 /GEN=MAB21L2 /FEA=FLmRNA /CNT=17 /TID=Hs.251390.0 /TIER=FL /STK=0 /UG=Hs.251390 /LL=10586 /DEF=Homo sapiens MAB21L2 protein (MAB21L2) mRNA, complete cds. /PROD=MAB21L2 protein /FL=gb:AF262032.1 gb:NM_006439.2	chr4q31	Hs.251390	mab-21-like 2 (C. elegans)	MAB21L2
202291_s_at	NM_000900	gb:NM_000900.1 /DB_XREF=gi:4505178 /GEN=MGP /FEA=FLmRNA /CNT=227 /TID=Hs.279009.0 /TIER=FL+Stack /STK=84 /UG=Hs.279009 /LL=4256 /DEF=Homo sapiens matrix Gla protein (MGP), mRNA. /PROD=matrix Gla protein /FL=gb:NM_000900.1 gb:M58549.1	chr12p13.1-p12.3	Hs.365706	matrix Gla protein	MGP
205680_at	NM_002425	gb:NM_002425.1 /DB_XREF=gi:4505204 /GEN=MMP10 /FEA=FLmRNA /CNT=29 /TID=Hs.2258.0 /TIER=FL /STK=6 /UG=Hs.2258 /LL=4319 /DEF=Homo sapiens matrix metalloproteinase 10 (stromelysin 2) (MMP10), mRNA. /PROD=matrix metalloproteinase 10 preproprotein /FL=gb:BC002	chr11q22.3	Hs.2258	matrix metalloproteinase 10 (stromelysin 2)	MMP10

Table 2 (continuation)

205330_at	NM_002430	gb:NM_002430.1 /DB_XREF=gi:4505222 /GEN=MN1 /FEA=FLmRNA /CNT=43 /TID=Hs.268515.0 /TIER=FL+Stack /STK=15 /UG=Hs.268515 /LL=4330 /DEF=Homo sapiens meningioma (disrupted in balanced translocation) 1 (MN1), mRNA. /PROD=meningioma 1 /FL=gb:NM_002430.1	chr22q12.1	Hs.268515	meningioma (disrupted in balanced translocation) 1	MN1
213924_at	BF476502	gb:BF476502 /DB_XREF=gi:11547329 /DB_XREF=naa27a03.x1 /CLONE=IMAGE:3255844 /FEA=EST /CNT=16 /TID=Hs.154145.3 /TIER=Stack /STK=9 /UG=Hs.154145 /LL=65258 /UG_GENE=FLJ11585 /UG_TITLE=hypothetical protein FLJ11585			Metallophosphoesterase 1	MPPE1
212096_s_at	AL096842	gb:AL096842.1 /DB_XREF=gi:5524930 /FEA=mRNA /CNT=243 /TID=Hs.7946.0 /TIER=Stack /STK=99 /UG=Hs.7946 /LL=57509 /UG_GENE=KIAA1288 /UG_TITLE=KIAA1288 protein /DEF=Homo sapiens mRNA; cDNA DKFZp586D1519 (from clone DKFZp586D1519).	chr8p22	Hs.7946	mitochondrial tumor suppressor 1	MTUS1
217800_s_at	NM_030571	gb:NM_030571.1 /DB_XREF=gi:13386479 /GEN=MGC10924 /FEA=FLmRNA /CNT=361 /TID=Hs.9788.0 /TIER=FL+Stack /STK=152 /UG=Hs.9788 /LL=80762 /DEF=Homo sapiens hypothetical protein MGC10924 similar to Nedda4 WW-binding protein 5 (MGC10924), mRNA. /PROD=hypothetical	chr5q31.3	Hs.9788	Nedda4 family interacting protein 1	NDFIP1
223315_at	AF278532	gb:AF278532.1 /DB_XREF=gi:11120047 /FEA=FLmRNA /CNT=97 /TID=Hs.102541.0 /TIER=FL+Stack /STK=49 /UG=Hs.102541 /LL=59277 /UG_GENE=NTN4 /DEF=Homo sapiens beta-netrin mRNA, complete cds. /PROD=beta-netrin /FL=gb:AF119916.1 gb:AF297711.1 gb:NM_021229.1 gb:AF27	chr12q22-q23	Hs.102541	netrin 4	NTN4
236088_at	AV723308	gb:AV723308 /DB_XREF=gi:10826596 /DB_XREF=AV723308 /CLONE=HTBFC07 /FEA=EST /CNT=11 /TID=Hs.171136.0 /TIER=ConsEnd /STK=2 /UG=Hs.171136 /UG_TITLE=ESTs	chr1p13.3	Hs.111224	netrin G1	NTNG1
212582_at	AL049923	gb:AL049923.1 /DB_XREF=gi:4884169 /FEA=mRNA /CNT=140 /TID=Hs.109694.0 /TIER=Stack /STK=25 /UG=Hs.109694 /LL=57601 /UG_GENE=KIAA1451 /UG_TITLE=KIAA1451 protein /DEF=Homo sapiens mRNA; cDNA DKFZp564E2282 (from clone DKFZp564E2282).	chr12q14	Hs.109694	oxysterol binding protein-like 8	OSBPL8

Table 2 (continuation)

223435_s_at	A1268404	gb:A1268404 /DB_XREF=gi:3887571 /DB_XREF=qm05e10.x1 /CLONE=IMAGE:1880970 /FEA=FLmRNA /CNT=73 /TID=Hs.167399.0 /TIER=Stack /STK=13 /UG=Hs.167399 /LL=56143 /UG_GENE=PCDHA5 /UG_TITLE=protocadherin alpha 5 /FL=gb:NM_018908.1 gb:AF152313.1	chr5q31	Hs.247734	protocadherin alpha 9 /// protocadherin alpha subfamily C, 2 /// protocadherin alpha subfamily C, 1 /// protocadherin alpha 13 /// protocadherin alpha 12 /// protocadherin alpha 11 /// protocadherin alpha 10 /// protocadherin alpha 8 /// protocadherin alpha 7 /// protocadherin alpha 6 /// protocadherin alpha 5 /// protocadherin alpha 4 /// protocadherin alpha 3 /// protocadherin alpha 2 /// protocadherin alpha 1	PCDHA9 /// PCDHAC2 /// PCDHAC1 /// PCDHA13 /// PCDHA12 /// PCDHA11 /// PCDHA10 /// PCDHA8 /// PCDHA7 /// PCDHA6 /// PCDHA5 /// PCDHA4 /// PCDHA3 /// PCDHA2 /// PCDHA1
155860_s_at	BQ894022	gb:BQ894022 /DB_XREF=gi:22286036 /DB_XREF=AGENCOURT_8122690 /CLONE=IMAGE:6180918 /TID=Hs2.383511.1 /CNT=7 /FEA=mRNA /TIER=ConsEnd /STK=0 /UG=Hs.383511 /UG_TITLE=Homo sapiens HSPDE1A mRNA for calmodulin-dependent phosphodiesterase, partial cds, N-terminal	chr2q32.1	Hs.416061	phosphodiesterase 1A, calmodulin-dependent	PDE1A
208510_s_at	NM_015869	gb:NM_015869.1 /DB_XREF=gi:7705548 /GEN=PPARG /FEA=FLmRNA /CNT=4 /TID=Hs.100724.1 /TIER=FL /STK=0 /UG=Hs.100724 /LL=5468 /DEF=Homo sapiens peroxisome proliferative activated receptor, gamma (PPARG), mRNA. /PROD=peroxisome proliferative activated receptorg	chr3p25	Hs.387667	peroxisome proliferative activated receptor, gamma	PPARG
206007_at	NM_005807	gb:NM_005807.1 /DB_XREF=gi:5031924 /GEN=PRG4 /FEA=FLmRNA /CNT=26 /TID=Hs.218791.0 /TIER=FL /STK=0 /UG=Hs.218791 /LL=10216 /DEF=Homo sapiens proteoglycan 4, (megakaryocyte stimulating factor, articular superficial zone protein) (PRG4), mRNA. /PROD=megakary	chr1q25-q31	Hs.432458	proteoglycan 4	PRG4
206805_at	NM_006080	gb:NM_006080.1 /DB_XREF=gi:5174672 /GEN=SEMA3A /FEA=FLmRNA /CNT=12 /TID=Hs.2414.0 /TIER=FL /STK=0 /UG=Hs.2414 /LL=10371 /DEF=Homo sapiens sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A (SEMA3A), mRNA. /PROD=sema dom	chr7p12.1	Hs.252451	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	SEMA3A
206941_x_at	NM_012431	gb:NM_012431.1 /DB_XREF=gi:6912649 /GEN=SEMA3E /FEA=FLmRNA /CNT=7 /TID=Hs.212414.0 /TIER=FL /STK=0 /UG=Hs.212414 /LL=9723 /DEF=Homo sapiens sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E (SEMA3E), mRNA. /PROD=sema d	chr7q21.11	Hs.528721	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E	SEMA3E

Table 2 (continuation)

226492_at	AL036088	gb:AL036088 /DB_XREF=gi:5405713 /DB_XREF=DKFZp564J0223_s1 /CLONE=DKFZp564J0223 /FEA=mRNA /CNT=49 /TID=Hs.191098.0 /TIER=Stack /STK=19 /UG=Hs.191098 /LL=57618 /UG_GENE=KIAA1479 /UG_TITLE=KIAA1479 protein	chr15q21.1	Hs.191098	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	SEMA6D
223121_s_at	AW003584	gb:AW003584 /DB_XREF=gi:5850500 /DB_XREF=wq98h04.x1 /CLONE=IMAGE:2480119 /FEA=FLmRNA /CNT=207 /TID=Hs.31386.0 /TIER=Stack /STK=26 /UG=Hs.31386 /LL=6423 /UG_GENE=SFRP2 /UG_TITLE=secreted frizzled-related protein 2 /FL=gb:AF311912.1	chr4q31.3	Hs.31386	secreted frizzled-related protein 2	SFRP2
206634_at	NM_005413	gb:NM_005413.1 /DB_XREF=gi:4885596 /GEN=SIX3 /FEA=FLmRNA /CNT=14 /TID=Hs.227277.0 /TIER=FL /STK=1 /UG=Hs.227277 /LL=6496 /DEF=Homo sapiens sine oculis homeobox (Drosophila) homolog 3 (SIX3), mRNA. /PROD=sine oculis homeobox (Drosophila) homolog 3 /FL=gb.N	chr2p16-p21	Hs.227277	sine oculis homeobox homolog 3 (Drosophila)	SIX3
223044_at	AL136944	gb:AL136944.1 /DB_XREF=gi:12053382 /GEN=DKFZp586J0624 /FEA=FLmRNA /CNT=341 /TID=Hs.5944.0 /TIER=FL+Stack /STK=188 /UG=Hs.5944 /LL=30061 /DEF=Homo sapiens mRNA; cDNA DKFZp586J0624 (from clone DKFZp586J0624); complete cds. /PROD=hypothetical protein /FL=gb.	chr2q32	Hs.409875	solute carrier family 40 (iron-regulated transporter), member 1	SLC40A1
209921_at	AB040875	gb:AB040875.1 /DB_XREF=gi:13516845 /GEN=hcCT /FEA=FLmRNA /CNT=45 /TID=Hs.6682.1 /TIER=FL+Stack /STK=33 /UG=Hs.6682 /LL=23657 /DEF=Homo sapiens hcCT mRNA for cystineglutamate exchanger, complete cds. /PROD=cystineglutamate exchanger /FL=gb:AB040875.1	chr4q28-q32	Hs.6682	solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	SLC7A11
222784_at	AJ249900	gb:AJ249900.1 /DB_XREF=gi:10432430 /GEN=smoc1 /FEA=FLmRNA /CNT=89 /TID=Hs.14144.0 /TIER=Stack /STK=33 /UG=Hs.14144 /LL=64093 /DEF=Homo sapiens mRNA for secreted modular calcium-binding protein (smoc1 gene). /PROD=secreted modular calcium-binding protein /	chr14q24.2	Hs.14144	SPARC related modular calcium binding 1	SMOC1
227752_at	AA005105	gb:AA005105 /DB_XREF=gi:1448894 /DB_XREF=zh96f09.s1 /CLONE=IMAGE:429161 /FEA=EST /CNT=38 /TID=Hs.18441.0 /TIER=Stack /STK=11 /UG=Hs.18441 /UG_TITLE=ESTs		Hs.425023	serine palmitoyltransferase, long chain base subunit 2-like (aminotransferase 2)	SPTLC2L
203000_at	BF967657	gb:BF967657 /DB_XREF=gi:12334872 /DB_XREF=602287358T1 /CLONE=IMAGE:4374495 /FEA=FLmRNA /CNT=403 /TID=Hs.90005.0 /TIER=Stack /STK=18 /UG=Hs.90005 /LL=11075 /UG_GENE=SCGN10 /UG_TITLE=superiorcervical ganglia, neural specific 10 /FL=gb:NM_007029.1 gb:D50375	chr8q21.13	Hs.90005	stathmin-like 2	STMN2
211276_at	AF063606	gb:AF063606.1 /DB_XREF=gi:12002041 /FEA=FLmRNA /CNT=1 /TID=Hs.17481.0 /TIER=FL /STK=0 /UG=Hs.17481 /DEF=Homo sapiens brain my048 protein mRNA, complete cds. /PROD=brain my048 protein /FL=gb:AF063606.1			transcription elongation factor A (SII)-like 2	TCEAL2

Table 2 (continuation)

206243_at	NM_003256	gb:NM_003256.1 /DB_XREF=gi:4507514 /GEN=TIMP4 /FEA=FLmRNA /CNT=25 /TID=Hs.190787.0 /TIER=FL+Stack /STK=16 /UG=Hs.190787 /LL=7079 /DEF=Homo sapiens tissue inhibitor of metalloproteinase 4 (TIMP4), mRNA. /PROD=tissue inhibitor of metalloproteinase 4precurso	chr3p25	Hs.190787	TIMP metalloproteinase inhibitor 4	TIMP4
203661_s_at	BC002660	gb:BC002660.1 /DB_XREF=gi:12803650 /FEA=FLmRNA /CNT=110 /TID=Hs.170453.0 /TIER=FL+Stack /STK=19 /UG=Hs.170453 /LL=7111 /UG_GENE=TMOD /DEF=Homo sapiens, tropomodulin, clone MGC:3643, mRNA, complete cds. /PROD=tropomodulin /FL=gb:NM_003275.1 gb:M77016.1 gb:	chr9q22.3	Hs.374849	tropomodulin 1	TMOD1
221085_at	NM_005118	gb:NM_005118.1 /DB_XREF=gi:4827031 /GEN=TNFSF15 /FEA=FLmRNA /CNT=2 /TID=Hs.241382.0 /TIER=FL /STK=0 /UG=Hs.241382 /LL=9966 /DEF=Homo sapiens tumor necrosis factor (ligand) superfamily, member 15 (TNFSF15), mRNA. /PROD=tumor necrosis factor (ligand) super	chr9q32	Hs.241382	tumor necrosis factor (ligand) superfamily, member 15	TNFSF15
202341_s_at	AA149745	gb:AA149745 /DB_XREF=gi:1720818 /DB_XREF=z002h04.s1 /CLONE=IMAGE:566551 /FEA=FLmRNA /CNT=143 /TID=Hs.12372.0 /TIER=Stack /STK=18 /UG=Hs.12372 /LL=23321 /UG_GENE=KIAA0517 /UG_TITLE=tripartite motif protein TRIM2 /FL=gb:AF220018.1 gb:NM_015271.1	chr4q31.3	Hs.435734	tripartite motif-containing 2	TRIM2
242162_at	AA904430	gb:AA904430 /DB_XREF=gi:3039553 /DB_XREF=ok07112.s1 /CLONE=IMAGE:1507151 /FEA=EST /CNT=5 /TID=Hs.122049.0 /TIER=ConsEnd /STK=1 /UG=Hs.122049 /UG_TITLE=ESTs, Weakly similar to T2D4_HUMAN TRANSCRIPTION INITIATION FACTOR TFIID 100 KDA SUBUNIT (H.sapiens)	chr2q36.3	Hs.424594	WD repeat domain 69	WDR69
206373_at	NM_003412	gb:NM_003412.1 /DB_XREF=gi:4507970 /GEN=ZIC1 /FEA=FLmRNA /CNT=19 /TID=Hs.41154.0 /TIER=FL /STK=7 /UG=Hs.41154 /LL=7545 /DEF=Homo sapiens Zic family member 1 (odd-paired Drosophila homolog) (ZIC1), mRNA. /PROD=Zic family member 1 (odd-paired Drosophila homo			Zic family member 1 (odd-paired homolog, Drosophila)	ZIC1
210910_s_at	BC000487	gb:BC000487.1 /DB_XREF=gi:12653432 /FEA=FLmRNA /CNT=3 /TID=Hs.296380.1 /TIER=FL /STK=0 /UG=Hs.296380 /LL=22932 /UG_GENE=POMZP3 /DEF=Homo sapiens, Similar to POM (POM121 rat homolog) and ZP3 fusion protein, clone MGC:8359, mRNA, complete cds. /PROD=Similar	chr7q11.23	Hs.296380	zona pellucida glycoprotein 3 (sperm receptor) // POM (POM121 homolog, rat) and ZP3 fusion	ZP3 // POMZP3
					collomin	COLM

FULL CITATIONS FOR REFERENCES REFERRED TO IN THE SPECIFICATION

1. Sayah A, English JC, 3rd. Rheumatoid arthritis: a review of the
5 cutaneous manifestations. *J Am Acad Dermatol* 2005;53(2):191-209.
2. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin
North Am* 2001;27(2):269-81.
3. Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet*
2001;358(9285):903-11.
- 10 4. Ryan S. Rheumatology. Sharing care in an outpatient clinic. *Nurs
Stand* 1995;10(6):23-5.
5. Mor A, Abramson SB, Pillinger MH. The fibroblast-like synovial cell in
rheumatoid arthritis: a key player in inflammation and joint destruction. *Clin
Immunol* 2005;115(2):118-28.
- 15 6. Melnyk VO, Shipley GD, Sternfeld MD, Sherman L, Rosenbaum JT.
Synoviocytes synthesize, bind, and respond to basic fibroblast growth factor.
Arthritis Rheum 1990;33(4):493-500.
7. Manabe N, Oda H, Nakamura K, Kuga Y, Uchida S, Kawaguchi H.
Involvement of fibroblast growth factor-2 in joint destruction of rheumatoid
20 arthritis patients. *Rheumatology (Oxford)* 1999;38(8):714-20.
8. Allen JB, Manthey CL, Hand AR, Ohura K, Ellingsworth L, Wahl SM.
Rapid onset synovial inflammation and hyperplasia induced by transforming
growth factor beta. *J Exp Med* 1990;171(1):231-47.
9. Ota F, Maeshima A, Yamashita S, Ikeuchi H, Kaneko Y, Kuroiwa T, et
25 al. Activin A induces cell proliferation of fibroblast-like synoviocytes in
rheumatoid arthritis. *Arthritis Rheum* 2003;48(9):2442-9.
10. Gribi R, Tanaka T, Harper-Summers R, Yu J. Expression of activin A in
inflammatory arthropathies. *Mol Cell Endocrinol* 2001;180(1-2):163-7.

- 56 -

11. Sultan M, Wigle DA, Cumbaa CA, Maziarz M, Glasgow J, Tsao MS, et al. Binary tree-structured vector quantization approach to clustering and visualizing microarray data. *Bioinformatics* 2002;18 Suppl 1:S111-9.
12. Kasperkovitz PV, Timmer TC, Smeets TJ, Verbeet NL, Tak PP, van Baarsen LG, et al. Fibroblast-like synoviocytes derived from patients with rheumatoid arthritis show the imprint of synovial tissue heterogeneity: evidence of a link between an increased myofibroblast-like phenotype and high-inflammation synovitis. *Arthritis Rheum* 2005;52(2):430-41.
13. Spurrell DR, Oldford SA, Frost T, Larsen B, Codner D, Edgecombe A, et al. Discordant expression of HLA class II-associated co-chaperones and HLA-DRB alleles in cultured fibroblast-like synoviocytes. *Hum Immunol* 2004;65(12):1516-29.
14. Franke TF, Kaplan DR, Cantley LC. PI3K: downstream AKTion blocks apoptosis. *Cell* 1997;88(4):435-7.
15. 15. Cantley LC. The phosphoinositide 3-kinase pathway. *Science* 2002;296(5573):1655-7.
16. Zhang HG, Wang Y, Xie JF, Liang X, Liu D, Yang P, et al. Regulation of tumor necrosis factor alpha-mediated apoptosis of rheumatoid arthritis synovial fibroblasts by the protein kinase Akt. *Arthritis Rheum* 2001;44(7):1555-67.
17. Kim G, Jun JB, Elkon KB. Necessary role of phosphatidylinositol 3-kinase in transforming growth factor beta-mediated activation of Akt in normal and rheumatoid arthritis synovial fibroblasts. *Arthritis Rheum* 2002;46(6):1504-11.
18. Morel J, Audo R, Hahne M, Combe B. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces rheumatoid arthritis synovial fibroblast proliferation through mitogen-activated protein kinases and phosphatidylinositol 3-kinase/Akt. *J Biol Chem* 2005;280(16):15709-18.
19. Pritchard J, Tsui S, Horst N, Cruikshank WW, Smith TJ. Synovial fibroblasts from patients with rheumatoid arthritis, like fibroblasts from Graves'

- 57 -

- disease, express high levels of IL-16 when treated with Igs against insulin-like growth factor-1 receptor. *J Immunol* 2004;173(5):3564-9.
20. Hwang SY, Kim JY, Kim KW, Park MK, Moon Y, Kim WU, et al. IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-kappaB- and PI3-kinase/Akt-dependent pathways. *Arthritis Res Ther* 2004;6(2):R120-8.
21. Morel JC, Park CC, Zhu K, Kumar P, Ruth JH, Koch AE. Signal transduction pathways involved in rheumatoid arthritis synovial fibroblast interleukin-18-induced vascular cell adhesion molecule-1 expression. *J Biol Chem* 2002;277(38):34679-91.
22. Nakayamada S, Okada Y, Saito K, Tamura M, Tanaka Y. Beta1 integrin/focal adhesion kinase-mediated signaling induces intercellular adhesion molecule 1 and receptor activator of nuclear factor kappaB ligand on osteoblasts and osteoclast maturation. *J Biol Chem* 2003;278(46):45368-74.
23. Scott BB, Zaratini PF, Gilmarin AG, Hansbury MJ, Colombo A, Belpasso C, et al. TNF-alpha modulates angiopoietin-1 expression in rheumatoid synovial fibroblasts via the NF-kappa B signalling pathway. *Biochem Biophys Res Commun* 2005;328(2):409-14.
24. Migita K, Miyashita T, Maeda Y, Aoyagi T, Kawabe Y, Nakamura M, et al. FK506 suppresses the stimulation of matrix metalloproteinase 13 synthesis by interleukin-1beta in rheumatoid synovial fibroblasts. *Immunol Lett* 2005;98(2):194-9.
25. Hammaker DR, Boyle DL, Chabaud-Riou M, Firestein GS. Regulation of c-Jun N-terminal kinase by MEKK-2 and mitogen-activated protein kinase kinases in rheumatoid arthritis. *J Immunol* 2004;172(3):1612-8.
26. Kawasaki H, Komai K, Nakamura M, Yamamoto E, Ouyang Z, Nakashima T, et al. Human wee1 kinase is directly transactivated by and increased in association with c-Fos/AP-1: rheumatoid synovial cells overexpressing these genes go into aberrant mitosis. *Oncogene* 2003;22(44):6839-44.

- 58 -

27. Nykanen P, Helve T, Kankaanpaa U, Larsen A. Characterization of the DNA-synthesizing cells in rheumatoid synovial tissue. *Scand J Rheumatol* 1978;7(2):118-22.
28. Jacobs RA, Perrett D, Axon JM, Herbert KE, Scott DL. Rheumatoid
5 synovial cell proliferation, transformation and fibronectin secretion in culture. *Clin Exp Rheumatol* 1995;13(6):717-23.
29. Tsumuki H, Hasunuma T, Kobata T, Kato T, Uchida A, Nishioka K. Basic FGF-induced activation of telomerase in rheumatoid synoviocytes. *Rheumatol Int* 2000;19(4):123-8.
- 10 30. Yudoh K, Matsuno H, Nezuka T, Kimura T. Different mechanisms of synovial hyperplasia in rheumatoid arthritis and pigmented villonodular synovitis: the role of telomerase activity in synovial proliferation. *Arthritis Rheum* 1999;42(4):669-77.
- 15 31. Dunphy J. The fibroblast-a unique ally for the surgeon. *The New England Journal of Medicine* 1963;268:1367-77.
32. Quan TE, Cowper S, Wu SP, Bockenstedt LK, Bucala R. Circulating fibrocytes: collagen-secreting cells of the peripheral blood. *Int J Biochem Cell Biol* 2004;36(4):598-606.
- 20 33. Phillips RJ, Burdick MD, Hong K, Lutz MA, Murray LA, Xue YY, et al. Circulating fibrocytes traffic to the lungs in response to CXCL12 and mediate fibrosis. *J Clin Invest* 2004;114(3):438-46.
34. Barth PJ, Ebrahimsade S, Ramaswamy A, Moll R. CD34+ fibrocytes in invasive ductal carcinoma, ductal carcinoma in situ, and benign breast lesions. *Virchows Arch* 2002;440(3):298-303.
- 25 35. Schmidt M, Sun G, Stacey MA, Mori L, Mattoli S. Identification of circulating fibrocytes as precursors of bronchial myofibroblasts in asthma. *J Immunol* 2003;171(1):380-9.
36. Pilling D, Buckley CD, Salmon M, Gomer RH. Inhibition of fibrocyte differentiation by serum amyloid P. *J Immunol* 2003;171(10):5537-46.

- 59 -

37. Mori L, Bellini A, Stacey MA, Schmidt M, Mattoli S. Fibrocytes contribute to the myofibroblast population in wounded skin and originate from the bone marrow. *Exp Cell Res* 2005;304(1):81-90.
38. Abe R, Donnelly SC, Peng T, Bucala R, Metz CN. Peripheral blood
5 fibrocytes: differentiation pathway and migration to wound sites. *J Immunol* 2001;166(12):7556-62.
39. Bucala R, Spiegel LA, Chesney J, Hogan M, Cerami A. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med* 1994;1(1):71-81.
- 10 40. Chesney J, Bacher M, Bender A, Bucala R. The peripheral blood fibrocyte is a potent antigen-presenting cell capable of priming naive T cells in situ. *Proc Natl Acad Sci U S A* 1997;94(12):6307-12.
41. Reines BP. Is rheumatoid arthritis premature osteoarthritis with fetal-like healing? *Autoimmun Rev* 2004;3(4):305-11.
- 15 42. Buckley CD. Why does chronic inflammatory joint disease persist? *Clin Med* 2003;3(4):361-6.
43. Matthey DL, Dawes PT, Nixon NB, Slater H. Transforming growth factor beta 1 and interleukin 4 induced alpha smooth muscle actin expression and myofibroblast-like differentiation in human synovial fibroblasts in vitro:
20 modulation by basic fibroblast growth factor. *Ann Rheum Dis* 1997;56(7):426-31.
44. Ruger B, Giurea A, Wanivenhaus AH, Zehetgruber H, Hollemann D, Yanagida G, et al. Endothelial precursor cells in the synovial tissue of patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum* 2004;50(7):2157-
25 66.
45. Kurosaka D, Yasuda J, Yoshida K, Yasuda C, Toyokawa Y, Yokoyama T, et al. Kinetics of circulating endothelial progenitor cells in mice with type II collagen arthritis. *Blood Cells Mol Dis* 2005.

- 60 -

46. Grisar J, Aletaha D, Steiner CW, Kapral T, Steiner S, Seidinger D, et al. Depletion of endothelial progenitor cells in the peripheral blood of patients with rheumatoid arthritis. *Circulation* 2005;111(2):204-11.
47. Vittal R, Horowitz JC, Moore BB, Zhang H, Martinez FJ, Toews GB, et al. Modulation of prosurvival signaling in fibroblasts by a protein kinase inhibitor protects against fibrotic tissue injury. *Am J Pathol* 2005;166(2):367-75.
48. Horowitz JC, Lee DY, Waghray M, Keshamouni VG, Thomas PE, Zhang H, et al. Activation of the pro-survival phosphatidylinositol 3-kinase/AKT pathway by transforming growth factor-beta1 in mesenchymal cells is mediated by p38 MAPK-dependent induction of an autocrine growth factor. *J Biol Chem* 2004;279(2):1359-67.
49. Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. Constitutive phosphorylation of focal adhesion kinase is involved in the myofibroblast differentiation of scleroderma fibroblasts. *J Invest Dermatol* 2005;124(5):886-92.
50. Irish JM, Hovland R, Krutzik PO, Perez OD, Bruserud O, Gjertsen BT, et al. Single cell profiling of potentiated phospho-protein networks in cancer cells. *Cell* 2004;118(2):217-28.
51. Perez OD, Nolan GP. Simultaneous measurement of multiple active kinase states using polychromatic flow cytometry. *Nat Biotechnol* 2002;20(2):155-62.
52. Perez OD, Mitchell D, Jager GC, South S, Murriel C, McBride J, et al. Leukocyte functional antigen 1 lowers T cell activation thresholds and signaling through cytohesin-1 and Jun-activating binding protein 1. *Nat Immunol* 2003;4(11):1083-92.
53. Perez OD, Mitchell D, Jager GC, Nolan GP. LFA-1 signaling through p44/42 is coupled to perforin degranulation in CD56+CD8+ natural killer cells. *Blood* 2004;104(4):1083-93.

- 61 -

54. Sachs K, Perez O, Pe'er D, Lauffenburger DA, Nolan GP. Causal protein-signaling networks derived from multiparameter single-cell data. *Science* 2005;308(5721):523-9.

55. Kannan K, Ortmann, RA, Kimpel D. Animal models of rheumatoid
5 arthritis and their relevance to human disease. *Pathophysiology* 2005;12:167-181.

56. Holmdahl R, Bockermann R, Bäcklund J, Yamada H. The molecular pathogenesis of collagen-induced arthritis in mice - a model for rheumatoid arthritis. *Ageing Research Reviews* 2002;1:135-147.

WE CLAIM:

1. A method of diagnosing or monitoring rheumatoid arthritis in a subject, comprising the steps:
 - 5 determining the activation state of a circulating CD3⁻CD45⁺collagen⁺ fibrocyte from a sample from the subject; and
 - comparing the activation state of the fibrocyte from the sample with a control sample from a subject or group of subjects who do not have rheumatoid arthritis; wherein the activation state of the fibrocyte is determined
10 by measuring the phosphorylation levels of signaling molecules, and wherein an increase in the activation state of the fibrocyte as compared to the control is indicative of rheumatoid arthritis.
2. The method according to claim 1, wherein the signaling molecules
15 comprise STAT5.
3. The method according to claim 1 or 2, wherein the circulating fibrocyte further stains positive for CD14, CD34 and prolyl 4-hydroxylase.
- 20 4. A method of identifying a substance to treat rheumatoid arthritis, comprising the steps:
 - (a) determining the activation state of circulating CD3⁻CD45⁺collagen⁺ fibrocytes from a sample from a subject administered an amount of the substance; and
 - 25 (b) comparing the activation state of the fibrocyte from the sample with a control sample from a subject or group of subjects who do not have rheumatoid arthritis; wherein the activation state of the fibrocyte is determined by measuring the phosphorylation levels of signaling molecules, and wherein a decrease in the activation state of the fibrocyte as compared to the control is
30 indicative that said substance is suitable for treatment of rheumatoid arthritis.
5. The method according to claim 4, wherein the signaling molecules comprise STAT5.

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6. The method according to claim 4 or 5, wherein the circulating fibrocytes further stains positive for CD14, CD34 and prolyl 4-hydroxylase.

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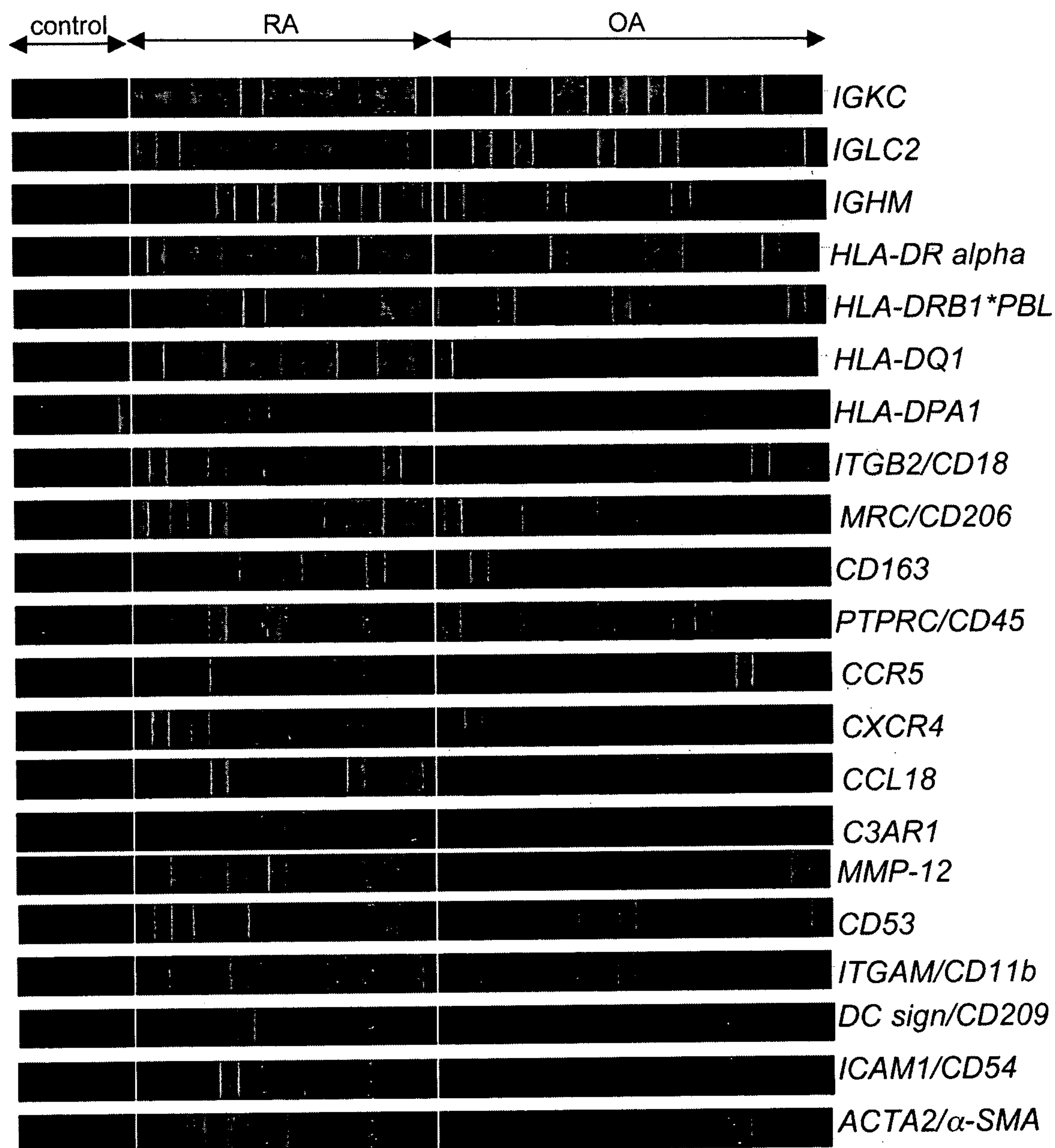
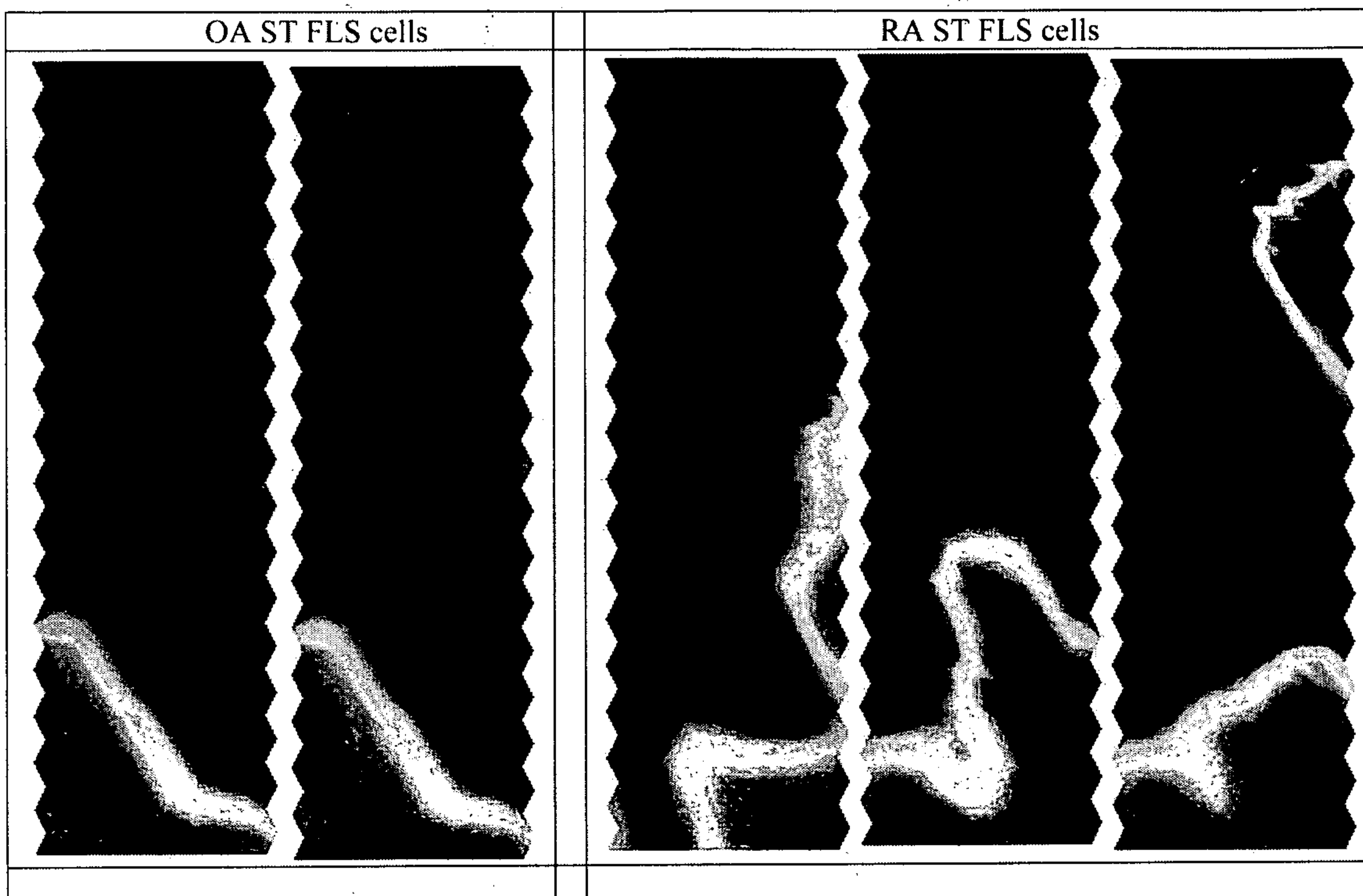
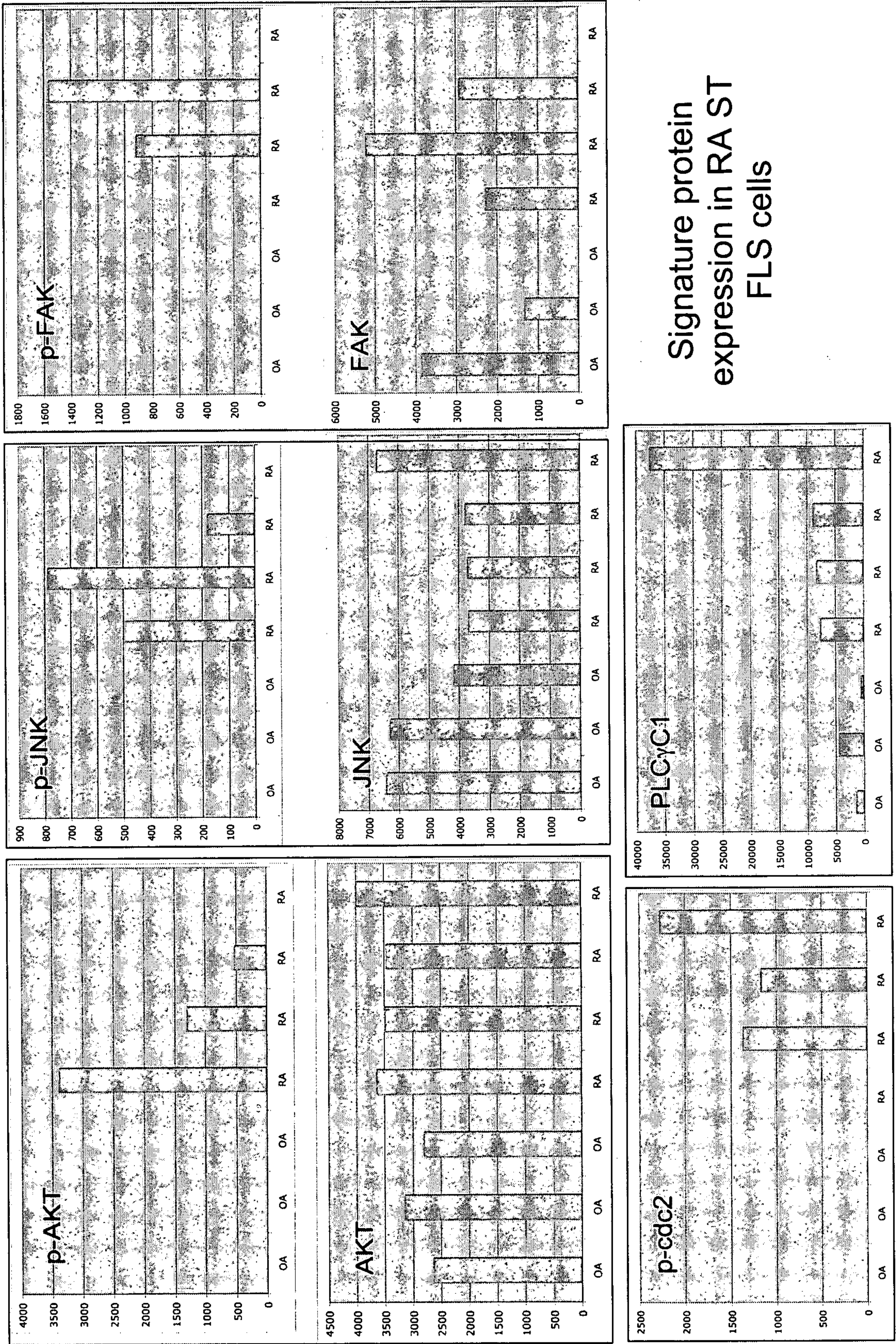
FIGURE 1**Gene expression levels in ST FLS cells: Affymetrix analysis**

FIGURE 2



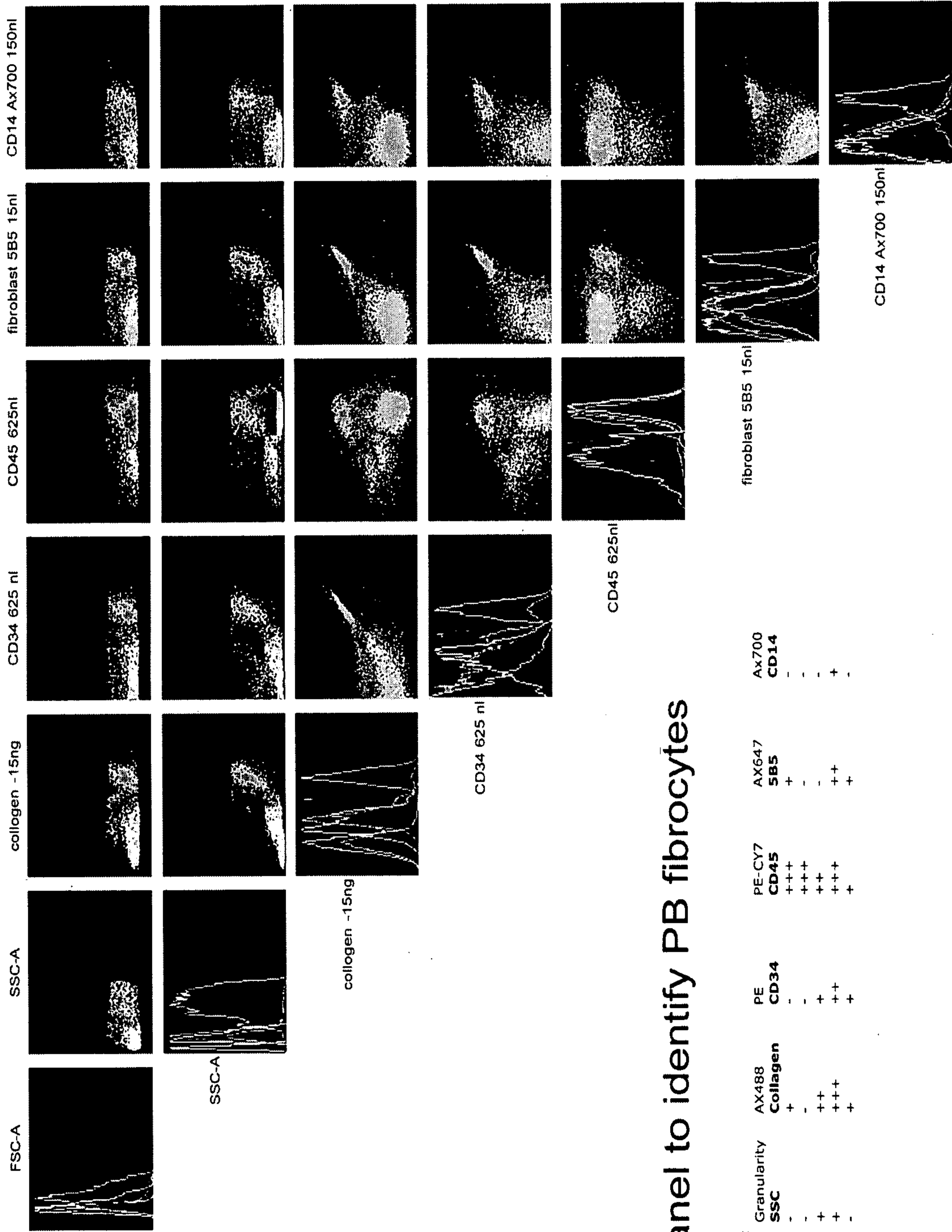
Representative heat maps of phospho-protein signature profiles

FIGURE 3



Signature protein
expression in RA ST
FLS cells

FIGURE 4A



Staining panel to identify PB fibrocytes

Cluster	Measurement				
	Size	Granularity	AX488	PE	AX700
red	-	SSC	+	-	-
green	-	-	-	-	-
blue	-	+	+++	++	+
orange	+	+	+++	++	+
light blue	-	-	+	+	-

FIGURE 4B

Immunostaining of a single PB derived fibrocyte

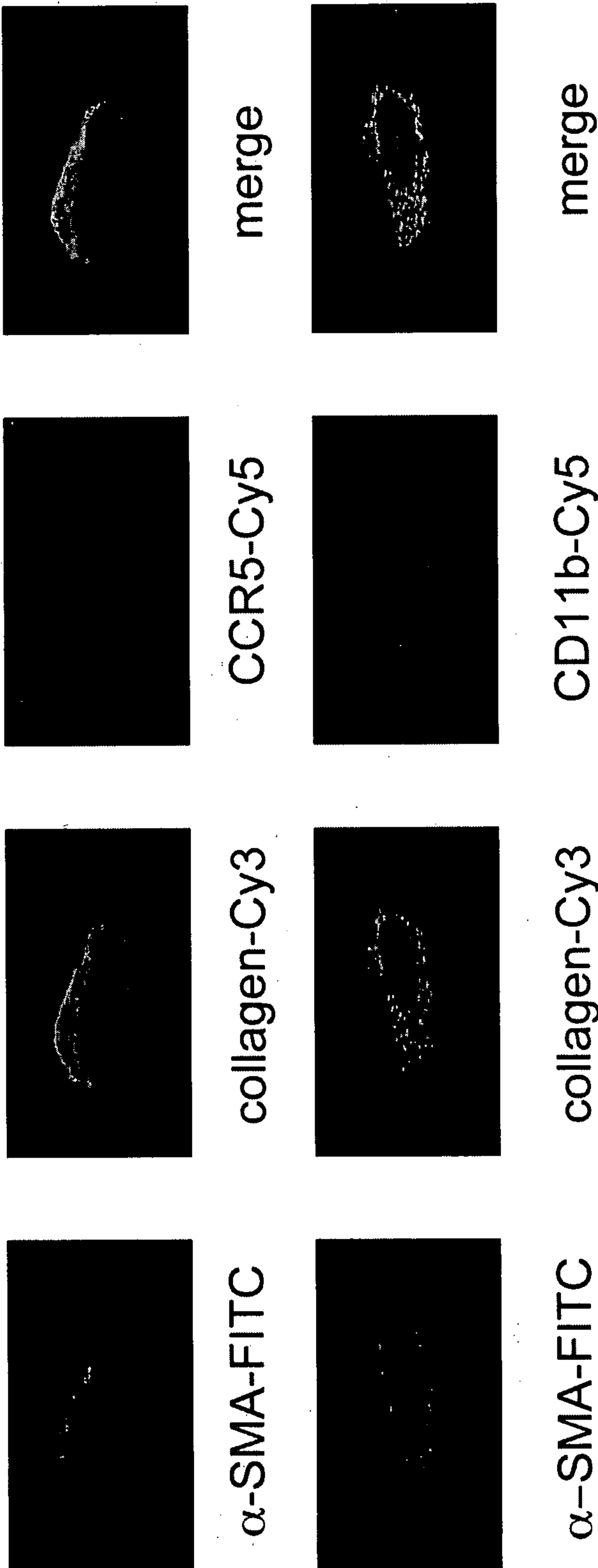
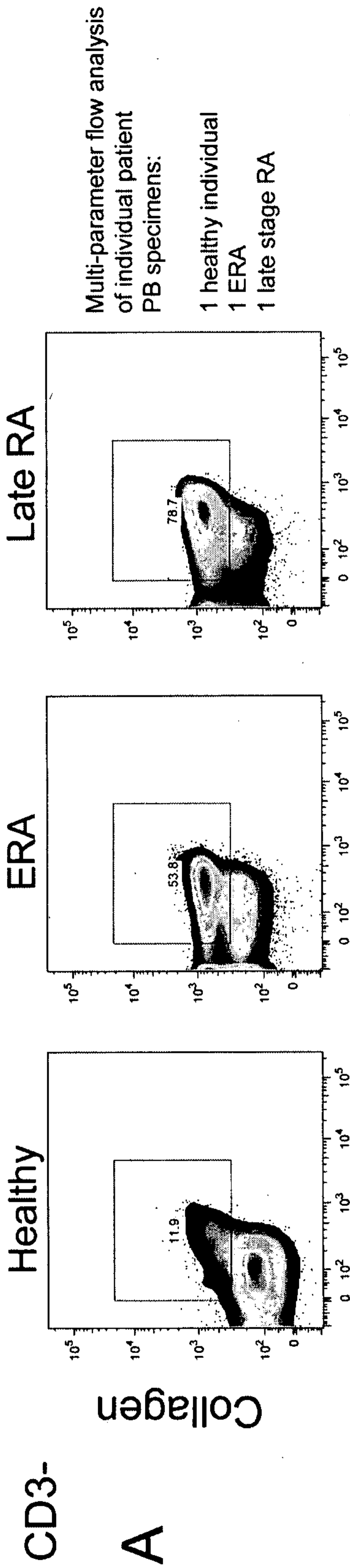


FIGURE 5

Intracellular analysis for phospho-STAT3 in CD3⁻, collagen⁺ PB fibrocytes



Phospho-pSTAT3

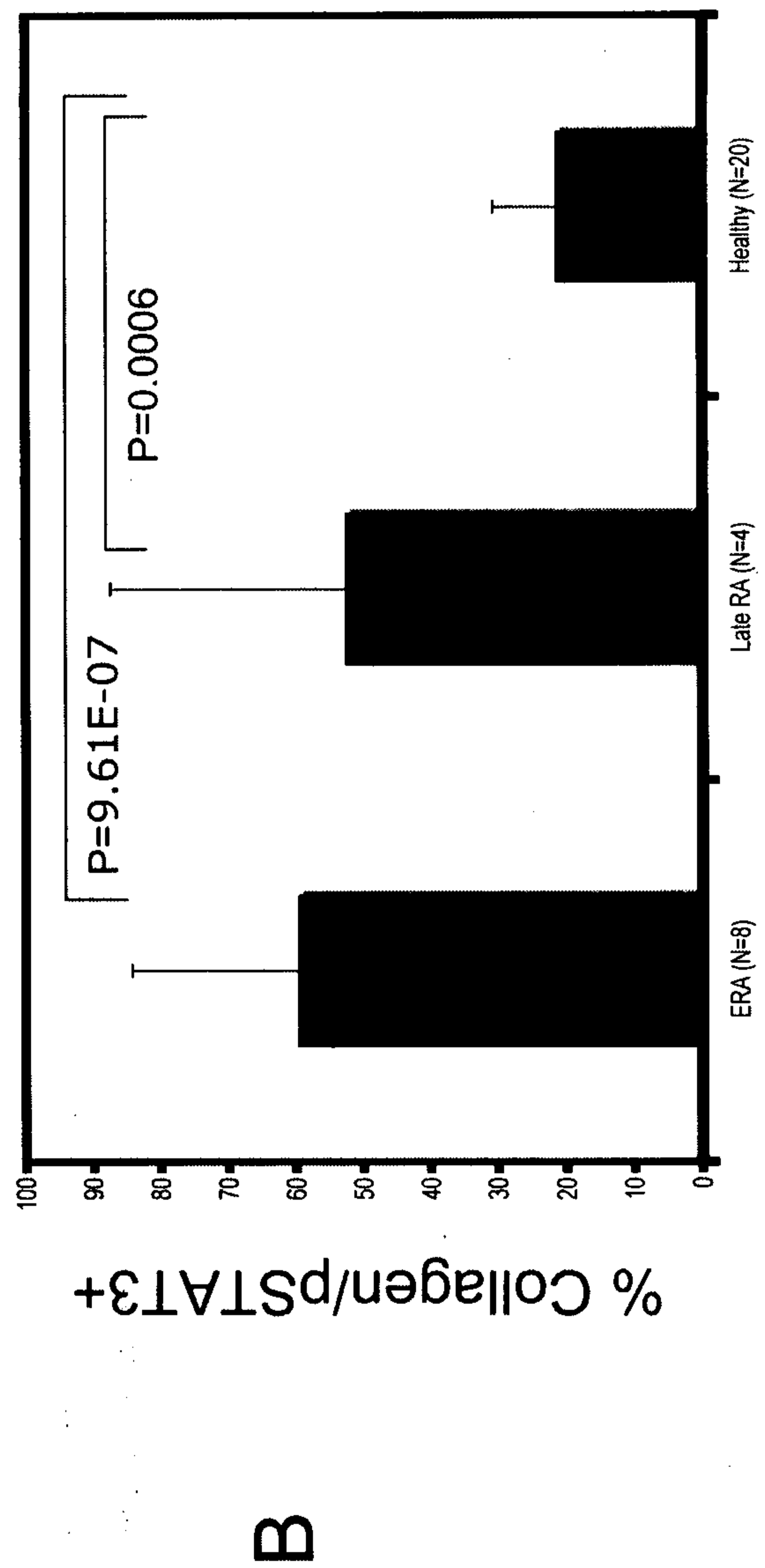


FIGURE 6

Intracellular analysis for phospho-STAT5 in CD3⁻, collagen⁺ PB fibrocytes

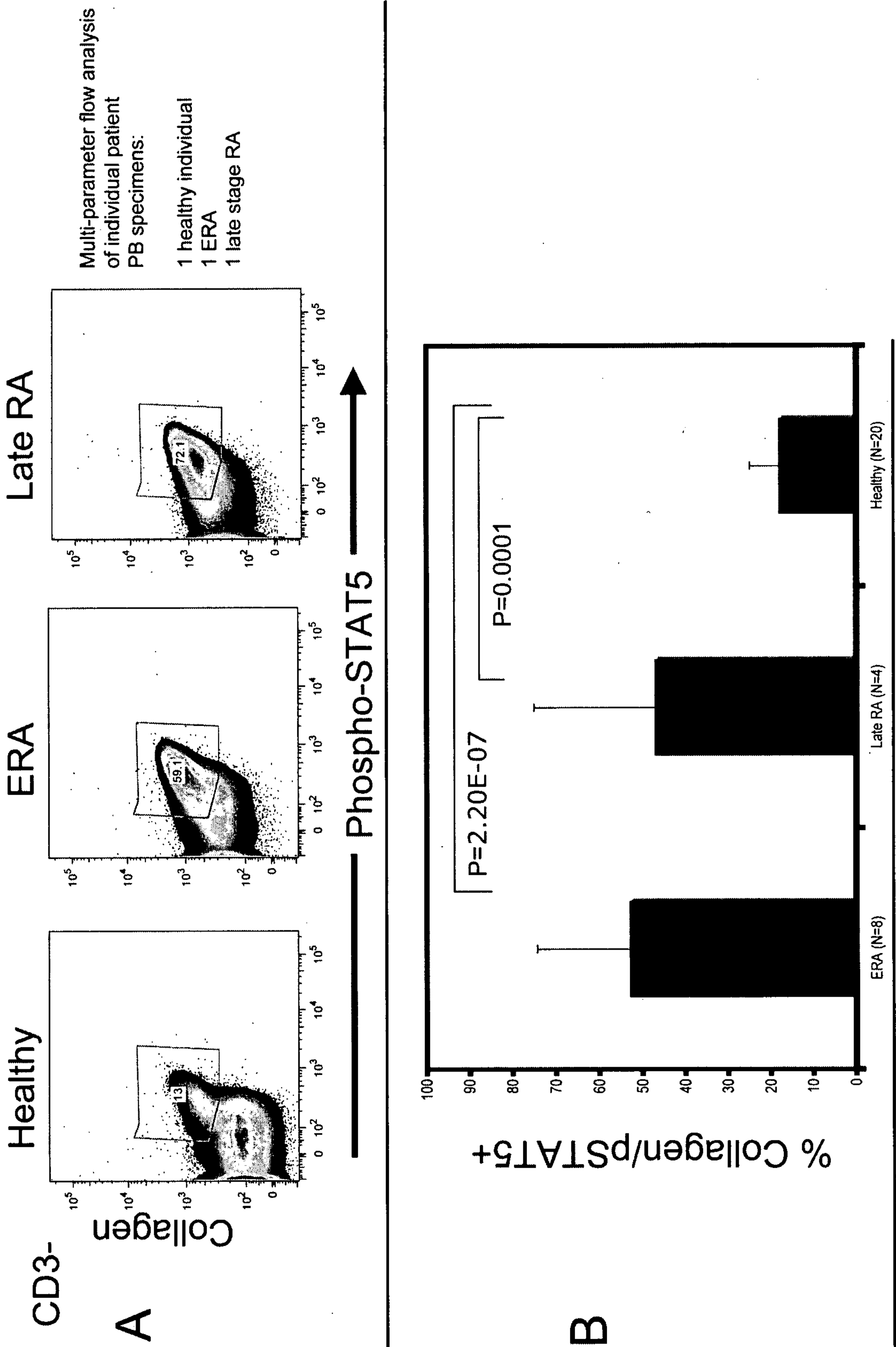


FIGURE 7

Intracellular analysis for phospho-Erk in CD3⁻, collagen⁺ PB fibrocytes

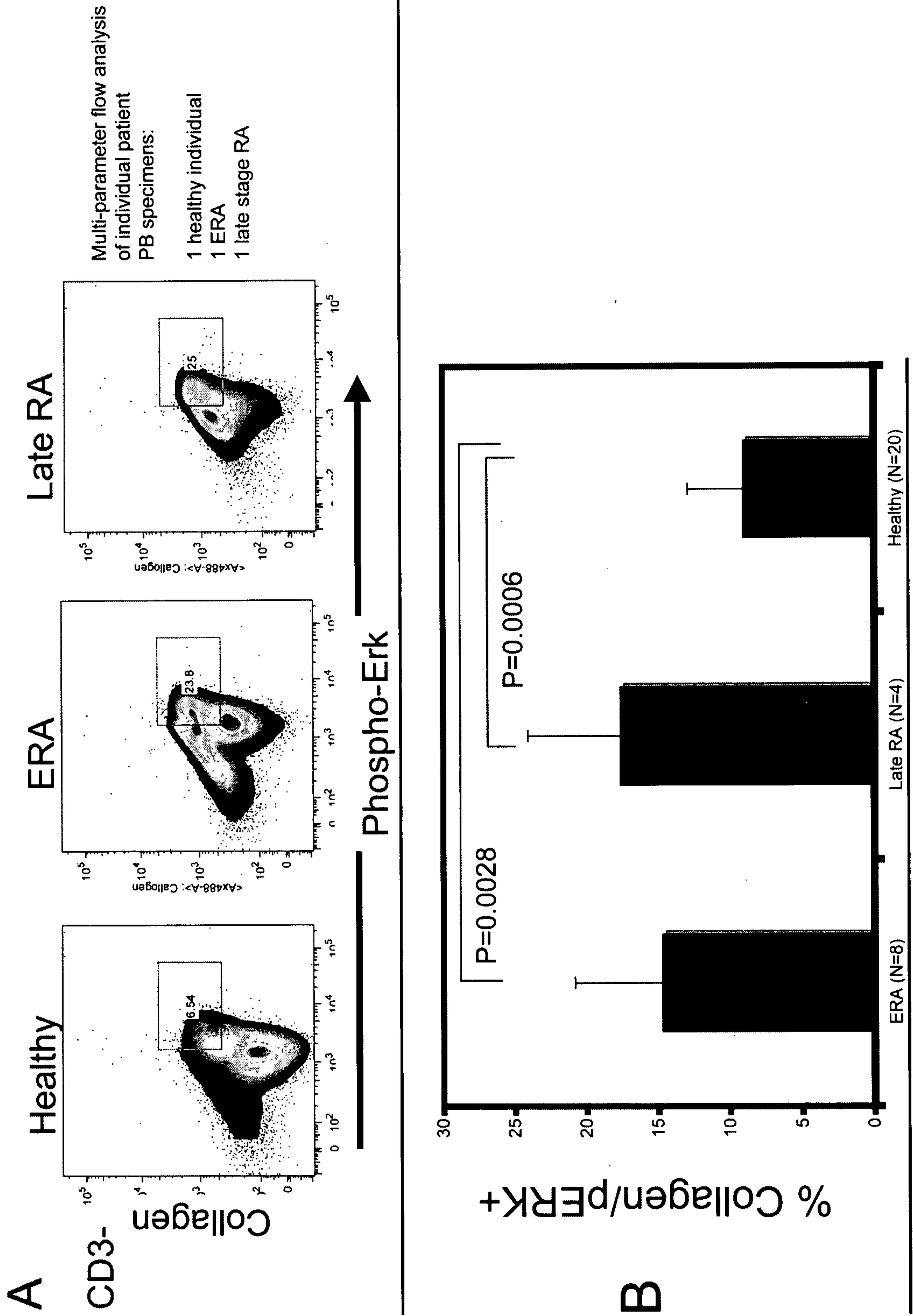


FIGURE 8

Intracellular analysis for phospho-p38 in CD3⁻, collagen⁺ PB fibrocytes

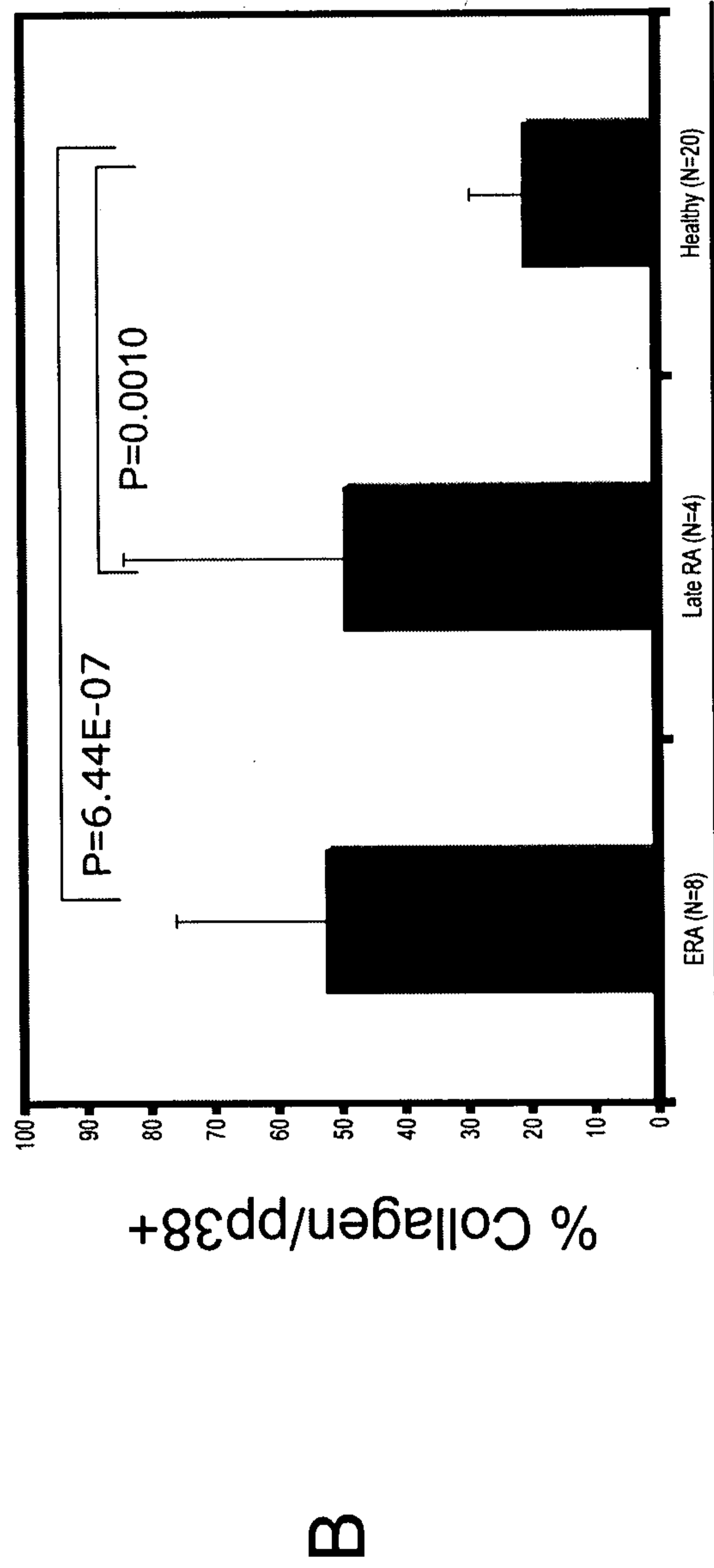
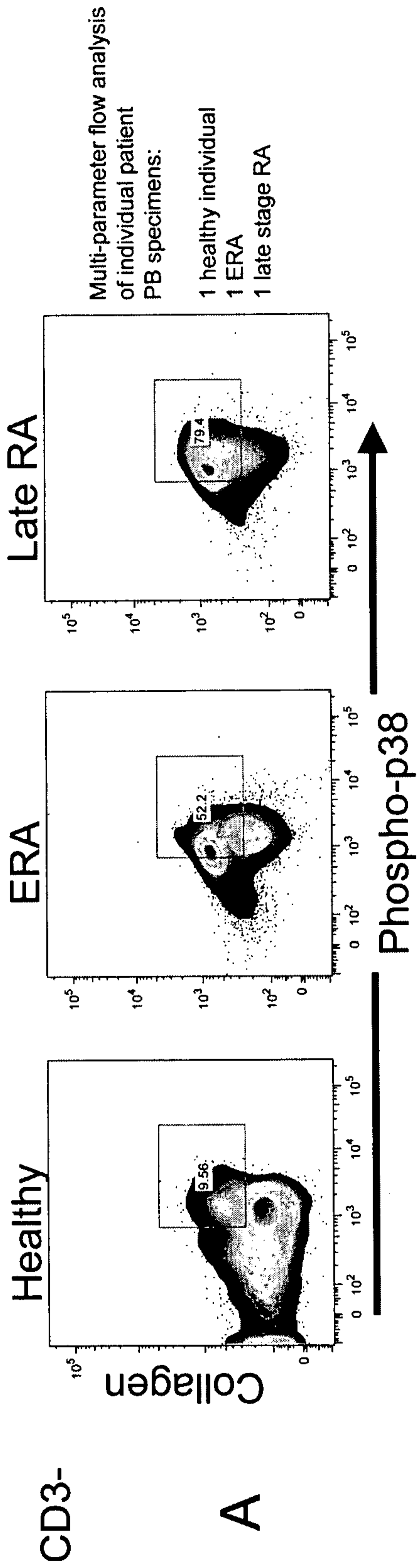


FIGURE 9

Sub-populations & primary cells are critical for phosph-flow analyses

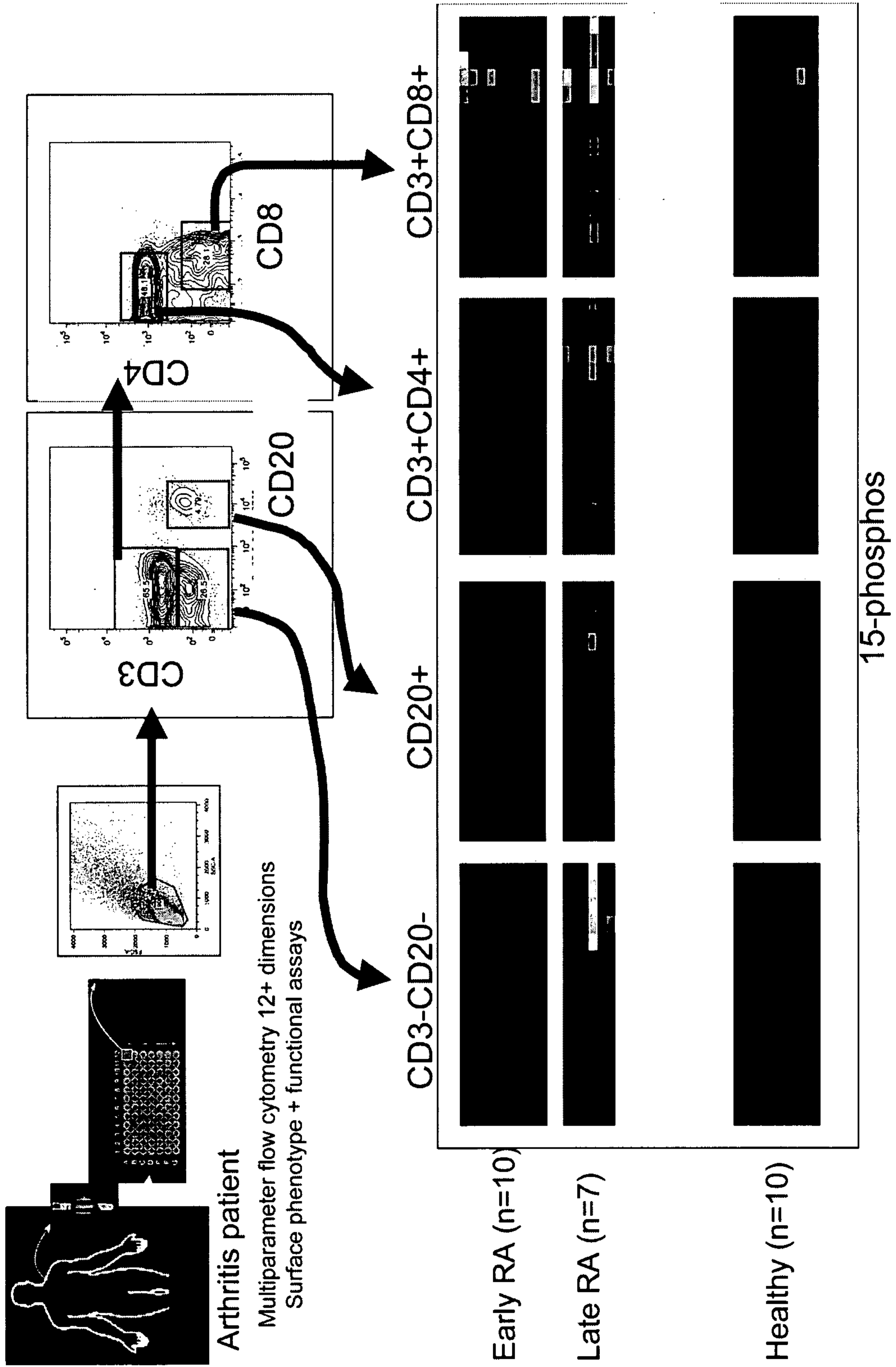


FIGURE 10

Predicting Clinical Progression in PBMC CD3+ cells

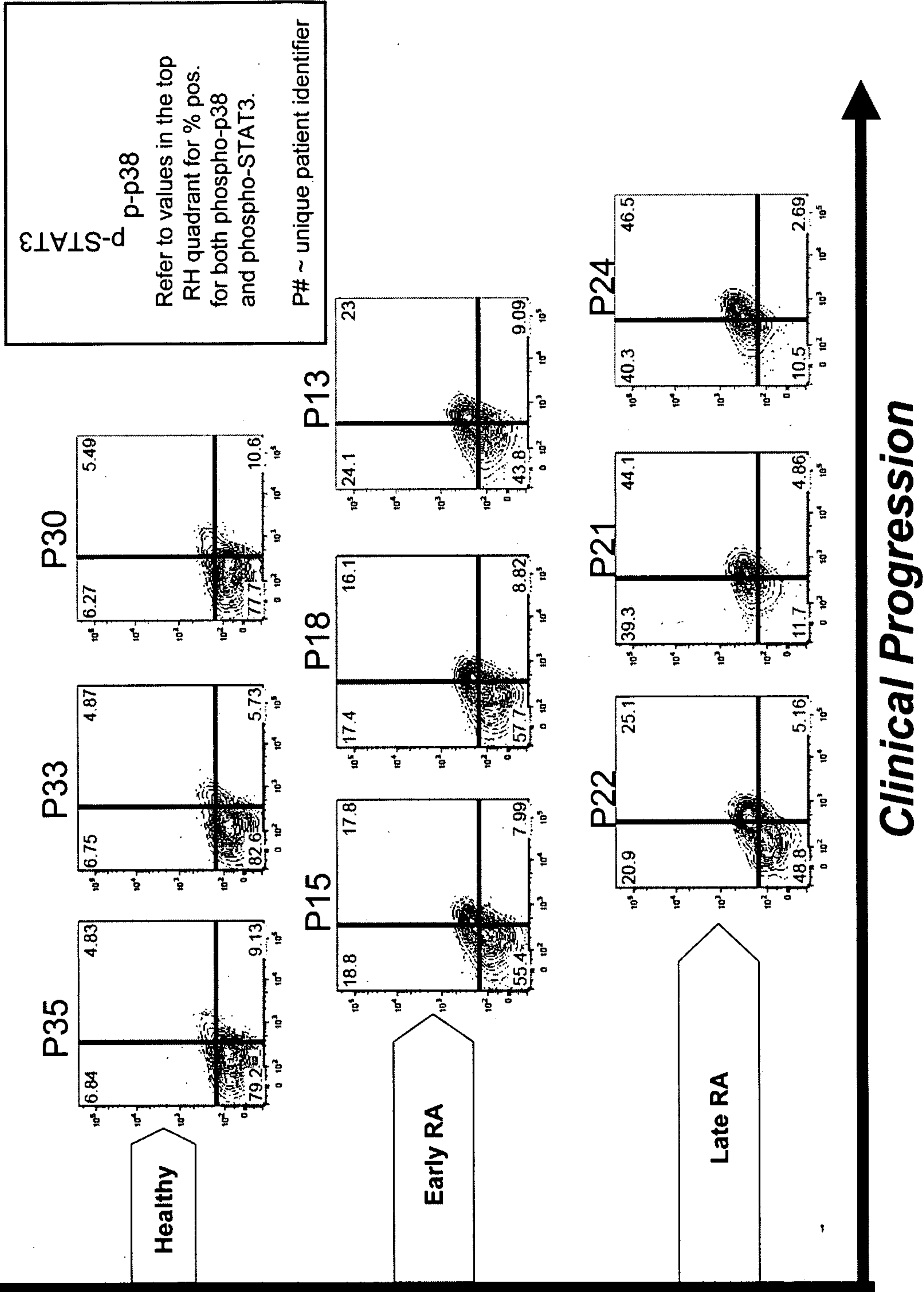


FIGURE 11

Risk-stratify patients according to signal taxonomy

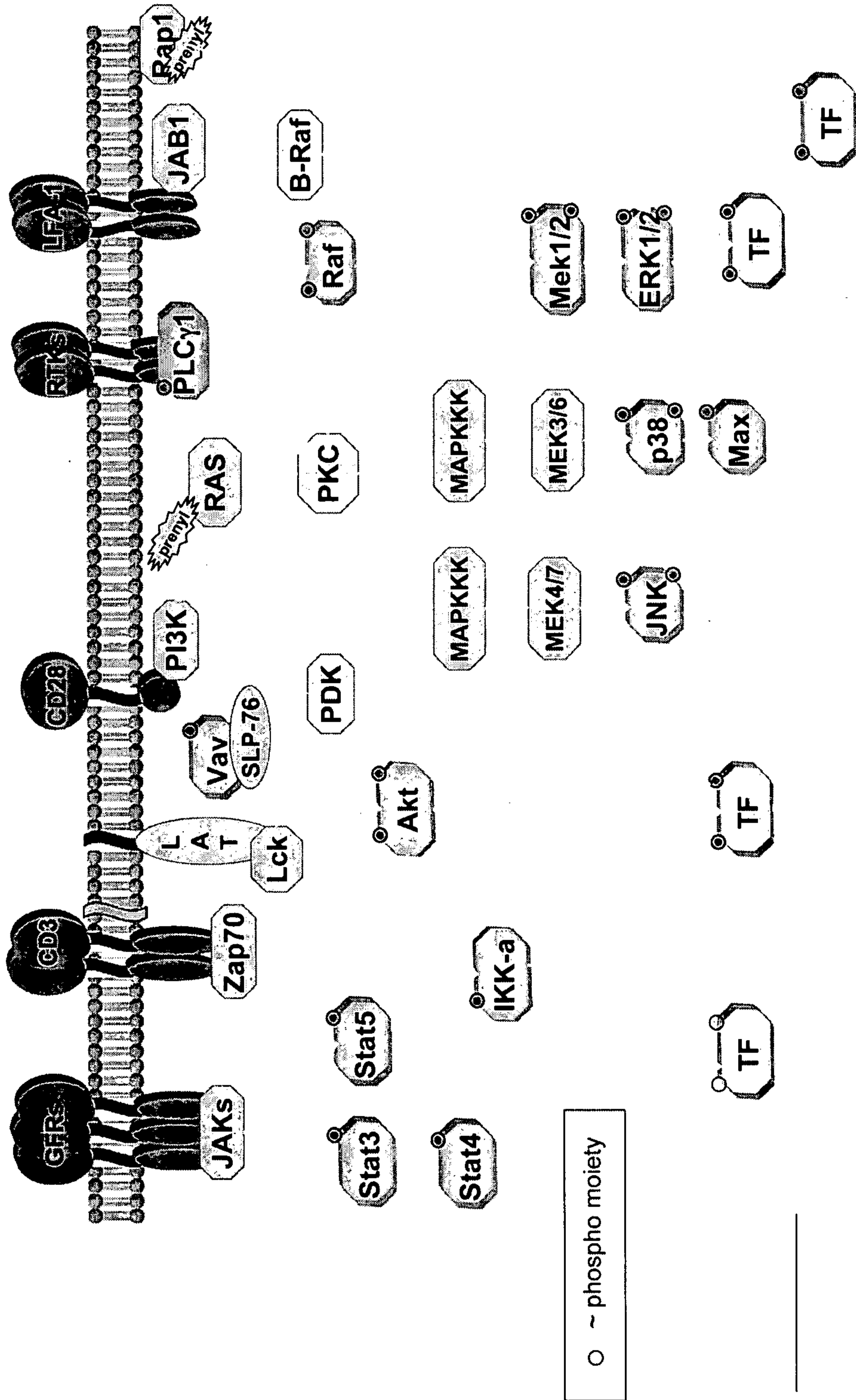
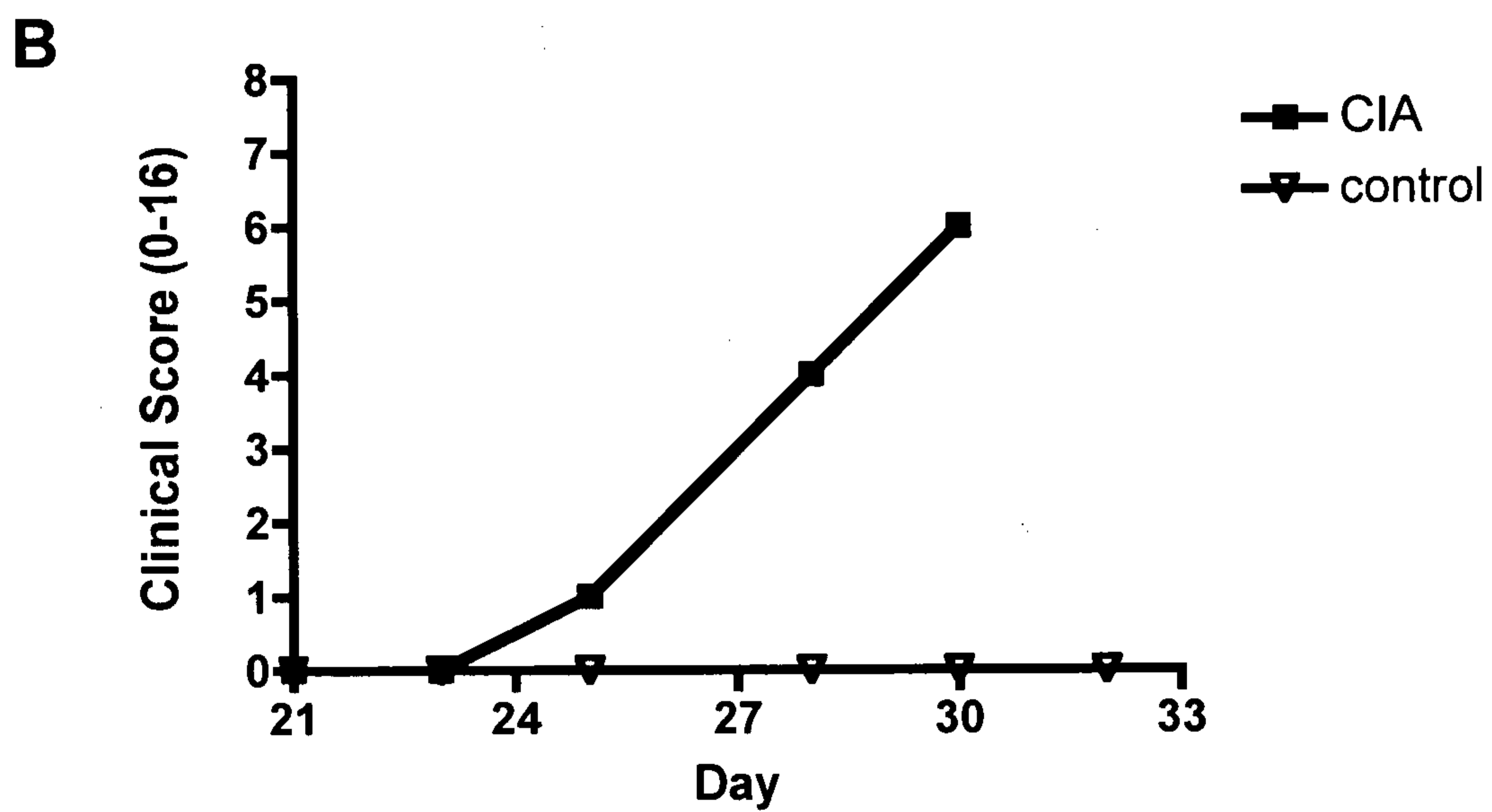
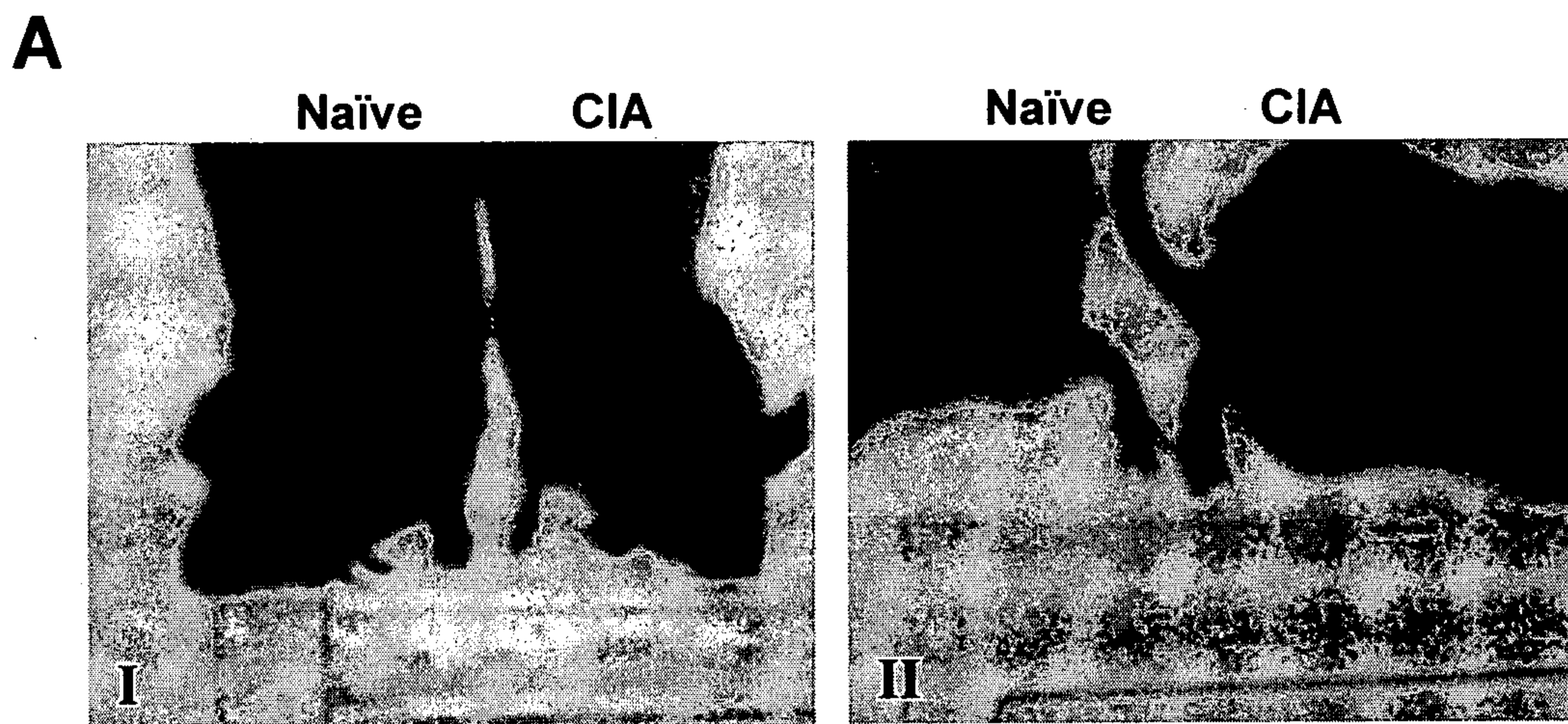
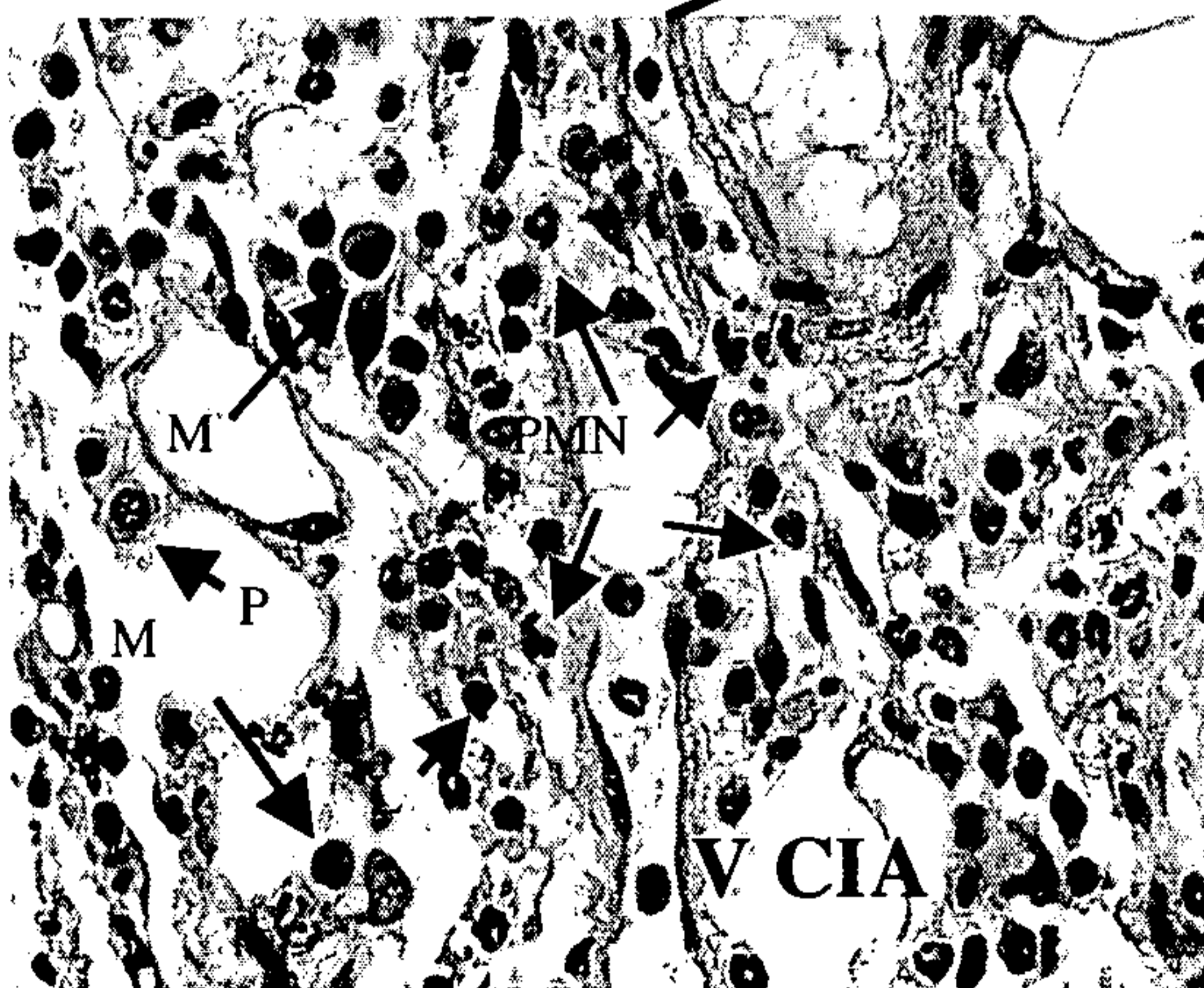
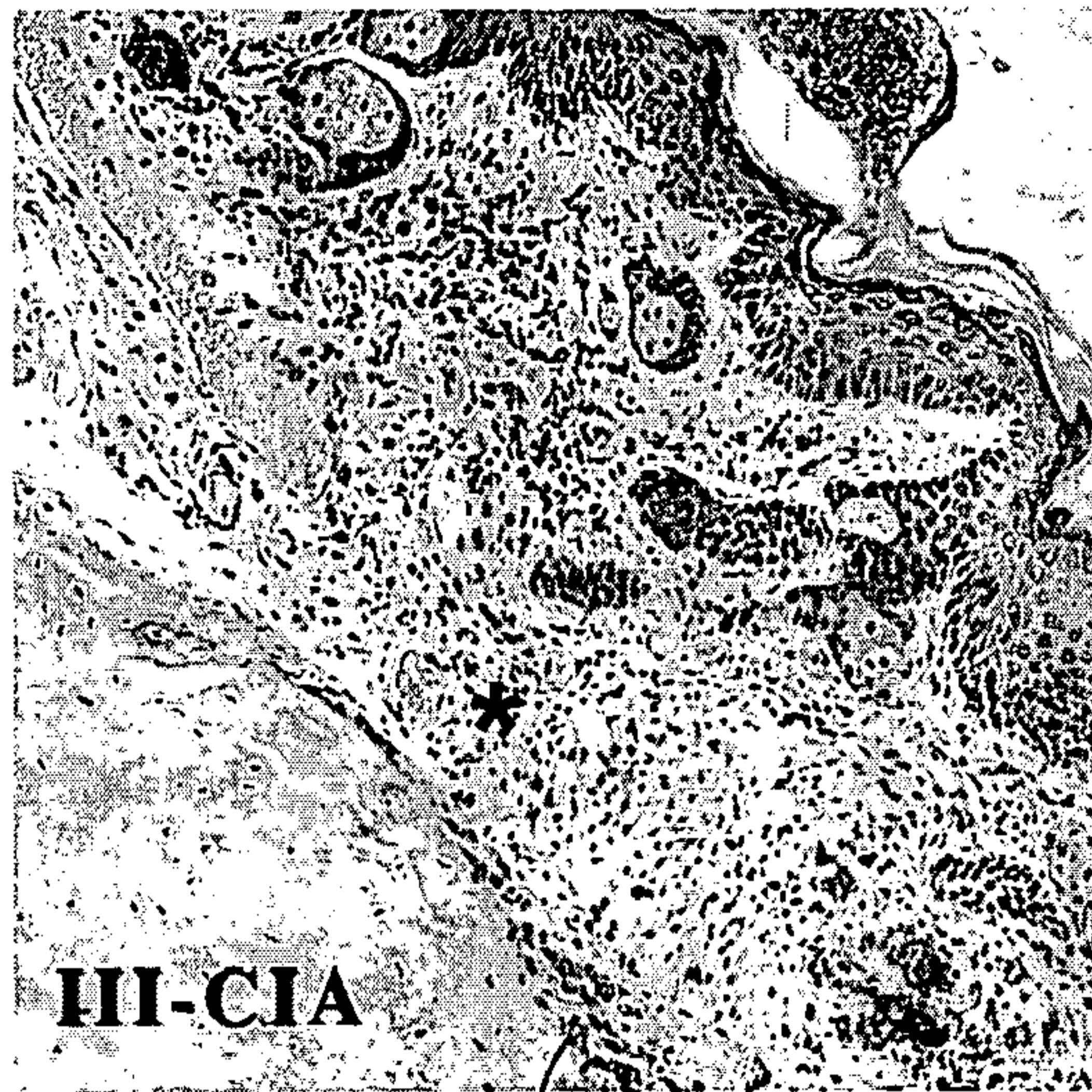
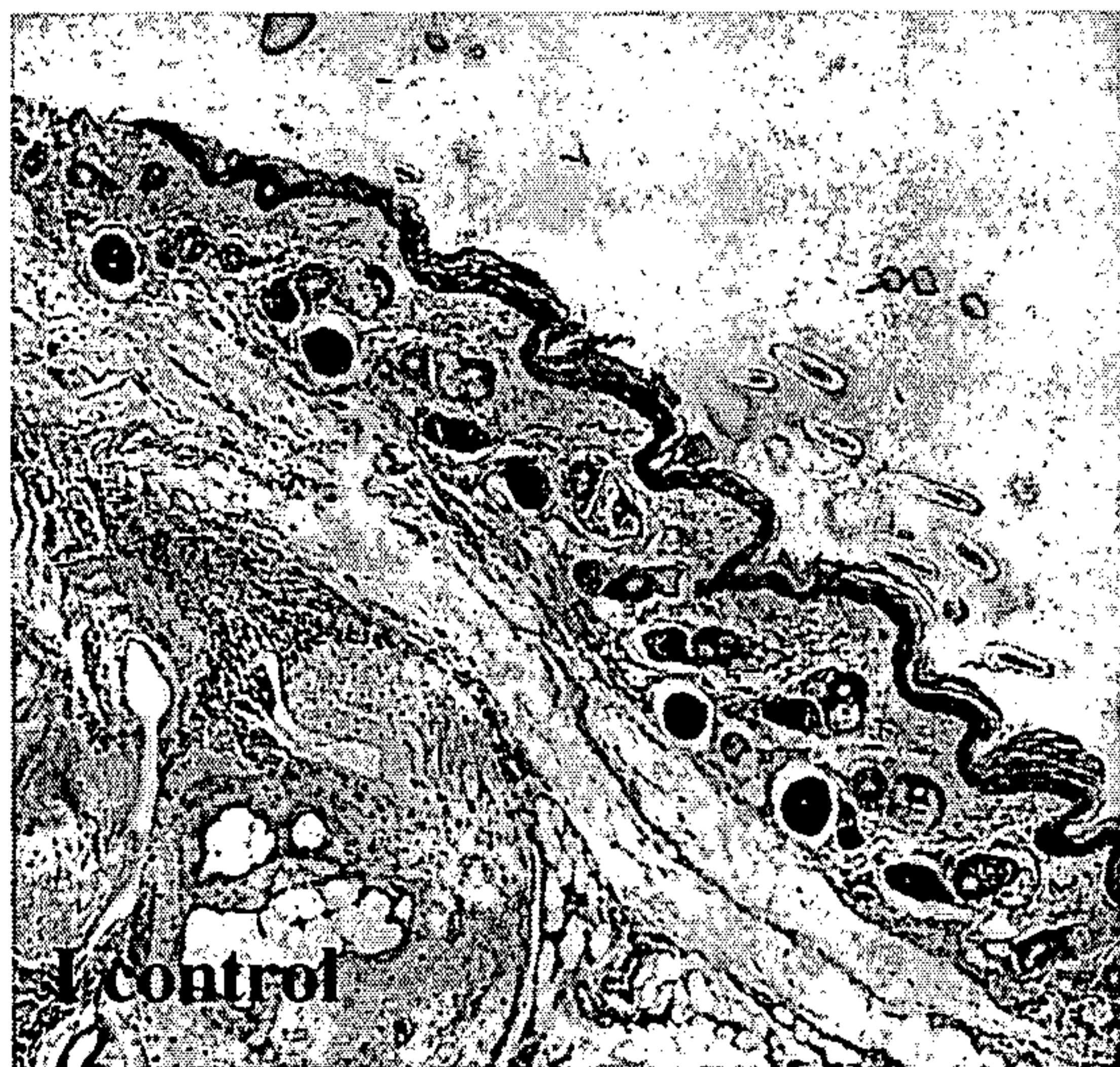


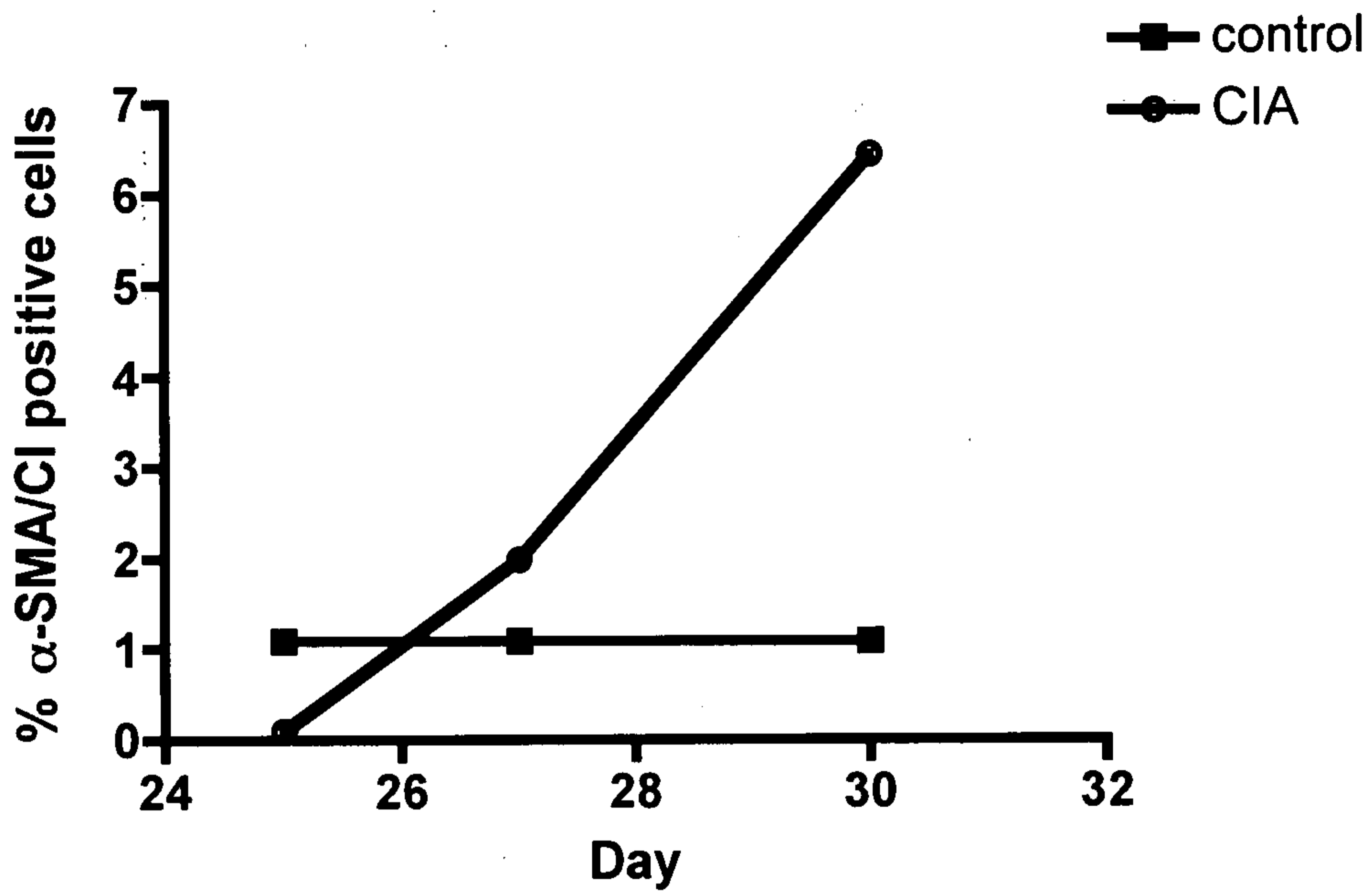
FIGURE 12



C



D



E

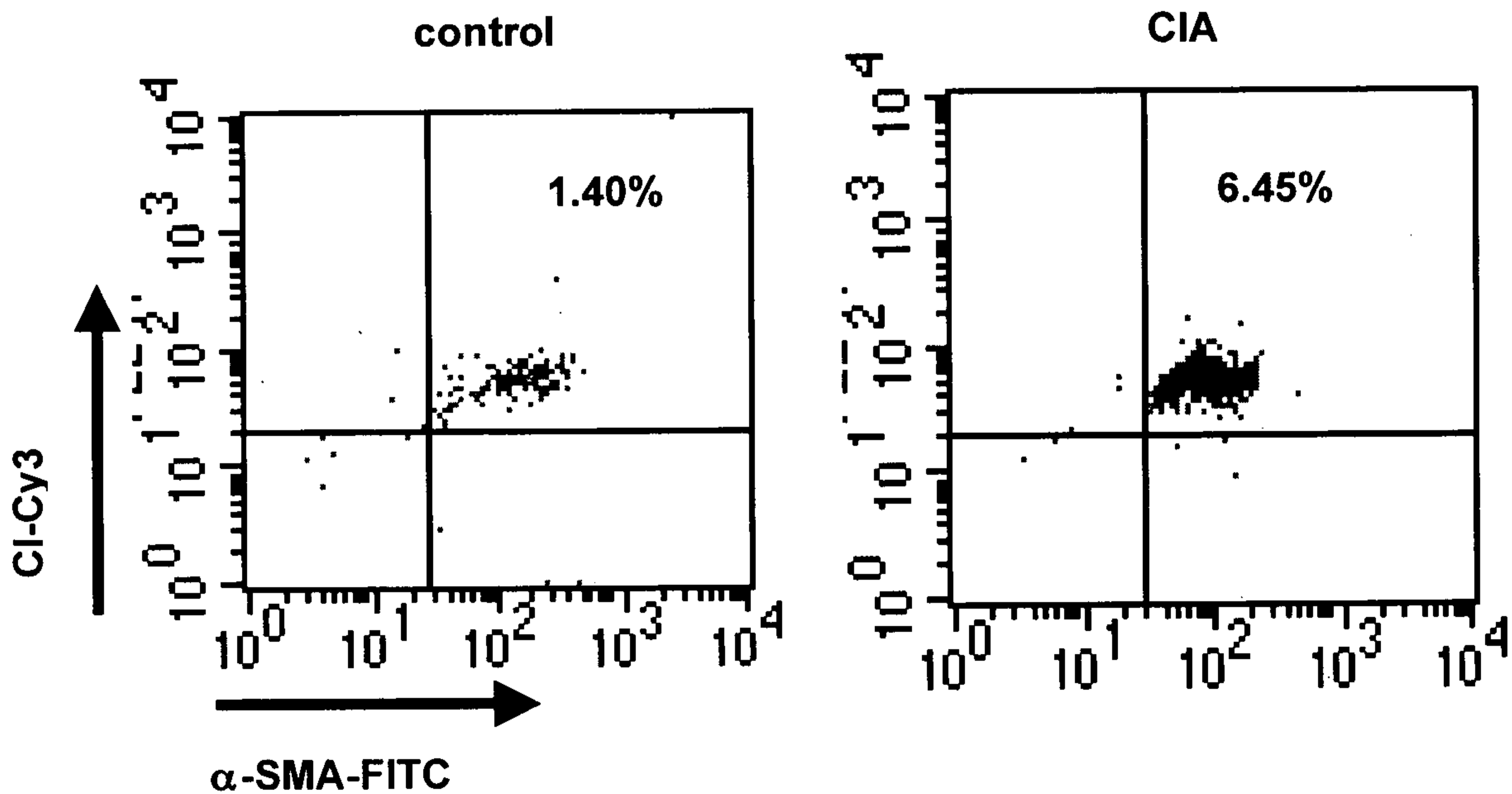
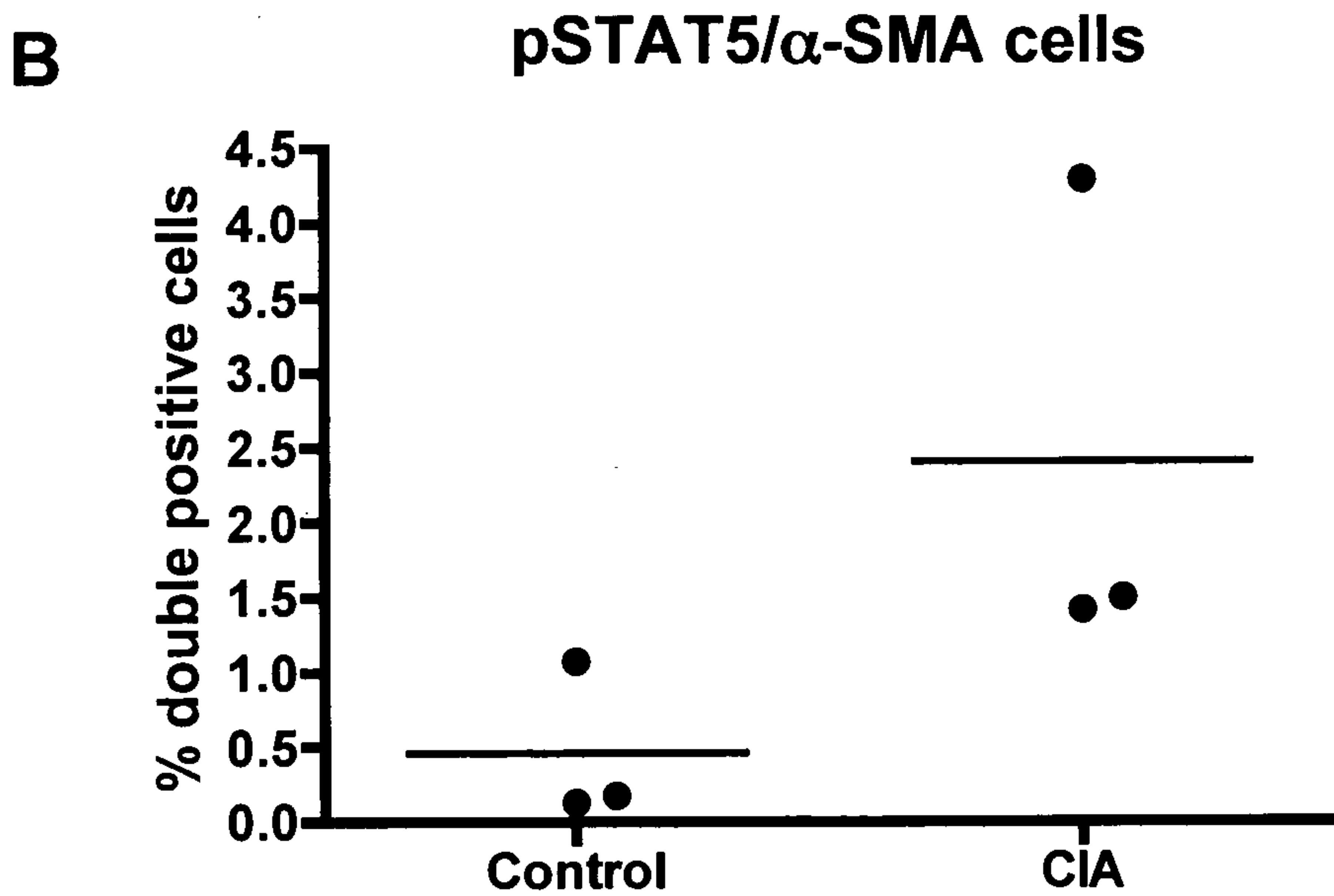
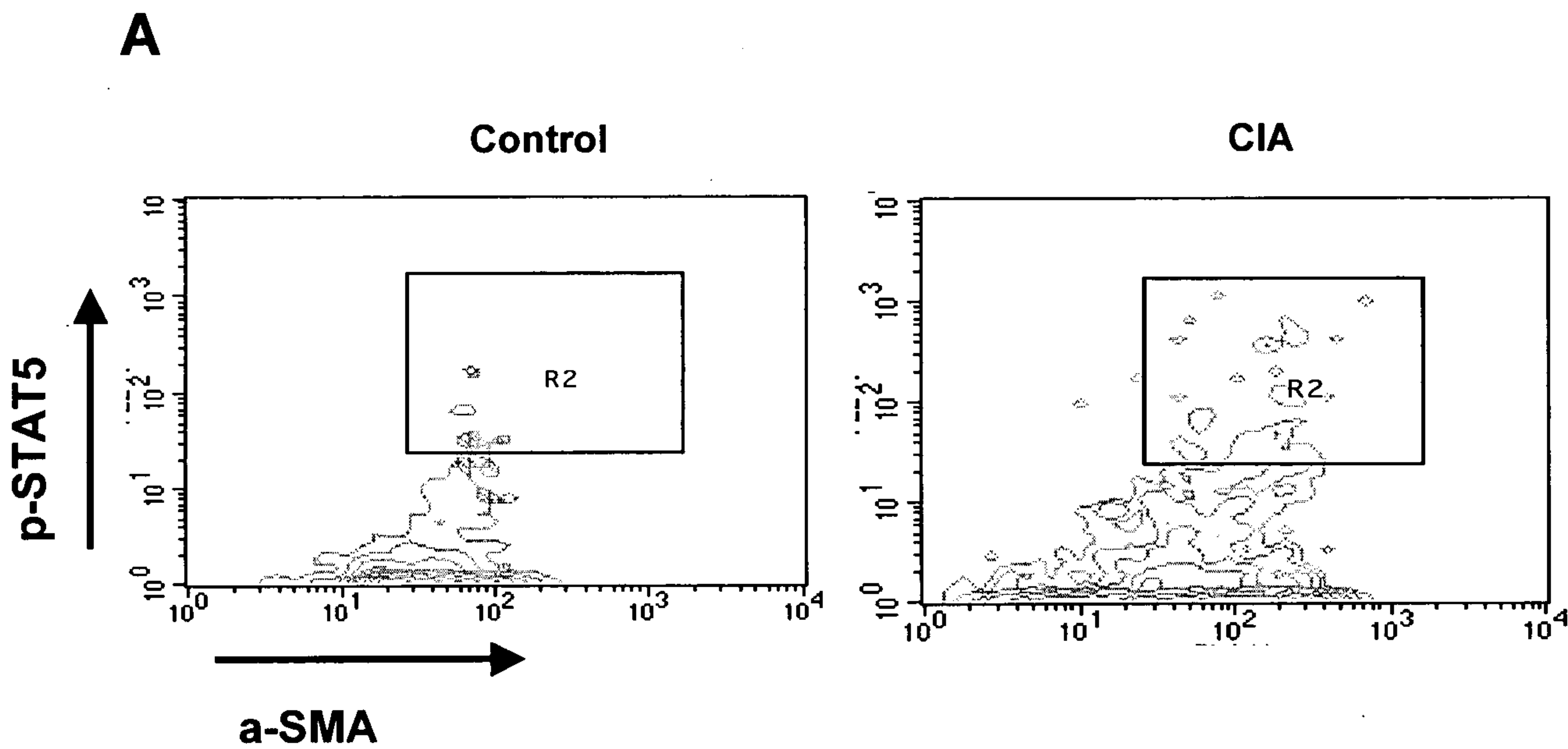
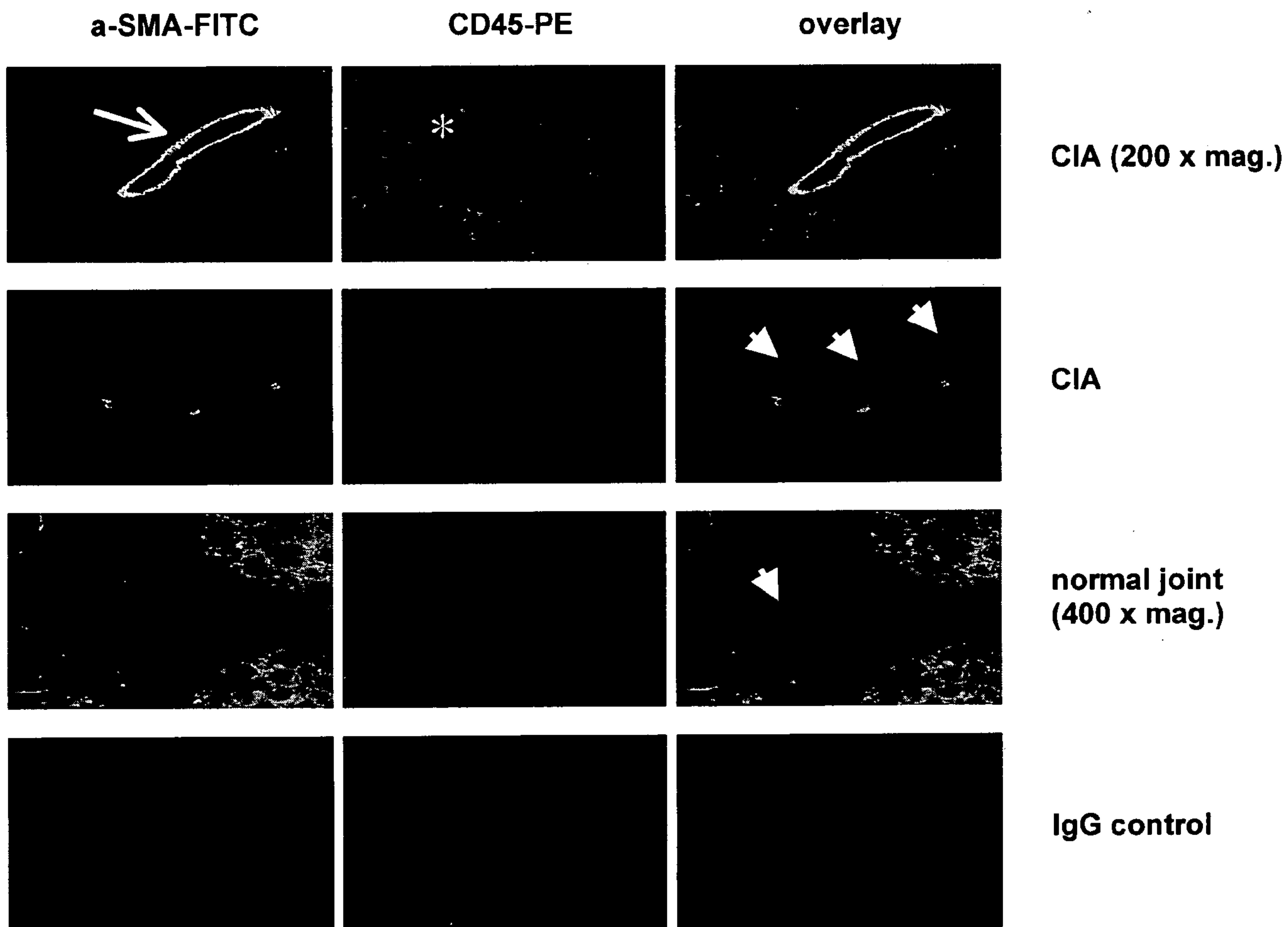


FIGURE 13



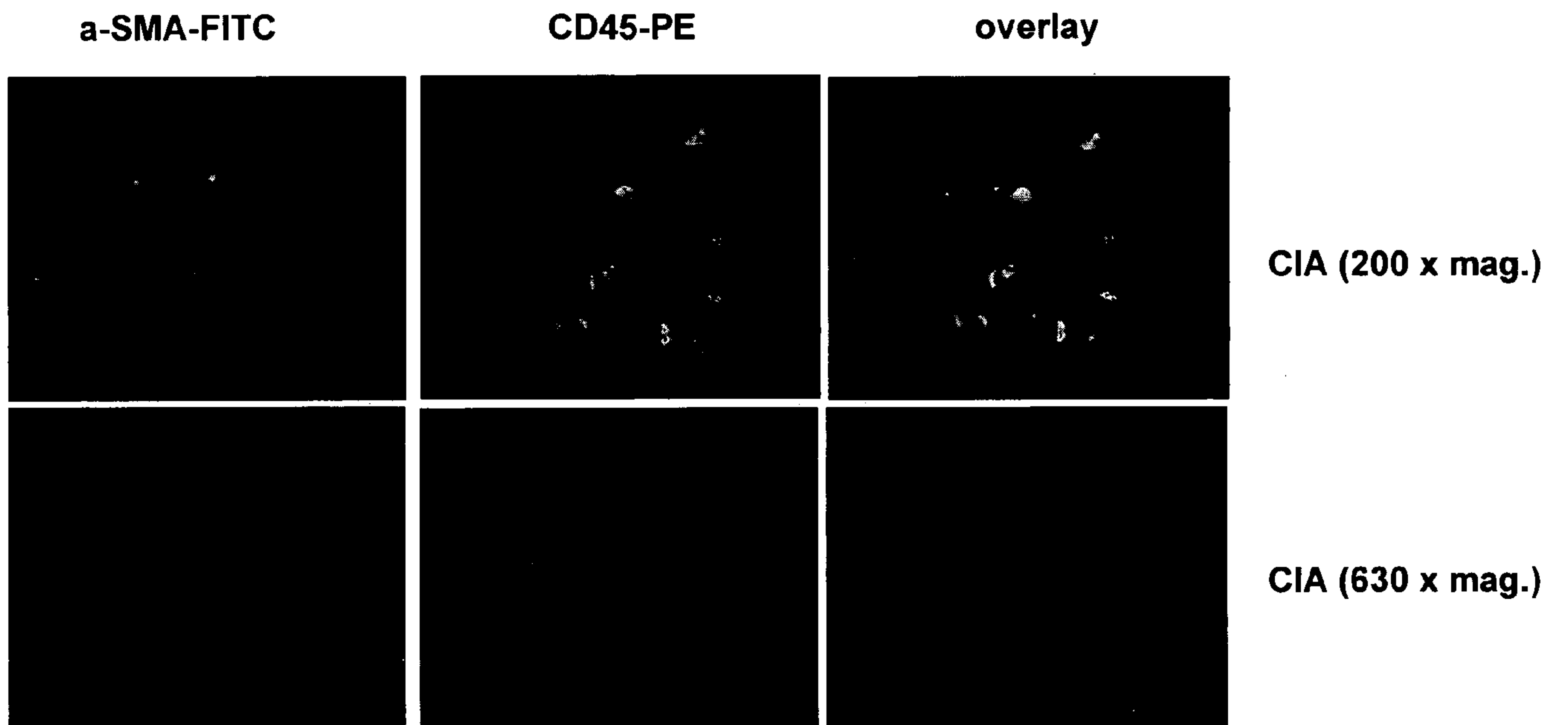
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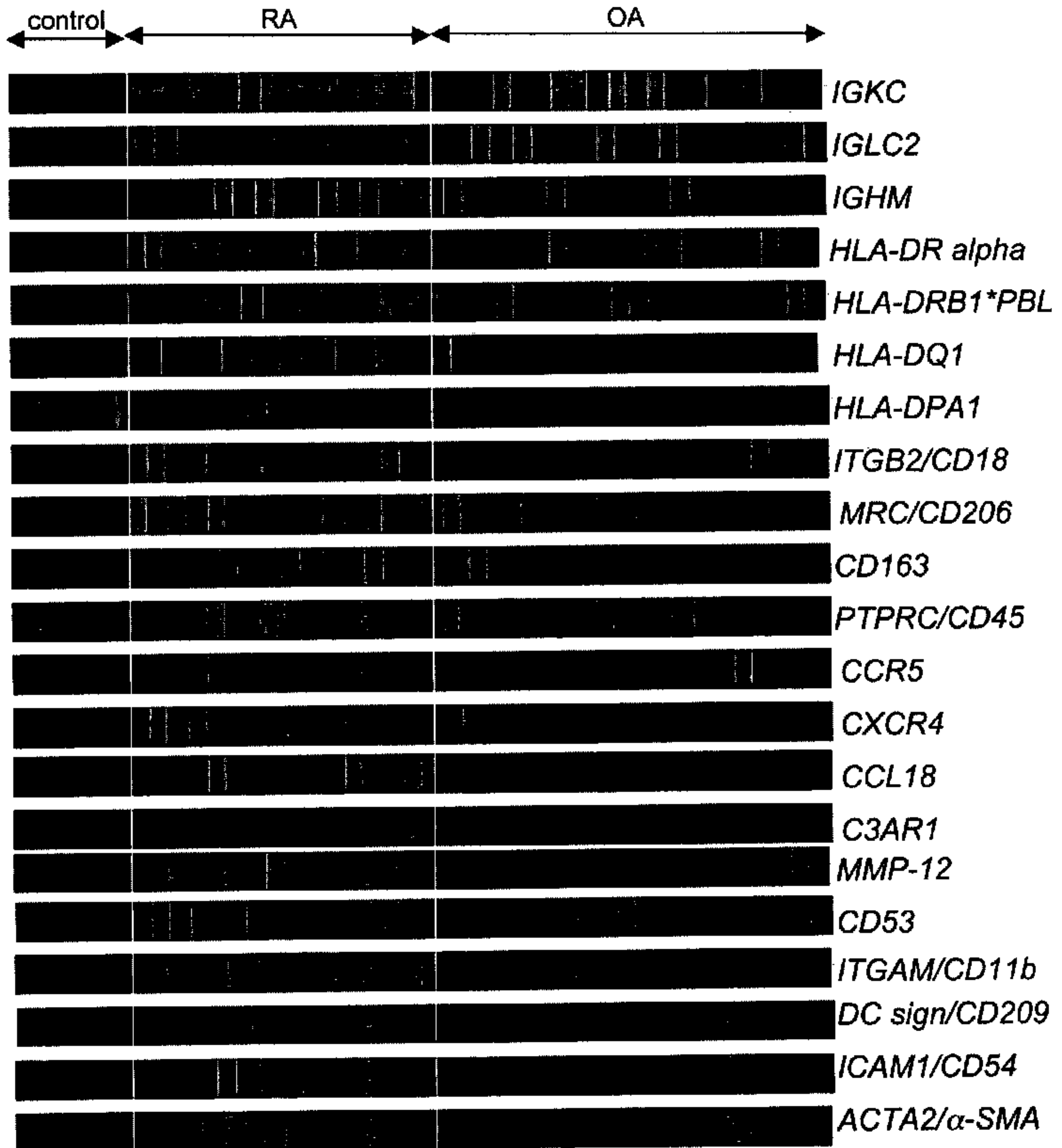
FIGURE 14



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FIGURE 15





Gene expression levels in ST FLS cells: Affymetrix analysis