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(54) Title: METHODS OF TREATING SARCOIDOSIS

(57) Abstract: The present invention provides a method of treating sarcoidosis, comprising administering to a subject in need thereof, a therapeutically effective dose of a JAK/STAT inhibitor. Also, the present invention provides a JAK/STAT inhibitor for use in the treatment of sarcoidosis.



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Title: Methods of treating sarcoidosis

5 FIELD OF THE INVENTION

The invention is in the field of medical diagnosis and monitoring of disease progression. In particular, the present invention pertains to methods of predicting disease progression in non-treated pulmonary sarcoidosis (PS) patients (wherein presence of the prognostic biomarker is
10 indicative of chronic disease), to methods of devising treatment plans for PS patients (comprising measuring the prognostic biomarker and devising treatment based on the outcome). Also, the present invention pertains to methods of identifying patients with PS eligible for treatment with an anti-PS drug comprising testing the patient for the prognostic biomarker,
15 wherein the patient is eligible for treatment if the biomarker is present. The invention further provides for methods of treating PS, comprising testing for the presence of biomarker to confirm presence or stage of disease and administering a therapeutically effective amount of an anti-PS drug to the patient if the sample tests positive. The invention further provides for
20 methods of treating PS comprising administering a specific interleukin 23 blocker, or administering a JAK/STAT inhibitor.

BACKGROUND OF THE INVENTION

Pulmonary sarcoidosis (PS) is a systemic disease, very
25 heterogeneous in both clinical presentation as well as disease course. It may lead to chronic inflammation and subsequently development of severe pulmonary fibrosis in up to 20-25% of patients.

Non-necrotizing granulomas are the key pathological feature. These aggregates of differentiated immune cells contain a core with alveolar

macrophages, multinucleated giant cells and a shell comprised of mostly T-cells.

Diagnosis of PS is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. The diagnosis of pulmonary sarcoidosis is preferably conform
5 guidelines of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Frequently observed immunological features are depression of cutaneous delayed-type
10 hypersensitivity and a heightened helper T cell type 1 (Th1) immune response at sites of disease.

All sarcoidosis patients are currently treated first-line with corticosteroids, notably prednisolone. Additional treatment with non-corticosteroids, such as methotrexate (MTX) or tumor necrosis factor (TNF)–
15 inhibitor therapy (e.g. infliximab or adalimumab) is available.

Currently, no prognostic analysis exists to indicate who is at risk of developing chronic PS. In patients with Löfgren's syndrome the HLA-DR3(+) haplotype is known to be associated with a particularly good prognosis in this acute form of sarcoidosis. Yet, 30-50% of HLA-DR3(-)
20 patients still develops chronic disease. With current methodology, it is difficult to detect patients at risk for developing end-stage (chronic) disease.

There is however a need for the possibility to determine whether a pulmonary sarcoidosis (PS) patient has an increased risk of developing a chronic, progressive disease pattern. With the first-line steroid treatment
25 having severe side-effects on patients, such as weight gain and development of diabetes, a prognostic biomarker could offer steroid dose-sparing possibilities to patients not at risk of developing chronic disease.

At the same time, in undertreated or refractory patients which are at risk of developing chronic disease patterns, a new prognostic biomarker
30 could serve as a therapeutic target in order to improve their prognosis.

SUMMARY OF THE INVENTION

The present inventors have found that the number of T helper cells of the Th17 lineage that produce interferon, and in particular their
5 quantity within the population of all memory CD4⁺ T cells is predictive of a chronic disease pattern in sarcoidosis.

Hence, in a first aspect, the present invention provides a method for typing a pulmonary sarcoidosis (PS) patient as having an increased risk of developing a chronic, disease pattern, the method comprising the steps of:
10 a) enumerating in a sample obtained from said patient the Th17.1 cells within said population of total CD4⁺ T cells, optionally including enumerating in said sample the total CD4⁺ T cells; b) calculating the proportion of Th17.1 cells to the total CD4⁺ T cells; c) comparing said proportion of Th17.1 cells to a control value, and d) typing said patient as
15 having an increased risk of developing a chronic, preferably a chronic progressive, disease pattern if said proportion is increased relative to the control value.

In a preferred embodiment of a method of the invention, the chronic disease pattern is a progressive disease pattern.

20 The control value can be any group of subjects not suffering from chronic or progressive sarcoidosis. For instance, healthy human subjects can provide very suitable control values. Likewise, samples obtained from individuals who undergo bronchoscopy for non-related illnesses, such as for community-acquired pneumonia or chronic obstructive pulmonary disease
25 may serve as control values in aspects of this invention.

In an alternative preferred embodiment of this aspect of the invention, the methods may comprise the step of a) enumerating in a sample obtained from said patient the total memory CD4⁺ T cells and the Th17.1 cells within said population of total memory CD4⁺ T cells; and the step of b)
30 calculating the proportion of Th17.1 cells to the total memory CD4⁺ T cells.

It was found that the quantity of Th17.1 cells within the population of memory CD4⁺ T cells was most predictive of chronic sarcoidosis. However, enumerating the Th17.1 cells may also occur within the population of total CD4⁺ T cells, in particular in samples known to contain high proportions of memory CD4⁺ T cells as part of the total CD4⁺ T cell population. Hence, embodiments wherein Th17.1 cells are enumerated as part of the total CD4⁺ T cells are particularly useful in applications utilizing BALF as a sample, since >95% of all CD4⁺ T cells in BALF is memory CD4⁺ T cell.

In preferred embodiment, the invention provides a method as described above wherein the method further comprises, in addition to enumerating the Th17.1 cells in step a), also, and preferably as a part of step a), the step of enumerating the Th1 cells within said population of total (memory) CD4⁺ T cells in said sample.

Preferably, therefore, a method of the invention as described above comprises the step of a) enumerating in a sample obtained from said patient the total memory CD4⁺ T cells the Th17.1 cells, and the Th1 cells within said population of total memory CD4⁺ T cells.

Preferably, a method of the invention as described above further comprises the step of b) calculating the proportion of Th17.1 cells to the total memory CD4⁺ T cells.

Preferably, a method of the invention as described above further comprises the step of c) calculating the proportion of Th1 cells to the total memory CD4⁺ T cells.

Preferably, a method of the invention as described above further comprises the step of d) calculating the ratio between the proportions calculated in steps b) and c).

Preferably, a method of the invention as described above further comprises the step of e) comparing the ratio obtained in step d) to a control value.

Preferably, a method of the invention as described above further comprises the step of f) typing said patient as having an increased risk of developing a chronic, preferably a chronic progressive, disease pattern if said ratio is increased relative to the control value.

5 In most preferred embodiments of aspects of this invention, the above preferred embodiments are combined.

In preferred embodiments in aspects of this invention, the sample in a method as described above, is a tissue or tissue aspirate sample, preferably a bronchoalveolar lavage fluid (BALF) or a mediastinal lymph
10 node (MLN) sample, preferably from a non-treated pulmonary sarcoidosis (PS) patient.

In further preferred embodiments in aspects of this invention, the control sample is a corresponding (same sample site) sample from a healthy subject, a subject not suffering from chronic and/or progressive sarcoidosis,
15 a sarcoidosis patient experiencing disease resolution, or a pooled sample of either or a mixture of these.

In another aspect, the present invention provides the use of Th17.1-cells or ratio of Th17.1/Th1 populations as predictive/prognostic biomarker in pulmonary sarcoidosis.

20 In another aspect, the predictive biomarker used herein is the BALF IL-12p40 protein level, which level is highest in patients developing chronic disease.

In another aspect, the present invention provides a method of treating of treating sarcoidosis in a subject in need thereof, comprising:
25 administering to a subject in need thereof, a therapeutically effective dose of a specific interleukin 23 blocker, preferably selected from tildrakizumab, and guselkumab. This treatment is based on altering Th17-cell differentiation. A specific IL-23 blocker only targets IL-23. Such a specific blocker is preferred over dual blockers, which may also block other
30 interleukines.

In another aspect, the present invention provides a specific interleukin 23 blocker, preferably selected from tildrakizumab and guselkumab, for use in the treatment of pulmonary sarcoidosis.

Interfering with cytokine receptor signaling, such as the IFN- γ receptor, offers another possibility for treating sarcoidosis in the context of this invention. The Janus kinase (JAK)/Signal Transducer and Activator of Transcription Factor (STAT)-1 axis is upregulated in sarcoidosis and IFN- γ induces STAT1 expression. This provides a link between Th17.1 cells and JAK/STAT signaling, and possible implications for suppressive effects of this pathway on Th17-cell differentiation. Altering Th17-cell differentiation (e.g. IL-23 blockade) or effector cytokine signaling (e.g. JAK/STAT inhibition) are proposed herein as a novel treatment strategies, preferably in stratified patient populations.

In aspects of this invention, also non pulmonary sarcoidosis diseases are contemplated for indications in aspects of this invention. Hence, the term pulmonary sarcoidosis may, in aspects of his invention be extended to applications of non pulmonary sarcoidosis. In alternative embodiments therein, pulmonary sarcoidosis is a preferred embodiment.

In another aspect, the present invention provides a method of treating sarcoidosis in a subject in need thereof, comprising: administering to a subject in need thereof, a therapeutically effective dose of a JAK/STAT inhibitor, preferably baricitinib. Baricitinib is known to interfere in effector cytokine signaling (e.g. the IFN- γ signaling pathway, i.e. the effector cytokine produced by Th17.1 cells). This treatment aspect is therefore based on altering Th17-cell effector cytokine signaling.

In another aspect, the present invention provides a method of treating sarcoidosis, comprising administering to a subject in need thereof, a therapeutically effective dose of a JAK/STAT inhibitor, most preferably a JAK1 inhibitor.

In a preferred embodiment of this aspect, the sarcoidosis is chronic sarcoidosis.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor interferes with IFN- γ receptor signaling.

5 In preferred embodiments of aspect of the invention, the JAK/STAT inhibitor is a JAK1 inhibitor. The JAK1 inhibitor may, e.g., be a JAK1-selective inhibitor, or a JAK1-JAK2 inhibitor (i.e. an inhibitor that inhibits both JAK1 and JAK2), or a JAK1-JAK3 inhibitor (i.e. an inhibitor that inhibits both JAK1 and JAK3).

10 In another preferred embodiment of this aspect, the JAK/STAT inhibitor is selected from Baricitinib, Tofacinib, Peficitinib, Filgotinib, and Upadacitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Baricitinib. In a preferred embodiment hereof, Baricitinib is
15 administered at an oral dose of 1-10 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Filgotinib. In a preferred embodiment hereof, Filgotinib is administered at an oral dose of 1-500, preferably 50-200 mg, such as 80-100 mg once daily.

20 In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Tofacitinib. In a preferred embodiment hereof, Tofacitinib is administered at an oral dose of 1-10 mg, preferably about 5 mg twice daily, preferably in immediate release form; or about 10 mg once daily, preferably in extended release form.

25 In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Peficitinib. In a preferred embodiment hereof, Peficitinib is administered at an oral dose of 100-150 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Upadacitinib. In a preferred embodiment hereof, Upadacitinib is
30 administered at an oral dose of 15-30 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is selected from tofacinib, peficitinib, filgotinib, and upadacitinib.

In some preferred embodiments of aspects of this invention, the JAK/STAT inhibitor, in particular the JAK1 inhibitor, is not baricitinib. In
5 certain another preferred embodiment of aspects of this invention, the JAK/STAT inhibitor, in particular the JAK1 inhibitor, is not filgotinib. In certain another preferred embodiment of aspects of this invention the JAK/STAT inhibitor, in particular the JAK1 inhibitor, is not Ruxolitinib.

In preferred embodiments of aspects of this invention, the JAK2
10 inhibiting effect of a JAK1-JAK2 inhibitor, or the JAK3 inhibiting effect of a JAK1-JAK3 inhibitor is not relied on for therapeutic efficacy. Hence, in most preferred embodiments of this invention, the JAK1 inhibitor is preferably as selective as possible for inhibiting the JAK1 target.

In another aspect, the present invention provides a JAK/STAT
15 inhibitor, most preferably a JAK1 inhibitor, for use in the treatment of sarcoidosis.

In a preferred embodiment of this aspect, the sarcoidosis is pulmonary sarcoidosis, most preferably chronic pulmonary sarcoidosis.

In another preferred embodiment of this aspect, the JAK/STAT
20 inhibitor interferes with IFN- γ receptor signaling.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is a JAK1 inhibitor.

The present inventors have now discovered that JAK1 inhibitors are highly effective in treating PS. One of skill will understand that the
25 term JAK1 inhibitor includes reference to a JAK1-selective inhibitor, a JAK1-JAK2 inhibitor (i.e. an inhibitor that inhibits both JAK1 and JAK2), and a JAK1-JAK3 inhibitor (i.e. an inhibitor that inhibits both JAK1 and JAK3). All of these are able to inhibit JAK1.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is selected from Baricitinib, Tofacinib, Peficitinib, Filgotinib, and Upadacitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is selected from Tofacinib, Peficitinib, Filgotinib, and Upadacitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Baricitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor, preferably baricitinib, is administered at 1-10 mg once daily oral dose.

In treatment aspects of this invention, suitable dosages for baricitinib include 4 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Filgotinib. In a preferred embodiment hereof, Filgotinib is administered at an oral dose of 1-500, preferably 50-200 mg, such as 80-100 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Tofacinib. In a preferred embodiment hereof, Tofacinib is administered at an oral dose of 1-10 mg, preferably about 5 mg twice daily, preferably in immediate release form; or about 10 mg once daily, preferably in extended release form.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Peficitinib. In a preferred embodiment hereof, Peficitinib is administered at an oral dose of 100-150 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is Upadacitinib. In a preferred embodiment hereof, Upadacitinib is administered at an oral dose of 15-30 mg once daily.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is selected from Tofacinib, Peficitinib, Filgotinib, and Upadacitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is not baricitinib.

In another preferred embodiment of this aspect, the JAK/STAT inhibitor is not filgotinib.

5 In aspects of this invention the JAK/STAT inhibitor may also be selected from any of the JAK/STAT inhibitors cited hereinabove including the group of JAK1 inhibitors Ruxolitinib, Itacitinib (INCB39110), INCB54707, Abrocitinib, Solcitinib and AZD4205.

In aspects of this invention the JAK/STAT inhibitor is
10 administered in dose that reduces IFN- γ production in Th17.1 cells, preferably in Th17.1 cells in the BALF of sarcoidosis patients, more preferably pulmonary sarcoidosis patients.

In aspects of this invention, the administration of the JAK/STAT inhibitor is for treatment of sarcoidosis, preferably pulmonary sarcoidosis,
15 wherein said treatment comprises the administration of a therapeutically effective dose and regimen of the JAK/STAT inhibitor, preferably by oral administration of the drug.

A therapeutically effective dose and/or regimen as defined herein, preferably blocks or lowers IFN- γ production in Th17.1 cells (in BALF) of a
20 patient in need of said treatment.

A therapeutically effective dose and/or regimen as defined herein, refers to a treatment involving at least partial counteraction of the reduced pulmonary function associated with pulmonary sarcoidosis. A therapeutically effective dose and/or regimen as defined herein, may also, in
25 preferred embodiments of aspects of this invention, be defined as a dose and regimen associated with an increase in at least 5% of Forced Vital Capacity (FVC) as measured by FEV testing, a decrease in ^{18}F -FDG-PET uptake of at least 10% and/or an improvement of inflammatory activity measured as a decline in biomarker soluble interleukin-2 receptor (sIL-2R) of at least 20-
30 40%, preferably at least 40% compared to the untreated patient (e.g.

baseline levels, prior to treatment). sIL-2R is preferably determined in blood, preferably in a blood sample, preferably about 3-6 months after the start of the treatment. A reduction 40% relative to baseline levels is generally considered clinically relevant also in the case of PET SUV max
5 values.

In aspects of this invention, treatment may optionally further comprise subjecting the patient to an FEV test for determining Forced vital capacity (FVC; the total amount of air exhaled during the FEV test).

In aspects of this invention, treatment may optionally further
10 comprise subjecting the patient to ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) in order to determine maximum standardized uptake value (SUVmax) as an inflammatory marker. Positive treatment outcome, and hence attainment of therapeutically effective dose and/or regimen, is associated with a reduction in SUVmax of at least 10% in one or
15 both lungs.

One of skill will understand that a therapeutically effective dose and/or regimen in aspects of this invention result in clinically significant improvements in patient health, and may as such be referred to as clinically effective dose or regimen

20 One of skill will appreciate that the JAK/STAT inhibitor may be administered in the form of a pharmaceutically acceptable salt, solvate, polymorph, or metabolite.

In certain preferred embodiments of aspects of the present invention, the JAK1 inhibitor is not baricitinib.

25 In certain preferred embodiments of aspects of the present invention, the sarcoidosis is pulmonary sarcoidosis, preferably chronic pulmonary sarcoidosis.

In certain other preferred embodiments of aspects of the present invention, treatment involves at least partial counteraction of the reduced
30 pulmonary function associated with pulmonary sarcoidosis.

In certain other preferred embodiments of aspects of the present invention, improved pulmonary function is and increase in at least 5% of Forced Vital Capacity (FVC) as measured by FEV testing, compared to baseline levels prior to treatment.

5 In certain other preferred embodiments of aspects of the present invention, a therapeutically effective dose is associated with a decrease in ¹⁸F-FDG-PET uptake of at least 10%, and/or an improvement of inflammatory activity measured as a decline in the soluble interleukin-2 receptor (sIL-2R) of at least 20%, compared to baseline levels prior to
10 treatment.

The above treatment regimens are aimed at reducing the harmful effect of these Th17.1 cells in sarcoidosis. In this way it is aimed to improve the prognosis by inhibiting chronic inflammation in this disease.

In another aspect, the present invention provides a method of
15 identifying patients with pulmonary sarcoidosis eligible for treatment with an anti-pulmonary sarcoidosis drug comprising testing the patient for the prognostic biomarker Th17.1-cells or ratio of Th17.1/Th1 cells, as defined herein above, wherein the patient is eligible for treatment if the biomarker level is increased relative to a control value. One of skill will understand
20 that control values can be obtained for this aspect as described for other aspects herein.

In another aspect, the present invention provides a method of treating pulmonary sarcoidosis, comprising identifying a patient with pulmonary sarcoidosis as eligible for treatment with an anti-pulmonary
25 sarcoidosis drug as described above, and administering to eligible patients a therapeutically effective amount of an anti-pulmonary sarcoidosis drug as described above.

DESCRIPTION OF THE DRAWINGS

Figure 1. Significant increase of Th17.1 cells in sarcoidosis MLN compared with controls CCR6- T cell subsets (CCR4-CXCR3+ Th1 cells and CCR4+CXCR3- Th2 cells) and CCR6+ T cell subsets (CCR4+CXCR3- Th17 cells, CCR4+CXCR3+ DP Th cells and CCR4-CXCR3+ Th17.1 cells) were determined in CD45RA-FoxP3^{low/int} total memory CD4+ T cells (see Figure 5 for gating strategy) from sarcoidosis BALF (n=36) and from control MLN (n=22) and sarcoidosis MLN (n=17). A. Proportions of Th1, Th2, Th17, CCR6+ DP and Th17.1 cells of total memory CD4+ T cells in sarcoidosis BALF. B. A pie-chart showing mean percentages of Th1, Th2, Th17, CCR6+ DP, Th17.1 and unclassified cells (which include CCR6-CCR4-CXCR3- cells, CCR6-CCR4+CXCR3+ cells and CCR6+CCR4-CXCR3- cells) of total memory CD4+ T cells in sarcoidosis BALF. C. Proportions of CCR6+ total memory T cells in MLN. D. Proportions of Th1, Th2, Th17, CCR6+ DP and Th17.1 cells of total memory CD4+ T cells in MLN. E. Pie-chart showing mean percentages of Th1, Th2, Th17, CCR6+ DP, Th17.1 and unclassified cells (which include CCR6-CCR4-CXCR3- cells, CCR6-CCR4+CXCR3+ cells and CCR6+CCR4-CXCR3- cells) of total memory CD4+ T cells in MLN.

Statistics: Horizontal lines indicate the median values; in A significance was determined using a Wilcoxon signed rank test. *** $p \leq 0.001$ (represents sarcoidosis Th17.1 cells versus either sarcoidosis Th1, Th2 or Th17 or DP cells). In C and D significance was determined using a Mann-Whitney U test, ** $p < 0.01$ *** $p < 0.001$. Abbreviations: CCR: C-C chemokine receptor, CXCR: CXC chemokine receptor, BALF: broncho-alveolar lavage fluid, MLN: mediastinal lymph nodes, DP: double-positive, Th: T helper, SRC: sarcoidosis.

Figure 2. Th17.1 cells and CCR6+ DP cells are highly proliferative in sarcoidosis MLN Expression of Ki67 was determined ex-vivo in Th1, Th17, CCR6+ DP and Th17.1 cells in control and sarcoidosis MLN. A. Proportions Ki67+ total memory T cells (data are from 15 controls and 13 patients). B. Proportions of Ki67+ cells in control (n=10) and sarcoidosis

MLN (n=9). C. Representative flow cytometry analysis of Th17, CCR6+ DP and Th17.1 cells in MLN from one control and one sarcoidosis patient. D. Delta (Δ) MFI of CTLA4 (data are from 17 controls and 13 patients).

Statistics: Horizontal lines indicate median values. Significance was determined using a Mann-Whitney U test. * $p < 0.05$ *** $p < 0.001$. In B significance between median values of paired samples was determined using a Wilcoxon signed rank test (# $p < 0.05$: sarcoidosis DP cells versus either sarcoidosis Th1, Th17 or Th17.1). Abbreviations: DP: double-positive, Th: T helper, Ctrl: control, SRC: sarcoidosis, MFI: mean fluorescent intensity, CTLA4: cytotoxic T lymphocyte antigen 4.

Figure 3. Higher Th17.1 cell proportions in sarcoidosis MLN and BALF than PB Proportions Th17, CCR6+ DP and Th17.1 cells were determined in total memory CD4+ T cells from sarcoidosis PB, MLN and BALF. A-C. Proportions of Th17, CCR6+ DP and Th17.1 cells of total memory CD4+ T cells. Statistics: Horizontal lines indicate median values and significance was determined using a Mann-Whitney U test, *** $p < 0.001$. Data are from 35 (PB), 17 (MLN) and 36 (BALF) patients. Abbreviations: CCR: C-C chemokine receptor, PB: peripheral blood, MLN: mediastinal lymph nodes, BALF: broncho-alveolar lavage fluid, DP: double-positive, Th: T helper.

Figure 4. Higher BALF Th17.1 cell proportions in patients developing chronic disease than patients undergoing resolution. Disease course of a subgroup of patients (n=25) was determined 2 years after study inclusion and flow cytometric analyses. Resolution of disease (n=7) was defined by the absence of abnormalities on the chest X-ray and clinical symptoms. Patients with residual abnormalities on chest X-ray, but without need for treatment were designated as non-progressive chronic (n=11); and patients with need for treatment were designated as progressive chronic (n=7). A-B. Proportions Th17.1 and Th1 cells of total memory CD4+ T cells at time of diagnosis. C. Ratio of the proportions of Th17.1 versus Th1 cells.

Statistics: Horizontal lines indicate median values and significance was determined using a Mann-Whitney U test, * $p < 0.05$ ** $p < 0.01$.

Abbreviations: Th: T helper.

Figure 5. A. Five CD3+CD4+ T cell populations were characterized according to CD45RA and intracellular FoxP3 expression [Miyara M, Yoshioka Y, Kitoh A, et al. 2009. Immunity 30(6):899-911], i.e. CD45RA+FoxP3- naïve T cells, CD45RA-FoxP3- memory T cells, CD45RA-FoxP3^{int} activated (non-suppressive/-regulatory) T cells, CD45RA+FoxP3^{int} naïve regulatory T cells and CD45RAFoxP3^{high} activated Tregs. The total memory T cell pool consists of memory T cells plus activated T cells. The total (non-suppressive/-regulatory) T cell pool consists of naïve T cells plus total memory T cells. B. Th cell subsets can be classified according to chemokine-receptor expression. CCR6- memory T cells subsets, including CCR4-CXCR3+ Th1 cells and CCR4+CXCR3- Th2 cells; and CCR6+ T cell subsets, which include CCR4+CXCR3- Th17 cells, CCR4+CXCR3+ DP Th cells and CCR4-CXCR3+ Th17.1 cells. Th17.1 cells (i.e. IFN- γ -producing Th17 cells) contain both IL-17A+/IFN- γ + (Th17/Th1) cells and IFN- γ -single-positive cells. CCR6+CCR4+CXCR3+ DP cells are thought to reflect an intermediate Th17 and Th17.1 cell population, expressing both ROR γ t/IL-17A and T-bet/IFN- γ in patients with rheumatoid arthritis (RA). Abbreviations: CCR: C-C chemokine receptor, CXCR: CXC chemokine receptor, DP: double-positive, Th: T helper, Treg: regulatory T cells.

Figure 6. Flowchart describing the donated material (BALF, MLN, and/or PB) by the 55 sarcoidosis patients in this study.

Figure 7. Representative flow cytometry analysis of BALF (A) and MLN (B) from one sarcoidosis patient and one control. Abbreviations: CCR: C-C chemokine receptor, BALF: broncho-alveolar lavage fluid, MLN: mediastinal lymph nodes, SRC: sarcoidosis, Ctrl: control.

Figure 8. Proportions of total CCR6+ and Th1 cells were determined in total memory CD4+ T cells from sarcoidosis PB, MLN and

BALF. A-B. Proportions of total CCR6+ and Th1 cells of total memory CD4+ T cells. Statistics: Horizontal lines indicate median values and significance was determined using a Mann-Whitney U test, * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. Data are from 35 (PB), 17 (MLN) and 36 (BALF) patients.

- 5 Abbreviations: CCR: C-C chemokine receptor, PB: peripheral blood, MLN: mediastinal lymph nodes, BALF: broncho-alveolar lavage fluid, DP: double-positive, Th: T helper.

Figure 9. Proportions Th17 and Th17.1 cells were determined in total memory CD4+ T cells from sarcoidosis patient that donated either both
 10 PB and MLN (n=17) or PB and BALF (n=15). A-B. Proportions of Th17 and Th17.1 cells of total memory CD4+ T cells in PB and MLN of 17 sarcoidosis patients. C-D. Proportions of Th17 and Th17.1 cells of total memory CD4+ T cells in PB and BALF of 15 sarcoidosis patients. Statistics: Significance between median values of paired samples was determined using a Wilcoxon
 15 signed rank test, * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. Abbreviations: PB: peripheral blood, MLN: mediastinal lymph nodes, BALF: broncho-alveolar lavage fluid, Th: T helper.

Figure 10. Disease course of a subgroup (n=25) of patients was determined 2 years after study inclusion. Resolution of disease (n=7) was
 20 defined by the absence of abnormalities on the chest X-ray and clinical symptoms. Patients with residual abnormalities on chest X-ray, but without need for treatment were designated as non-progressive chronic (n=11); and patients with need for treatment as progressive chronic (n=7). A. Proportions Th17 cells of total memory CD4+ T cells at time of diagnosis. B.
 25 Ratio of proportions Th17.1 versus Th17 cells. Statistics: Data are presented as boxplots and whiskers that show the 10-90 percentile of the data. Significance was determined using a Mann-Whitney U test. Abbreviations: BALF: bronchoalveolar lavage fluid, Th: T helper, SRC: sarcoidosis.

Figure 11 shows the pulmonary function (FVC percent predicted)
 30 and the treatment regimen of the patient described in Example 2.

Figure 12 shows the ¹⁸F-FDG-PET scan of the patient described in Example 2 at November 2017 (prior to baricitinib treatment) and March of 2018 (following 3 months of baricitinib treatment).

Figure 13 shows the targets of Baricitinib in sarcoid granuloma
5 pathogenesis.

Figure 14 shows the effect of tofacitinib on the mRNA expression of IFN- γ (relative to 18S expression) in Th17, Th17.1 and Th1 cells as described in Example 3.

Figure 15 shows the effects of baricitinib, tofacitinib and filgotinib
10 on STAT1 phosphorylation in IFN- γ stimulated monocytes of healthy subjects and sarcoidosis patients (top graph), and the effects of baricitinib, tofacitinib and filgotinib on STAT5 phosphorylation in naïve IL-2 stimulated CD4 T-cells of healthy subjects and sarcoidosis patients (bottom graph) as described in Example 4.

15

DETAILED DESCRIPTION OF THE INVENTION

Disease diagnosis and prognosis

The term “pulmonary sarcoidosis”, abbreviated “PS” is used herein in their art-recognized meaning, and denotes a disease involving
20 abnormal collections of inflammatory cells that form lumps known as granulomas. The cause of PS is unknown. The disease usually begins in the lungs, skin, or lymph nodes, and can manifest itself throughout the body. Multiple complaints may be present with sarcoidosis in general. The most common is fatigue, which can last for a long time even if disease activity is
25 no longer present. Overall malaise, shortness of breath, joint complaints, temperature increase, weight loss and skin complaints may be present. In general, the prognosis is good, and especially the acute form (see below) usually causes few problems; the complaints will gradually decrease automatically. If sarcoidosis is present in the heart, kidneys, liver and / or
30 central nervous system, or extensive presence in the lungs, then the

outcome is less favorable. In sarcoidosis, staging is a way to indicate the location of granulomas- the lungs, the lymph nodes, or both- and the nature of the disease, and unlike in cancer, staging is no direct indication of severity. Chest radiograph changes are divided into four stages: 1.bihilar lymphadenopathy (granulomas in the lymph nodes); 2.bihilar lymphadenopathy and reticulonodular infiltrates (granulomas in the lungs); 3.bilateral pulmonary infiltrates (granulomas in the lungs, but not in the lymph nodes); 4.fibrocystic sarcoidosis typically with upward hilar retraction, cystic and bullous changes (scarring in the lungs- pulmonary fibrosis - which is irreversible). Individuals with stages 2 and 3 radiographs often have the chronic, progressive disease. As indicated, the radiograph stages are not a progression. A patient might have stage two sarcoidosis, and then with treatment or time become stage one, or three, or go into remission altogether. Sometimes there is an acute syndrome with fever, general malaise, painful and swollen joints, particularly affecting the ankles, with red to purple patches on the skin, called erythema nodosum. This pattern is also referred to as Löfgren Syndrome. The symptoms can be present for a while, but usually disappear within two years, even without treatment. If symptoms last longer than 2 years, the disease is referred to as having a chronic pattern. It is an aspect of this invention to provide a prognostic biomarker for this chronic form or status of sarcoidosis, preferably in all stages of the disease, more preferably in the progressive stages. The term chronic sarcoidosis refers to a multisystemic disorder of unknown cause that is characterized by the formation of immune granulomas in involved organs (sarcoidosis), wherein the symptoms develop gradually over a time period of at least 2 years, and get worse over time to the point where the patient becomes severely affected. This latter aspect is also indicated as chronic progressive.

Aspects of this invention are preferably aimed at the chronic progressive form of PS, also referred to as chronic sarcoidosis herein, which term does not refer to the acute form of PS referred to as Löfgren Syndrome.

Diagnosis of PS is established when clinicoradiological findings
5 are supported by histological evidence of noncaseating epithelioid cell granulomas. The diagnosis of pulmonary sarcoidosis is preferably conform guidelines of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Generally, sonographic features
10 of mediastinal or hilar lymph nodes are obtained, and presence of granules in lymph nodes on endobronchial ultrasound (EBUS) has a high specificity (99.3%) for the diagnosis of sarcoidosis.

Prognosis of PS, in aspects of this invention is performed based on the biomarker level (Th17.1 quantity or Th17.1/Th1 ratio) as part of the
15 total population of T cells, preferably of total CD4⁺ T cells, more preferably of total CD4⁺ T cells, more preferably as part of BALF or MLN.

The term “total memory CD4⁺ T cells”, as used herein, indicates the memory (e.g. CD45RA⁻) T cell subset of T helper (CD4⁺; Th) cells within the T cell (CD3⁺) fraction of lymphocytes, and in a preferred embodiment, as
20 explained in Figure 5, refers to the combined subpopulations of CD45RA⁻ FoxP3⁻ Memory T cells, plus CD45RA⁻FoxP3^{int} Activated (non-suppressive/non-regulatory) T cells, within the total CD3⁺CD4⁺ T cell population with the exclusion of suppressive or regulatory T (Tregs) cells. Tregs could contaminate the Th17.1 cell evaluation, and are therefore
25 preferably excluded.

In Figure 5, CD45RA was used to differentiate the naïve (CD45RA⁺) from memory (CD45RA⁻) T cell populations, whereas transcriptional factor FoxP3 served as a lineage specification factor of (regulatory) Treg cells. Hence, in the context of preferred embodiments of
30 this invention, aimed at enumerating the Th17.1 cell proportions in a

sample from an individual for use as a diagnostic and/or prognostic marker in sarcoidosis, the term “total memory CD4⁺ T cells” preferably does not include CD45RA⁺FoxP3⁻ Naïve T cells, CD45RA⁺FoxP3^{int} Naïve Tregs, and CD45RA⁻FoxP3^{high} Activated Tregs. One of ordinary skill in the art will
5 understand that alternative markers for memory T cells, such as CD45RO, may be used on aspects of this invention. Th cell subsets can be classified according to 1) chemokine-receptor expression and/or 2) transcription factor expression. Based on chemokine-receptor expression (including the C-C chemokine receptor (CCR), and CXC chemokine receptor (CXCR), in
10 particular CCR6, CCR4, and CXCR3, the following subsets can be determined: CCR6⁻ memory T cells subsets include CCR4⁻CXCR3⁺ Th1 cells and CCR4⁺CXCR3⁻ Th2 cells; CCR6⁺ T cell subsets include CCR4⁺CXCR3⁻ Th17 cells, CCR4⁺CXCR3⁺ double-positive Th cells and CCR4⁻CXCR3⁺ Th17.1 cells.

15 Based on transcription factor expression, Th1 cells are identified as T-bet positive, Th2 cells as GATA3 positive, Th17 cells as ROR γ t positive and Th17.1 cells express both T-bet and ROR γ t.

 One of ordinary skill in the art will also understand that enumeration of Th17.1 cells in a sample in accordance with this invention
20 does not necessarily require marker-specific immunological gating methods, such as those based on flow cytometry, described herein. Alternative methods for enumerating Th17.1 cells based on alternate gating methods or markers, even by other means than flow cytometry, are envisioned within the context of the present invention. Such alternate methods could be based
25 on detection of Th17.1-specific gene expression profiles within the cell, production of (a combination of) specific proteins within the cell, or alternative cell-surface markers for either alternative gating or physical separation of cells that are not of interest.

 The term “T cell”, is used herein in its art-recognized meaning,
30 and denotes a CD3⁺ lymphocyte. Lymphocytes (T cells, B cells, and NK cells)

constitute the majority of the peripheral blood mononuclear cells (PBMCs). The T cell fraction is further subdivided into CD4⁺ and CD8⁺ T cells. CD4⁺ T cells are known as T helper (Th) cells and are further classified into various functional subtypes based on the expression profiles of specific cytokines, surface markers, or transcription factors. These include Th1 and Th17 cells as well as other described subpopulations such as Treg (regulatory T) cells, Th2, Th9, follicular helper, and TR1 types.

The term "Th17.1 cell", is used herein in its art-recognized meaning, and denotes a IFN- γ -producing Th17 cell, also classified as a CCR4⁺CXCR3⁺ subset of the CCR6⁺ memory T cells within the total memory CD4⁺ T cell (Th) population, or total T cell population in the BALF. As indicated above, CCR6⁺ T cells include a CCR4⁺ and CXCR3⁺ subset designated Th17.1 cells. Within Th17.1 cells, also different phenotypes of cells can be present: e.g. IL-17A⁺/IFN- γ ⁺ (indicated in literature as Th17/Th1-cells) cells and IFN- γ single-positive cells. CCR6⁺CCR4⁺CXCR3⁺ DP cells are thought to reflect an intermediate Th17 and Th17.1 cell population, expressing both ROR γ t/IL-17A and T-bet/IFN- γ . Th17.1 cells are not one single cell type, Th17-lineage cells are highly plastic and can change phenotype quickly. From benign to pathogenic

Interleukin-23 (IL-23) is required for terminal differentiation of Th17 cells and maintenance of the Th17 phenotype. IL-23 also induces IFN- γ production in Th17 cells, which then become Th17.1-cells. IL-23, which is composed of p19 and p40 subunits, is a proinflammatory cytokine that contributes to the formation and maintenance of Th17(1) cells in inflammatory autoimmune diseases. As such, the IL-23/Th17 pathway is a therapeutic target for the treatment of inflammatory arthritis. In fact, IL-23 plays an important role in Th17 cell signaling pathways, known to be up-regulated in, for instance, psoriasis and also within sarcoidosis. Antibodies that inhibit interleukin-23 can inhibit the expression of molecular and clinical disease characteristics associated with psoriasis. Guselkumab

(CNTO 1959, Janssen Research and Development) is a fully human IgG1 lambda monoclonal antibody that inhibits interleukin-23-specific intracellular and downstream signaling.

5 An aspect of the present invention pertains to the use of IL-23 inhibitors in the treatment of pulmonary sarcoidosis, through inhibition of the terminal differentiation of Th17 cells into Th17.1 cells.

The term “specific interleukin 23 blocker” is used in its art-recognized meaning, and refers to a compound that antagonizes or inhibits the activity of interleukin 23 (also referred to as IL-23, IL-23A, or IL23P19, all of which terms are synonymous herein). IL-23 is a heterodimeric cytokine composed of an IL12B (IL-12p40) subunit (that is shared with IL-12) and the IL23A (IL-23p19) subunit. In order to antagonize IL-23, recombinant, it is common knowledge to use fully human or humanized monoclonal antibodies (mAbs) designed to target either the p40 subunit or the p19 subunit. Many mAbs are now in clinical stage or are used for treatment of inflammatory diseases in which IL-23 is believed to play a pivotal role. The effect of IL-23 blockers in mitigating a large number of inflammatory diseases is now well established and recognized. A specific IL-23 blocker, as used herein, refers to a compound that antagonizes or inhibits the activity of interleukin 23, while preferably not affecting the activity of IL-12. Well known examples of such compounds are tildrakizumab (Ilumya™, Merck & Co, Inc.) and guselkumab (Tremfya™, Janssen). Administration of tildrakizumab is usually by subcutaneous injection, at a recommended dose of 100 mg at weeks 0, 4, and every twelve weeks thereafter. Tremfya™ is also administered as a 100 mg subcutaneous injection, with dosing regime of once every eight weeks, following two starter doses at weeks 0 and 4. The skilled person will understand that therapeutically effective dose for the treatment of sarcoidosis can be determined using routine experimentation, and taking into account the

pharmacodynamics of the compound. A suitable dose is 100 mg of the specific interleukin 23 blocker in the form of a humanized mAb.

The skilled person will understand that the term “specific interleukin 23 blocker” includes reference to anti-IL-23(p19) specific
5 antibodies tildrakizumab and guselkumab and antibodies equivalent thereto.

The skilled person will also recognize the existence of therapeutic antibodies such as ustekinumab and briakinumab, which are human monoclonal antibodies that neutralize both IL-12 as well as IL-23, and
10 hence, show IL23/IL-12 cross-reactivity. Specific interleukin 23 blockers as used herein do not show this cross reactivity to IL-12, and are therefore referred to as being IL-23-specific. Hence, treatment aspects of this invention are preferably not directed to the use of interleukin 23 blockers showing IL23/IL-12 cross-reactivity.

15 The skilled person will also understand that the term “specific interleukin 23 blocker” in the context of this invention refers to compounds, in particular antibodies, that prevent Th17-lineage subset differentiation into Th17.1 cells. Methods to determine such blocking or inhibition of differentiation are well within reach of the average skilled artisan, and may
20 include methods as described herein for typing samples of patients suffering from sarcoidosis. In vitro techniques permissive of Th17-lineage subset differentiation towards the Th17.1 phenotype, such as for instance described herein may be used wherein Th17 cells are brought under differentiation conditions in the presence (positive blocking test) and absence (negative
25 control) of the specific interleukin 23 blocker, and wherein blocking of the differentiation is indicative of the suitability of compound for potential use in therapeutic methods as described herein.

A further aspect of this invention pertains to treatment aspects comprising the use of a JAK/STAT inhibitor. The term “JAK/STAT
30 inhibitor” is used in its art-recognized meaning, and refers to a Janus kinase

inhibitor, also known as JAK inhibitor or jakinib, which compounds function by inhibiting the activity of one or more of the Janus kinase family of enzymes. It is currently established that the JAK family consists of four members, which mediate signaling of various cytokines and growth factors in humans. Cytokines bind to their respective receptors, thereby activating JAK complexes, formed from combinations of JAK1, JAK2, JAK3, and tyrosine-protein kinase (TYK)2. Activated JAK complexes promote phosphorylation of signal transducers and activators of transcription (STATs), which regulate the expression of target genes. For instance, IFN- γ signaling is mediated by JAK1- JAK2 and STAT1 phosphorylation.

The term “JAK1 inhibitor”, as used herein, is used in its art-recognized meaning, and refers to a Janus kinase inhibitor or jakinib, i.e. a small-molecule drug that inhibits the activity of its target JAK1, a kinase that binds to the intracellular domain of the Type I/II cytokine receptor, thereby blocking cytokine signaling. The JAK1 inhibitor prevents JAK1 from phosphorylating STATs and other substrates, so that intracellular signals cannot be transduced. Because JAKs are critical for multiple different cytokines, jakinibs block the action of a range of cytokines. The selectivity of JAK inhibitors is extensively reviewed by Schwartz et al., 2017 (Nat Rev Drug Discov. 2017 December 28; 17(1):1-41), to which explicit reference is made in the context of the term JAK1 inhibitor. In this review many first-generation jakinibs that block multiple JAKs and therefore inhibit the actions of a large variety of cytokines, as well as several newer pan-JAK inhibitors are indicated in Table 3 and Table 4 of Schwartz et al., 2017. Express reference is made to these Tables for indicating suitable JAK1 inhibitors for use in this invention. Suitable JAK1 inhibitors for use in this invention include jakinibs that block JAK1, optionally in addition to blocking other kinases. Examples of suitable first-generation JAK1 inhibitors include ruxolitinib, tofacitinib, and baricitinib, which block JAK1-JAK2, JAK1-JAK3 and JAK1-JAK2, respectively. A newer pan-jakinib is

peficitinib which has IC₅₀ of 3.9, 5.0, 0.71 and 4.8 nmol/L for JAK1, JAK2, JAK3 and TYK2 enzymatic activity respectively. A variety of next-gen JAK inhibitors is also indicated in Tables 3 and 4 of Schwartz et al., 2017, including small molecule drugs that are selective for one particular JAK isoform. Filgotinib, Upadacitinib, and Solcitinib are examples thereof and selectively block JAK1, and are referred to herein as JAK1-selective inhibitors, all of which are useful in aspects of this invention. One of skill in the art will thus understand that the term “JAK1 inhibitor” includes reference to a JAK1-selective inhibitor, a JAK1-JAK2 inhibitor, a JAK1-JAK3 inhibitor, and a JAK1-TYK2 inhibitor.

The present inventors set out to investigate if JAK inhibition could be used in treating chronic granulomatous disease, in particular chronic sarcoidosis. It was found that while such patients can be non-responsive to anti-TNF α therapy, e.g. based on infliximab or adalimumab, JAK1-2 inhibition with baricitinib (LY3009104; CAS# 1187594-09-7) proved an effective therapy (see Examples below). Baricitinib blocks IFN- γ -signaling. As the present inventors have found that increased proportions of IFN- γ -producing Th17.1-cells correlate with patients developing chronic sarcoidosis, treatment aspects involving the use of a JAK/STAT inhibitor are aimed at mitigating the effect IFN- γ which is best achieved by use of a JAK1 and/or JAK2 inhibitor, as it is well established that the IFN- γ receptor activates JAK1 and JAK2. Hence, a preferred compound for use in aspects of this invention relating to JAK/STAT inhibitors is baricitinib. Baricitinib is a low-molecular-weight compound that binds to the ATP-binding site of the Janus kinase. Baricitinib is a reversible inhibitor of the Janus kinases JAK1 and JAK2. In aspects of this invention, the JAK/STAT inhibitor is preferably a JAK1 and JAK2 (i.e. a JAK1-2 combined) inhibitor or a JAK1 or JAK2 (i.e. a JAK1/2) inhibitor, more preferably a JAK1 inhibitor.

Although safety-data on long-term baricitinib treatment are still limited, an acceptable safety profile is emerging from the studies in RA,

wherein once daily oral doses of baricitinib 2 - 4 mg are provided (Dougados et al. 2017. Ann Rheum Dis 76:88-95; Genovese et al. 2016. N Engl J Med 374:1243-52; Taylor et al. 2017. N Engl J Med;376:652-62). Generally, oral doses between 0.1 to 20 mg per day of the JAK/STAT inhibitor can be
5 applied in treatment of sarcoidosis, preferably chronic sarcoidosis, with preferred doses ranging from 1-10 mg once daily, more preferably 2-5 mg once daily.

The skilled artisan will recognize that other JAK/STAT inhibitors may be equally efficacious in treatment aspects of this invention. Many JAK
10 inhibitors are now in clinical stage or are used for treatment of inflammatory diseases. The effect of JAK inhibitors in the treatment of diseases such as RA, psoriasis, and inflammatory bowel disease (IBD) is well established and recognized. Well known examples of such JAK inhibitors include Tofacinib (CP-690550; CAS# 477600-75-2) and Peficitinib
15 (ASP015K, JNJ-54781532; CAS# 944118-01-8), both of which target JAK1 and JAK3. Further well known examples of such JAK inhibitors also include Filgotinib (GLPG0634; CAS#: 1206161-97-8) and Upadacitinib (ABT-494; CAS# 1310726-60-3), both of which target JAK1. Any of these may be used in aspects of this invention, preferably the more specific JAK1 inhibitors.
20 As indicated herein, those that interfere with cytokine receptor signaling of IFN- γ (JAK1, JAK2, or JAK1-JAK2) are preferred.

The skilled person will also understand that, as explained above, treating sarcoidosis in the context of this invention by interfering with IFN- γ receptor signaling is aimed at inhibiting or blocking the IFN- γ induced
25 STAT1 expression. Hence, the term "JAK/STAT inhibitor" in the context of this invention refers to compounds that prevent JAK signaling through IFN- γ . Methods to determine whether a compound exhibits such blocking or inhibiting effect are well within reach of the average skilled artisan, and may include methods wherein inhibition of intracellular STAT1
30 phosphorylation by a test inhibitor in response to stimulation of whole cells

ex vivo with IFN- γ is measured, e.g., by using flow cytometry as described in Vakkila et al. 2008 Scand J Immunol 67:95–102, and wherein inhibition of intracellular STAT phosphorylation, preferably STAT1 phosphorylation (pSTAT1), is indicative of the suitability of the tested JAK/STAT inhibitor
5 as a therapeutic agent in treating sarcoidosis, preferably chronic sarcoidosis as described herein. An alternative method to measuring pSTAT1 inhibition by a test inhibitor for use in this invention, expression of STAT1 controlled genes or proteins, preferably CXCL9 and CXCL10, may be determined, in particular the increase or decrease in such expression, preferably a decrease
10 in response to the administration of the JAK inhibitor, as described in detail in the legend to Figure E1 in Meesilpavikkai, 2018 J Allergy Clin Immunol, Volume 142(1): pp 328–330.e2.

Alternatively to measuring pSTAT1 inhibition, one may measure pSTAT3 and pSTAT5 inhibition as indication of interference with cytokine
15 receptor signaling as these are signaling intermediates of IL-6 (and IL-23, a.o.) and IL-2 (and IL-7, a.o.) respectively.

Samples for diagnostic and prognostic purpose

The term “sample”, as used herein, refers to a biological sample
20 encompassing a variety of sample types obtained from an individual and can be used in a diagnostic or monitoring assay. The term encompasses blood and other liquid samples of biological origin, solid tissue samples, such as a biopsy specimen, or aspirate, or tissue cultures or cells derived therefrom and the progeny thereof. The term encompasses samples that have been
25 manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components. The term encompasses a clinical sample, and also includes cells in cell culture, cell supernatants, cell lysates, serum, plasma, biological fluids, and tissue samples.

The term “mediastinal lymph node” (abbr. MLN) is used herein in its art recognized meaning, and denotes several lymph node groups in the mediastinum, especially along the trachea, along the esophagus and between the lung and the diaphragm. As lymph is drained from the lung tissue it passes through subsegmental, segmental, lobar and interlobar lymph nodes to the hilar lymph nodes (HLN), which are located around the hilum of each lung. The lymph flows subsequently to the MLN from which the lymph drains to the left subclavian vein through lymphatic ducts.

One of skill in the art will understand that sampling of lymph nodes of the lungs in aspects of this invention may entail sampling of HLN as well as sampling of MLN. Cell samples of such lymph nodes may be obtained through fine-needle aspiration. Sampling of the MLN and obtaining an MLN aspirate is a preferred embodiment in aspects of this invention.

An even more preferred and less invasive sampling method is through bronchoalveolar lavage (BAL), a procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is injected into a small part of the lung and then collected for examination. Bronchoalveolar lavage is commonly used in immunological research as a means of sampling T-cell populations. It is not a standard procedure when diagnosing sarcoidosis, as it is not always necessary.

Suitable samples for use in methods of the present invention may thus include, but are not limited to samples of T cells obtained from peripheral blood (PB), lungs, HLN or MLN. Samples of T cells in the lungs through procurement of BALF is preferred.

Methods of determining Th17.1 cell proportions

The term “typing”, as used herein, refers to differentiating or stratifying between individuals according to diagnostic or prognostic disease status. The typing is preferably based on a comparison of (i) a biomarker

level in a sample of an individual and (ii) a biomarker control value.

Preferably, the typing differentiates individuals suffering, or suspected of suffering from, PS, in a group having an increased risk of developing a chronic disease pattern and a group not having such an increased risk.

5 It is an aspect of this invention that the number of Th17.1 cells in a sample of an individual is measured as the biomarker for determining the diagnostic or prognostic disease status. Such measurements, however, may but do not necessarily need to provide the exact cell number as an outcome. The present inventors have found that it is the proportion of Th17.1 cells,
10 relative to other T cells in the sample of a subject, that – when compared to the corresponding proportion of Th17.1 cells in samples of healthy subjects or patients undergoing disease resolution – are elevated at time of diagnosis in patients subsequently developing chronic, in particular progressive, sarcoidosis.

15 Hence, in preferred embodiments of aspects of this invention, Th17.1 cells are preferably enumerated as a proportion of the total T cell population, even more preferably as a proportion of the total memory CD4+ T cell population as defined herein. Still, more preferably, Th17.1 cells are enumerated as a proportion of the total Th1 and/or Th17 cell
20 subpopulations.

In principle, any T cell subset can be used in determining the proportion of Th17.1 cells in aspects of this invention, including but not limited to:

- CCR6⁻ memory T cells subsets, including
 - 25 ○ CCR4⁻CXCR3⁺ Th1 cells
 - CCR4⁺CXCR3⁻ Th2 cells;
- CCR6⁺ T cell subsets, including
 - CCR4⁺CXCR3⁻ Th17 cells,
 - CCR4⁺CXCR3⁺ DP Th cells
 - 30 ○ Th17.1 cells in a healthy individual.

It is preferred that the number or proportion of Th17.1 cells in a sample of an individual is determined by flow cytometry. The benefit of flow cytometric analysis is that multiple cell (surface) markers can be determined simultaneously in a large number of cells, providing for an appropriate method for quantifying cell types. Flow cytometry data analysis is built upon the principle of gating. Gates and regions are placed around populations of cells with common characteristics, usually forward scatter, side scatter and marker expression, to investigate and to quantify these populations of interest.

In preferred embodiments of aspects of the present invention, the proportion of Th17.1 cells in the total T cell population in the BALF, more preferably in the total memory CD4⁺ T cell or Th population is determined, as a proportion of other T cell populations, preferably wherein the following Th cell subpopulations are enumerated by flow cytometry (cells classified according to chemokine-receptor expression):

- Th1: CCR6-CCR4-CXCR3+;
- Th17: CCR6+CCR4+CXCR3-; and
- Th17.1: CCR6+CCR4-CXCR3+.

One of ordinary skill in the art is capable of determining the various T cell populations denoted herein, for instance by using the antibodies identified in Table 2 in the Experimental section herein below. The skilled person is aware that alternative antibodies having the desired marker specificity can be used.

Using the methods described herein, the skilled person will be able to determine the presence or absence of higher proportions of Th17.1 cells in samples of sarcoidosis patients compared to control samples. Using the methods described herein, the skilled person will be able to determine when patients are at risk of developing chronic sarcoidosis, and specifically progressive chronic sarcoidosis with need for treatment, by determining the

presence of significantly higher Th17.1 proportions (e.g. Th17.1/Th1) relative to control values, e.g. in patients that show disease resolution.

It is also an aspect of this invention to provide a biomarker for progressive chronic sarcoidosis which is a lower proportion of Th1 cells.

5 It is also an aspect of this invention to provide a biomarker for progressive chronic sarcoidosis which is a higher proportion of Th17.1 cells in combination with a lower proportion of Th1 cells proportions, resulting in an increased Th17.1/Th1 ratio in patients at risk of developing chronic disease. Of all these, Th17.1 cells (i.e. IFN- γ -producing Th17 cells;
10 expressing CCR6, CXCR3, RORC and TBX21, but not CCR4) are most informative in diagnosis of disease occurrence and prediction of progression/prognosis of pulmonary sarcoidosis. In relation to this finding, it is of note that Th17.1-cells have a pathogenic phenotype, and Th17.1-cells are unresponsive to corticosteroid treatment.

15

Therapeutic targets and therapy

Based on functional prediction and protein network analyses, two specific SNPs in a candidate susceptibility gene predict a prominent role for IL-23/Th17-signaling pathway in the genetic aetiology of sarcoidosis
20 (Fischer et al 2011 and 2015). The present inventors consider that Th17.1-cells may constitute a suitable therapeutic target, for instance by using biologicals. It is therefore an aspect of this invention to treat or prevent progressive, chronic forms of sarcoidosis with IL23 inhibitors, such as anti-IL23 antibodies. A suitable biological having such activity includes
25 Guselkumab.

It is an aspect of this invention to provide a method for typing a pulmonary sarcoidosis (PS) patient as having an increased risk of developing a chronic, progressive disease pattern, and subsequently treating or preventing the development of chronic, progressive disease pattern in an

individual diagnosed as having such an increased risk by subjecting said subject to IL-23 inhibition therapy.

Also, the present invention considers that the genetic variations within the IL23R gene or other genes involved in the IL-23/Th17-signaling pathway predispose for (chronic) sarcoidosis. Hence, it is an aspect of this invention to reduce the number of Th17.1 cells in a patient for the purpose of supporting treatment of (chronic) sarcoidosis, by replacing, complementing or repairing genetic anomalies in the IL23R gene through gene therapy, Crispr/CAS or RNA interference technology.

For the purpose of clarity and a concise description, features are described herein as part of the same or separate aspects and preferred embodiments thereof, however, it will be appreciated that the scope of the invention may include embodiments having combinations of all or some of the features described.

The content of the documents referred to herein is incorporated by reference.

EXAMPLES

Example 1. Th17.1 ratios in BALF and MLN are linked to pulmonary sarcoidosis

Study design and subjects

Patients with pulmonary sarcoidosis were included at time of diagnosis. The diagnosis of sarcoidosis was made conform to the guidelines of the ATS/ERS/WASOG.

Exclusion criteria were use of immunomodulatory medication 3 months prior to study inclusion; respiratory tract infection 4 weeks prior to study inclusion; concomitant pulmonary disease (including chronic obstructive pulmonary disorder and asthma), autoimmune diseases, malignancies, human immunodeficiency virus seropositivity, pregnancy, and allergies.

For this study, in total 55 sarcoidosis patients donated BALF, MLN-derived fine-needle aspiration (FNA) or peripheral blood (PB). In total 32 of these patients donated material of multiple organs, see figure 6.

Disease course of a subgroup (n=25 with data available) of patients was determined 2 years after study inclusion. Resolution of disease was defined by the absence of abnormalities on chest X-ray and clinical symptoms. Patients with residual abnormalities on chest X-ray, but without need for treatment were designated as non-progressive chronic; and patients with need for treatment as progressive chronic.

Control MLN were collected from 22 lung transplantation donors without signs of pulmonary inflammation (routinely assessed by a chest X-ray and bronchoscopy).

The Medical Ethical Committee of the Erasmus MC Rotterdam approved this study. Written informed consent was obtained from every participant before study inclusion. Further subject characteristics are shown in Table 1.

Table 1. Study subject characteristics

Subject Characteristics	Ctrl (n=22)	Sarcoidosis (n=55)
Median age (min-max)	47 (15-70)	43 (24-75)
Sex (Male/Female)	6/16	36/19
Race (n (% of total))		
White		38 (69)
Black		8 (15)
Other		5 (9)
Unknown		4 (7)
Scadding Stage (n (% of total))		
Stage 0		5 (9) [†]
Stage I		20 (36)
Stage II		23 (42)
Stage III		4 (7)
Unknown		3 (6) ^{††}
Diagnosis was assessed by (n (% of total))		
TBB-EBB		17 (31)
BALF CD4/CD8 > 3,5		8 (15)

E(B)US-FNA		26 (47)
Other (e.g. mediastinoscopy, other biopsy)		4 (7)
Extrathoracic involvement (n (% of total))		
No/Yes		21/34
Skin		8 (15)
Eyes		16 (29)
Articular \$		22 (40)
Central nervous system		3 (6)
Other		6 (11)

Study materials

Bronchoscopy with BAL was performed as previously described [Ten Berge B, et al. 2012. Rheumatology (Oxford) 2012;51(1):37-46]. BALF
 5 cells and PB were processed as previously described [Ten Berge B, et al. 2012. Rheumatology (Oxford) 2012;51(1):37-46]. Oesophageal or endobronchial ultrasound guided (EUS- or EBUS)-FNA from draining MLN were performed with a 22G (or 19G) needle. MLN aspirates were filtered through a 100 µm cell strainer (BD Biosciences) and centrifuged. Cells were
 10 stored at -150 °C. Control MLN were collected from lung transplantation donors. Control MLN were processed as lymph node aspirates.

Flow cytometry

BALF, MLN and PB mononuclear cells were stained for intra- and
 15 extracellular markers using the antibodies shown in Table 2.

Table 2. Overview antibodies

Company	Antigen	Fluor chrome	Clone
eBiosciences ¹	CD3	APC-eFluor780	SK7
	CD4	AF700	OKT4
	FoxP3	PE	236A/E7
	CTLA4	PerCp-eFluor710	14D3
BD biosciences ²	CCR6	APC	11A9
	CXCR3	BV711	1C6/CXCR3
	Ki67	Pe-Cy7	B56
	CD28	BV605	CD28.2

	PD-1	BV786	EH12.1
	PD-1	BV711	EH12.1
	CD25	PE-Cy7	M-A251
	CD25	BV650	M-A251
	CD278 (ICOS)	BV650	DX29
R&D ³	CCR4	FITC	205410
Biolegend ⁴	CXCR3	BV421	G025H7
Invitrogen ⁵	CD45RA	PE-Texas Red	MEM-56

1, Thermo Fisher Scientific Inc., Waltham, USA; 2, Becton, Dickinson and Company, Franklin Lakes, USA; 3, R&D Systems Inc., Minneapolis, USA; 4, BioLegend, Inc., San Diego, USA; 5, Thermo Fisher Scientific Inc..

5 T helper subsets of CD45RA-FoxP3^{low/int} total memory Th cells (Figure 5A) were identified on the basis of chemokine-receptor expression (Figure 5B). Fixable Aqua Dead Cell Stain kit for 405 nm (Invitrogen, Molecular Probes) was used as live-dead marker. At least 100.000 cells per sample were measured on a Flow cytometer LSRII (BD Biosciences), and the
 10 mean fluorescent intensity of cytotoxic T-lymphocyte antigen 4 (CTLA4) was standardized to average expression in healthy control PB cells, stated as delta (Δ) MFI. Ki67 staining was used to assess the proliferative status of cell subsets.

15 Statistical analyses

Comparisons were performed using a Mann-Whitney U test or Wilcoxon signed rank test. p-values were two-sided, and analyses were performed using IBM SPSS Statistics 21. p<0.05 was considered statistically significant.

20

Results

1. Significant increase of Th17.1 cells in sarcoidosis MLN compared with controls

We previously found an increased presence of IFN- γ + Th17.1 cells
 25 in sarcoidosis BALF compared with controls [Ramstein J, et al. 2015. Am J

Respir Crit Care Med 2015 doi: 10.1164/rccm.201507-1499OC]. We questioned whether Th17.1 cells are also increased in sarcoidosis MLN compared with controls. Since Th17.1 cells are primarily thought to be progeny of Th17 cells, we aimed to quantify Th1, Th2 and all CCR6+ Th subpopulations in sarcoidosis BALF (n=36), sarcoidosis MLN (n=17) and control MLN (n=22) (for gating strategy see Figure E2). The CCR6+ double-positive (DP) cells are thought to reflect an intermediate stage between Th17 and Th17.1 cells.

In sarcoidosis BALF Th17.1 cell proportions were higher than either Th1, Th2, Th17 or CCR6+ DP cells (Figure 1A) and thus represented the most predominant Th population in BALF (Figure 1B).

Similar to sarcoidosis BALF as described earlier herein, sarcoidosis MLN contained higher proportions of CCR6+ Th cells than control MLN (Figure 1C). Importantly, we identified significantly increased proportions of Th17.1 cells in sarcoidosis MLN compared with control MLN (Figure 1D). Furthermore, sarcoidosis MLN contains increased proportions of Th17.1 precursor cells, i.e. Th17 and CCR6+ DP cells, compared with controls (Figure 1D/E). In sarcoidosis MLN, Th1 cell proportions were significantly decreased compared with controls, although Th1 cells remained (like in controls) the most prominent memory T cell population (Figure 1D/E).

Taken together, these data show that sarcoidosis MLN contain increased proportions of Th17.1 cells compared with controls, paralleling the lungs.

2. Th17.1 cells and CCR6+ DP cells are highly proliferative in sarcoidosis MLN

The increase of Th17.1 cells in sarcoidosis MLN could be caused by enhanced proliferation, therefore we assessed proliferative status of T cell subsets. Proportions of proliferative (Ki-67+) CD4+ memory T cells were

significantly increased in sarcoidosis MLN compared with controls (Figure 2A). Interestingly, specifically Th17.1 cells and CCR6+ DP cells exhibited high fractions of proliferating Ki-67+ cells compared with controls (Figure 2B/C). This was particularly striking for the Th17.1 subpopulation, which in
5 controls contained only very few Ki-67+ cells. However, CCR6+ DP cells contained the highest fraction of proliferating cells (~15%, which was significantly higher than any of the other T cell subsets) in sarcoidosis MLN (Figure 2B). Interestingly, CCR6+ DP cells also showed decreased CTLA4 expression in sarcoidosis MLN compared with controls (Figure 2D) as we
10 have previously also shown for Th17 cells [Broos CE, et al. 2015. Am J Respir Crit Care Med 2015;192(6):763-65].

In summary, ex-vivo phenotyping identified Th17.1 cells as a highly proliferative Th subset in MLN of sarcoidosis patients compared with controls. Furthermore, CCR6+ DP cells also proliferate highly compared
15 with other Th cell subsets in sarcoidosis MLN.

3. Higher Th17.1 cell proportions in sarcoidosis MLN and BALF than PB

Next, we aimed to quantify Th17-derived CCR6+ populations
20 within sarcoidosis PB, MLN, and BALF. Remarkably, in sarcoidosis patients, the proportions of memory Th cells that were CCR6+ were significantly higher in BAL (~75%) and MLN (~31%) compared with PB (~19%) (Figure 7A). Whereas Th17 cell proportions were significantly lower in BALF than in MLN and PB (Figure 3A), Th17.1 cells were significantly
25 higher (Figure 3C). Proportions of CCR6+ DP cells were similar in MLN and BALF, but were significantly higher in BALF than PB (Figure 3B). CCR6-Th1 cell proportions were lower in sarcoidosis BALF compared with MLN (Figure 7B). Importantly, paired analyses of the subgroup of patients that donated material of multiple organs (either PB and MLN (n=17) or PB and
30 BALF (n=15)) also showed a significant decrease in Th17 cell and a

significant increase in Th17.1 cell proportions in MLN or BALF compared with PB of the same patient (Figure 7).

Taken together, these data show that Th17.1 cells are not a prominent population in the PB of sarcoidosis patients. Rather, patients
5 show an increase in Th17.1 cells in MLN, which is further enhanced in sarcoidosis lungs (e.g. BALF).

4. Higher BALF Th17.1 cell proportions in patients developing chronic disease than in patients undergoing 10 resolution

As Th17.1 cells are described to be pathogenic and highly present in sarcoidosis lungs, we questioned whether proportions of Th17.1 cells in BALF would associate with disease prognosis. Therefore, we determined the disease course of a subgroup (n=25) of our study cohort at ~2 years clinical
15 follow-up.

Interestingly, in patients developing chronic sarcoidosis, and specifically progressive chronic sarcoidosis with need for treatment, significantly higher BALF Th17.1 proportions were detected at time of diagnosis, compared with patients undergoing resolution (Figure 4A). In
20 contrast, Th1 proportions were lower in patients developing progressive chronic disease than patients undergoing disease resolution (Figure 4B), resulting in an increased Th17.1/Th1 ratio within BALF of patients developing chronic disease (Figure 4C). Although non-significant, Th17
25 proportions also showed a trend to be lower in patients developing chronic disease than in patients undergoing resolution (Figure 9A), and patients developing progressive chronic disease showed a higher Th17.1/Th17 ratio within BALF (Figure 9B).

In conclusion, these data suggest that development of chronic disease is significantly associated with numbers of Th17.1 cells in

sarcoidosis BALF, supporting a pathogenic role for these cells in the development of (chronic) pulmonary sarcoidosis.

Discussion

5 Our study is the first to show that Th17.1 cells are significantly increased in sarcoidosis MLN compared with control MLN, reflecting what we have previously found in sarcoidosis lungs [Ramstein J, et al. 2015. Am J Respir Crit Care Med 2015 doi:10.1164/rccm.201507-1499OC]. Furthermore, Th17.1 cell proportions are highest in the granulomatous BALF when
10 compared with sarcoidosis-derived MLN and PB. Higher proportions of Th17.1 cells in the lungs significantly correlated with development of chronic disease. Together these data suggest that Th17.1 cell proportions in pulmonary sarcoidosis can be evaluated as diagnostic and/or prognostic marker in clinical practice and could serve a new therapeutic target.

15 Since it was recognized that Th17 cells display considerable plasticity and can produce IFN- γ , it has become increasingly clear that IFN- γ -producing Th17 cells play a key role in the development of autoimmune diseases. Interferon- γ -producing Th17 cells, or so called Th17.1 cells, are described to be pathogenic in several autoimmune diseases and chronic
20 inflammatory disorders, including Crohn's disease and arthritis. In a previous study we clarified that specifically CCR6⁺ Th17.1 cells rather than classical CCR6⁻ Th1 cells are the major source for IFN- γ production in sarcoidosis BALF.

 Interestingly, here, we found that in sarcoidosis MLN not only
25 Th17.1 cells, but all CCR6⁺ Th cell subsets, including Th17 and CCR6⁺ DP cells were significantly enhanced compared with control MLN.

 Since Th17 and CCR6⁺ DP cells can be precursor cells of Th17.1 cells, these data suggest that initial Th17-lineage subset differentiation occurs within sarcoidosis MLN.

Next to supporting that Th17 cells are induced within sarcoidosis MLN, our data suggest that chronically inflamed sites such as sarcoidosis lungs (but possibly also granulomatous parts of the MLN) play a role in accelerating Th17.1 cell differentiation by inducing conversion of Th17
5 towards Th17.1 cells. For example, comparing different involved immunological compartments showed that specifically Th17.1 cells were augmented in sarcoidosis lungs compared with MLN and PB. In joints of patients with juvenile idiopathic arthritis, Th17.1 cell fractions were also found increased compared with PB and shared clonal ancestry with Th17
10 cells. Furthermore, although Th17.1 cells were abundantly present within sarcoidosis affected-organs, we identified CCR6+ DP cells, which were previously suggested to represent an intermediated stage between Th17 and Th17.1 cells, as the subset with the highest fraction of proliferating cells. Sarcoidosis CCR6+ DP cells also showed decreased coinhibitory
15 CTLA4 expression compared with controls, likely contributing to increased proliferative capacity. Previously, we have also observed a reduced CTLA4 expression in sarcoidosis MLN Th17 cells [Broos CE, et al. 2015. *Am J Respir Crit Care Med* 2015;192(6):763-65]. Aberrant expression of co-inhibitory receptors, such as CTLA4 on specific T cell subsets in sarcoidosis
20 is very likely to be part of disease pathogenesis, since clinical treatment with anti-CTLA4 has been associated with development of sarcoid-like granulomas in MLN of cancer patients. Finally, high levels of cytokines, such as IL-12 or IL-23, which can induce a Th17 shift towards Th17.1 cells are found in sarcoidosis lungs. Increased protein expression of IL-12 (p70
25 and p40) is found consistently within sarcoidosis lungs. Although IL-23p19 expression in sarcoid lungs remains uncertain, high expression of IL-12p40 compared with IL-12p70 may very well indicate elevated levels of IL-23, since IL-12p40 is also a subunit of IL-23. Notably, IL-23 transcription was enhanced in sarcoid skin lesion compared with controls, and serum amyloid
30 A (SAA), an antigen that was speculated to contribute to development of

chronic (pulmonary) sarcoidosis, has been described to increase IL-23 production by dendritic cells [Ather JL, Ckless K, Martin R, et al. 2011. J Immunol 187(1):64-73]. Strikingly, BALF IL-12p40 protein levels are highest in patients developing chronic disease. Our data cannot exclude the possibility of additional selective Th17.1 cell migration towards sarcoidosis lungs, attracted by high local co-expression of IP-10/CXCL10 and CCL20, ligands for CXCR3. Nevertheless, then also Th1 cell attraction towards sarcoidosis lungs would be expected as these cells also express CXCR3, and we did not find evidence for this phenomenon.

Highly clinically relevant, we found significantly higher Th17.1 cell proportions at time of diagnosis in lungs of patients who develop chronic disease compared to patients who underwent resolution. Together with our previous finding of increased BALF Th17.1 cells proportions in a population that included progressive patients who are on first-, second- and/or third-line therapy [Ramstein J, et al. 2015. Am J Respir Crit Care Med doi: 10.1164/rccm.201507-1499OC], these data strongly argue for a pathogenic role for Th17.1 cells in the development/progression of pulmonary sarcoidosis. Remarkably, two independent single-nucleotide polymorphisms (SNPs) within the IL23R gene locus were found to predispose for (chronic) sarcoidosis [Fischer A et al. 2011. European Respiratory Journal 37(3):610-16; Fischer A, et al. 2015. Am J Respir Crit Care Med 2015 doi: 10.1164/rccm.201503-0418OC] and IL-23R expression is essential for conversion of Th17 cells towards pathogenic Th17.1 cells during chronic inflammation in mice. The most recent genome-wide association study (GWAS) identified one SNP within the putative promoter region of the IL23R gene, which might influence IL-23R expression [Fischer A, et al. 2015. above]. The functional prediction and protein network analyses of the identified candidate susceptibility genes provided a prominent role for IL-23/Th17-signaling pathway in the genetic aetiology of sarcoidosis [Fischer A, et al. 2015. above]. Together with our data, this implies that genetic

variations within the IL23R gene or other genes involved in the IL-23/Th17-signaling pathway may predispose for (chronic) sarcoidosis, by supporting the conversion of Th17 to Th17.1 cells or by stabilizing Th17.1 cells.

Therefore, specific targeting of IL-23R signalling, e.g. by

- 5 Tildrakizumab/Guselkumab (anti-IL-23p19) which was recently described to be successful in psoriasis [Reich, K. et al. 2017. Lancet. 2017 Jul 15;390(10091):276-288; Gordon KB, Duffin KC, Bissonnette R, et al. 2015. N Engl J Med 373(2):136-44], is a proposed new therapeutic approach in (chronic) sarcoidosis.

- 10 In conclusion, this study shows that sarcoidosis CCR6+ Th17-lineage cells are significantly increased in the granulomatous MLN, and likely differentiate into Th17.1 cells in the lung microenvironment, where their presence significantly correlates with development of chronic disease.

- This study provides a new perspective on (i) sarcoidosis
15 pathogenesis, (ii) the value of Th17.1 cells as potential diagnostic/prognostic marker, and (iii) the potential of new therapeutic targets. Th17-lineage cells are increased in sarcoidosis MLN, and BALF Th17.1 cell proportions correlate with disease progression

20 **Example 2. JAK1–2 inhibition is an effective treatment in pulmonary sarcoidosis**

- This Example describes the successful treatment of a patient (54-year old male) with refractory sarcoidosis, by the use of baricitinib as the medicament for treatment. This molecule targets cytokine regulation
25 through Janus Kinases (JAK) 1 and 2, the signaling pathway of which has been indicated as a hypothetical target in the treatment of sarcoidosis.

- ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) was used to show diffuse pulmonary uptake and pulmonary function in the patient studied, as measured by Forced Vital Capacity (FVC). Both
30 declined progressively, despite treatment with corticosteroids, methotrexate

and tumor necrosis factor alpha blockers. During treatment with baricitinib, ¹⁸F-FDG-PET uptake decreased, FVC increased, and patients' quality of life improved. The present Example illustrates that JAK1-2 inhibition is a viable treatment strategy in therapy-resistant sarcoidosis.

5 The patient was diagnosed with pulmonary sarcoidosis in 1998 based on compatible clinical features and radiology, the histologic demonstration of noncaseating granulomas in a transbronchial biopsy, and the exclusion of alternative causes of granulomatous diseases, including tuberculosis. This diagnosis was made according to the American Thoracic
10 Society/European Respiratory Society international criteria (Statement on sarcoidosis. 1999. Am J Respir Crit Care Med 160:736-55).

 The patient was intermittently treated with prednisone for several years with good clinical response. After cessation of therapy, he was lost to follow up until 2015. There was a familial history of sarcoidosis. The
15 patient showed a productive cough and worsening shortness of breath. He also complained of arthralgia and fatigue. Total lung capacity was 79% of predicted value, and FVC and FEV1 were 75% of predicted values). Chest computed tomography (CT) showed upper lobe emphysema, symmetric and calcified mediastinal and hilar lymphadenopathy, nodular abnormalities
20 with a peribronchovascular distribution, and basal peribronchial reticulation with traction bronchiectasis compatible with chronic pulmonary sarcoidosis. The patient was referred to our sarcoidosis center for further treatment. He was qualified as a chronic patient.

 Initially, the patient had responded to high dose prednisone and
25 methotrexate with an increase in FVC but corticosteroids could not be tapered. Chest X-ray showed persistent parahilar and basal reticulonodular abnormality; additionally, DLCOc was still impaired (36% predicted) and the patient coughed excessively. From September 2016, infliximab 400mg (5 mg/kg bodyweight) was given intravenously at weeks 0 and 2 and every
30 subsequent 4 weeks until January 2017, while corticosteroids were tapered

(see Figure 11). Despite third-line therapy, chest CT demonstrated progression of preexistent bilateral parahilar pulmonary consolidations, without clinical and laboratory signs of infection. Infliximab antibody testing was negative. A diagnosis of progressive and refractory sarcoidosis was made, and the patient started again on high dose steroids and was switched to adalimumab 160 mg subcutaneously, followed by 80 mg and 40 mg weekly. In the subsequent months in 2017, FVC declined progressively (Figure 11). The patient was unable to perform diffusion capacity measurements due to excessive cough. He was treated with methylprednisone 1000mg daily for three consecutive days in September 2017, but ¹⁸F-FDG-PET scanning in November 2017 showed persistent intense pulmonary uptake as well as uptake in mediastinal, paracardiac, supraclavicular, and para-aortic lymph nodes (Figure 12). Additionally, FVC declined further (Figure 11). Soluble interleukin-2 receptor (sIL-2R), an inflammatory biomarker in sarcoidosis, was 35051 picograms per milliliter (pg/ml) in December 2017 (reference value <2500 pg/ml).

The patient consented to off-label treatment with baricitinib 4mg once daily, by oral administration. The patient subsequently stopped taking maintenance therapy with 5mg prednisone daily on his own initiative.

In this patient, the treatment effect of baricitinib and disease activity were measured by inflammatory markers (¹⁸F-FDG-PET uptake and serum sIL2R), pulmonary function parameter (FVC), and patient reported outcome (KSQ). In pulmonary sarcoidosis, ¹⁸F-FDG-PET with measurement of SUVmax and biomarker sIL-2R can be used for evaluating disease activity and treatment response (Treglia et al. 2014. Acad Radiol 21:675-84; Maturu et al. 2016. Sarcoidosis Vasc Diffuse Lung Dis 33:372-80).

In April 2018, following 4 months of treatment with baricitinib, no adverse events had occurred. There was an absolute increase of 7% in FVC predicted (Figure 11). Sarcoidosis inflammatory activity improved as

measured by a 45% decline in sIL-2R from 35051 pg/ml to 19287 pg/ml between December 2017 and March 2018. After three months, 18F-FDG PET scanning showed marked improvement compared to November 2017 (Figure 2), with a decrease of maximum standardized uptake value

5 (SUVmax) from 15.6 to 13.1 in the left lung and 17.3 to 12.3 in the right lung. Additionally, the patients' health status was assessed by the validated King's Sarcoidosis Questionnaire (KSQ; Patel et al. 2013. Thorax 68:57-65), which improved with a total score from 37.74 to 71.70 on a scale of 0-100.

This is the first report of the beneficial effect of JAK1-2 inhibition
10 in pulmonary sarcoidosis. Baricitinib, a selective and reversible inhibitor of JAK1 and JAK2, had shown clinical efficacy in treatment of rheumatoid arthritis (RA). It is currently registered for the treatment of patients with moderate to severely active RA with inadequate response or intolerance to one or more disease-modifying anti-rheumatic drugs in Europe. Sarcoidosis
15 is a complex idiopathic granulomatous disease with an unpredictable clinical course. Granulomas may affect almost any part of the human body. Pulmonary involvement is present in up to 95% and progression to irreversible pulmonary fibrosis was found in 17% of patients in a large United States sarcoidosis cohort. Pulmonary fibrosis leads to substantial
20 morbidity and mortality. Currently, no cure for progressive disease exists, and prolonged courses of glucocorticoids to suppress granulomatous inflammation remain the first-line treatment, despite side-effects such as diabetes, weight gain, and osteoporosis. Methotrexate or other immunomodulatory agents may be added as second-line steroid-sparing
25 treatment in refractory cases. Therapy targeting tumor necrosis factor alpha (TNF α) also shows positive effects on FVC in refractory sarcoidosis. However, no robust data on long term effect and best treatment strategy for this orphan disease exist.

It is well-established that major cytokines involved in sarcoidosis
30 pathology are TNF- α and IFN- γ (Figure 13). The present inventors have

found that increased proportions of IFN- γ -producing T helper 17 cells, called Th17.1-cells, are the source of IFN- γ in sarcoidosis BALF, and high proportions at diagnosis correlated with patients developing chronic sarcoidosis. Interestingly, Th17.1-cells are potentially resistant to the immunosuppressive effect of glucocorticoids, as a proportion express multidrug resistance protein-1. Based on the observation of enhanced JAK-STAT1 pathway activation in sarcoidosis, it was hypothesized that there was a potential role for IFN- γ signaling in sarcoidosis. The present inventors have now discovered that suppressing this IFN- γ signaling by the use of JAK/STAT inhibitors can effectively treat sarcoidosis.

The improvements in 18F-FDG-PET and serum biomarker sIL-2R observed in this study can be considered clinically relevant when compared to other studies (Vorselaars et al. 2015. Eur Respir J 46:175-85; Maturu et al., 2016. Sarcoidosis Vasc Diffuse Lung Dis 2016;33:372-80). Pulmonary function showed a 7% absolute increase of FVC predicted, following progressive FVC decline in the preceding months (Figure 11). Previous studies with TNF α blockers in sarcoidosis defined an absolute increase in FVC $\geq 5\%$ predicted as a positive response (Vosselaars et al., 2015). The patients' health status was measured by the validated KSQ2. This questionnaire combines organ specific, medication and general health status modules. In our patient, the general health score improved. Although the minimal important difference for this questionnaire has not yet been determined, we believe that this increase of 90% in score represents a clinically relevant improvement. After three months, the patient wished to continue treatment with baricitinib.

In this Example, a profound inflammatory and functional response to three months of JAK inhibition with baricitinib is described with improvement of quality of life in a patient with therapy refractory sarcoidosis. This favorable response shows that JAK1-2 inhibition is

effective in treating pulmonary sarcoidosis, in particular the chronic forms of the disease.

Example 3. Other JAK1-2 inhibitors are as effective as baricitinib in inhibiting JAK/STAT pathways in sarcoidosis patients

T-cell subsets were isolated from 2 healthy donors: Th17.1 cells (CD3+CD4+CD45RA-CCR6+CXCR3+CCR4-), Th17 cells (CD3+CD4+CD45RA-CCR6+CXCR3-CCR4+) and Th1 cells (CD3+CD4+CD45RA-CCR6-CXCR3+CCR4-) were purified and 100.000 cells were placed in culture and were stimulated with anti-CD3/CD28 for 3-4 days with and without tofacitinib (250 uM).

IFN- γ mRNA levels were examined. IFN- γ has been shown to be high in pathogenic Th17.1 cells (*see above*).

Results

The results of these tests are provided in Figure 14. It was observed that tofacitinib resulted in a marked decrease of IFN- γ mRNA levels in Th17.1 cells. These data indicate that the pathogenicity or pathogenic profile of Th17.1 cells is decreased/reduced by JAK inhibition.

Example 4. Phosphorylation of STATs in patient material

In this experiment, peripheral blood mononuclear cells (PBMCs) were isolated from 5 healthy donors and 9 sarcoidosis patients. $\sim 1 \times 10^6$ PBMCs were incubated with JAK inhibitors baricitinib (300 nM), tofacitinib (250 uM), or filgotinib (10 uM), or left untreated for 1 hr at 37 degrees Celsius.

Cells were then washed and stimulated with IFN- γ (1000 U/ml), or IL-2 (10 ng/ml), or left untreated (control) for 15 minutes at 37 degrees Celsius. Cells were then fixed and stained for phosphorylated STAT and CD3, CD4, CD8, CD45RA and a live/dead marker. Analysis was performed

using a BD LSR flowcytometer. Phospho-STAT1 was examined in IFN- γ stimulated cells and phospho-STAT5 was examined in IL-2 stimulated cells. Monocytes (Figure 15, top graph) were identified as Side scatter high cells, with intermediate CD4 expression. Naive CD4 T cells (Figure 15, bottom
5 graph) were CD3+ CD4+ CD45RA+.

Results

As shown in Figure 15, phospho-STAT response in Th-cells and monocytes of sarcoidosis patients is higher after cytokine stimulation than
10 in healthy subjects. Monocytes of sarcoidosis patients show a higher response to IFN- γ stimulation than healthy controls, as evidenced by higher phosphorylated STAT1 levels. Naive CD4 T-cells of sarcoidosis patients show a higher response after IL2 stimulation when compared to healthy controls as evidenced by higher phosphorylated STAT5 levels.

15 All of the tested JAK inhibitors (baricitinib (JAK1/2), tofacitinib (JAK1/3), filgotinib (JAK1)) successfully inhibit STAT1/5 phosphorylation in sarcoidosis.

This shows that a variety of JAK inhibitors can be used for treating sarcoidosis. After our successful treatment of a sarcoidosis patient
20 with baricitinib as described in Example 2, we are confident that also other JAK inhibitors that have an effect on JAK1 are suitable for use in treating sarcoidosis as described herein, since all tested JAK inhibitors have in common that they inhibit JAK1.

We have also determined that Th17.1 cells react the strongest to
25 JAK1 inhibition when compared to Th1 or Th17 cells. This supports our earlier finding that the pathogenic Th17.1 cell is a particularly suitable target for JAK inhibition therapy in sarcoidosis, in particular JAK1 inhibition. Following JAK1 inhibition, the Th17.1 cells produce less IFN- γ and are thereby rendered less pathogenic.

Claims

1. Method of treating sarcoidosis, comprising administering to a subject in need thereof, a therapeutically effective dose of a JAK1 inhibitor.
2. Method according to claim 1, wherein said sarcoidosis is
5 pulmonary sarcoidosis, preferably chronic pulmonary sarcoidosis.
3. Method according to claim 1 or 2, wherein said JAK1 inhibitor is a JAK1-selective inhibitor, a JAK1-JAK2 inhibitor or a JAK1-JAK3 inhibitor.
- 10 4. Method according to any one of claims 1-3, wherein said JAK1 inhibitor is selected from Baricitinib, Tofacinib, Peficitinib, Filgotinib, Upadacitinib, Ruxolitinib, Itacitinib, INCB54707, Abrocitinib, Solcitinib and AZD4205.
- 15 5. Method according to any one of claims 1-4, wherein said JAK1 inhibitor is not Baricitinib.
6. Method according to any one of claims 1-4, wherein said JAK1 inhibitor is administered:
20 - at a once daily oral dose of 1-10 mg in the case of Baricitinib;
- at a once daily oral dose of 50-200mg mg in the case of Filgotinib;
- at a twice daily oral dose of about 5 mg or a dose of about 10 mg once daily in the case of Tofacinib;
25 - at a once daily oral dose of 100-150 mg in the case of Peficitinib,
or
- at a once daily oral dose of about 15-30 mg in the case of Upadacitinib.

7. Method according to any one of claims 2-6, wherein said treatment involves at least partial counteraction of the reduced pulmonary function associated with pulmonary sarcoidosis.

5 8. A JAK1 inhibitor for use in the treatment of sarcoidosis.

9. JAK1 inhibitor for use according to claim 8, wherein said sarcoidosis is pulmonary sarcoidosis, preferably chronic pulmonary sarcoidosis.

10

10. JAK1 inhibitor for use according to claim 8 or 9, wherein said JAK1 inhibitor is a JAK1-selective inhibitor, a JAK1-JAK2 inhibitor or a JAK1-JAK3 inhibitor.

15 11. JAK1 inhibitor for use according to any one of claims 8-10, wherein said JAK1 inhibitor is selected from Baricitinib, Tofacitinib, Peficitinib, Filgotinib, Upadacitinib, Ruxolitinib, Itacitinib, INCB54707, Abrocitinib, Solcitinib and AZD4205.

20 12. JAK1 inhibitor for use according to any one of claims 8-11, wherein said JAK1 inhibitor is not Baricitinib.

13. JAK1 inhibitor for use according to any one of claims 8-12, wherein said JAK1 inhibitor is administered:

25 - at a once daily oral dose of 1-10 mg in the case of Baricitinib;

- at a once daily oral dose of 50-200mg mg in the case of Filgotinib;

- at a twice daily oral dose of about 5 mg or a dose of about 10 mg once daily in the case of Tofacitinib;

- at a once daily oral dose of 100-150 mg in the case of Peficitinib,
- or
- at a once daily oral dose of about 15-30 mg in the case of Upadacitinib.

5

14. JAK1 inhibitor for use according to any one of claims 9-13, wherein said treatment involves at least partial counteraction of the reduced pulmonary function associated with pulmonary sarcoidosis.

10

Figure 1

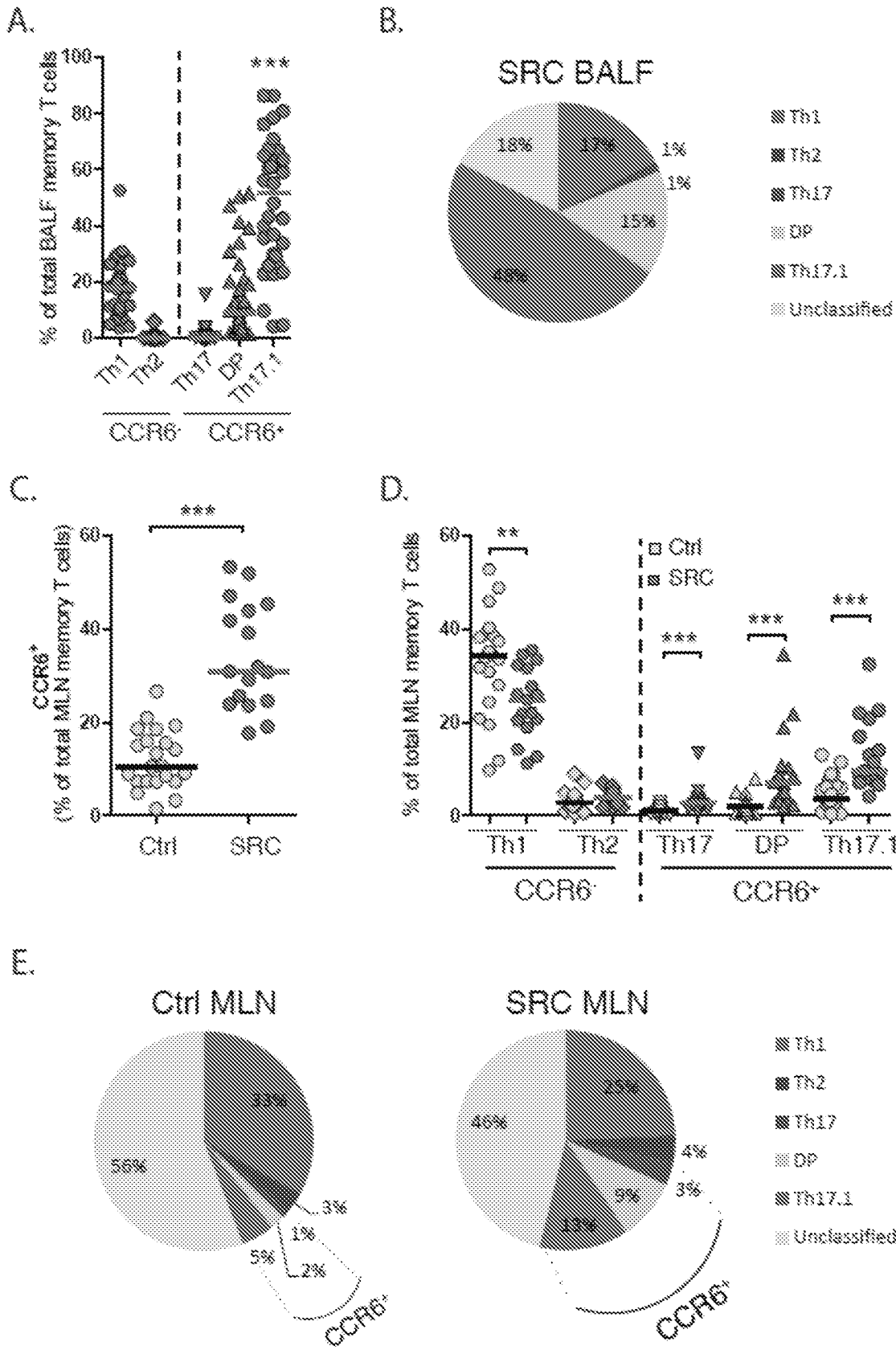
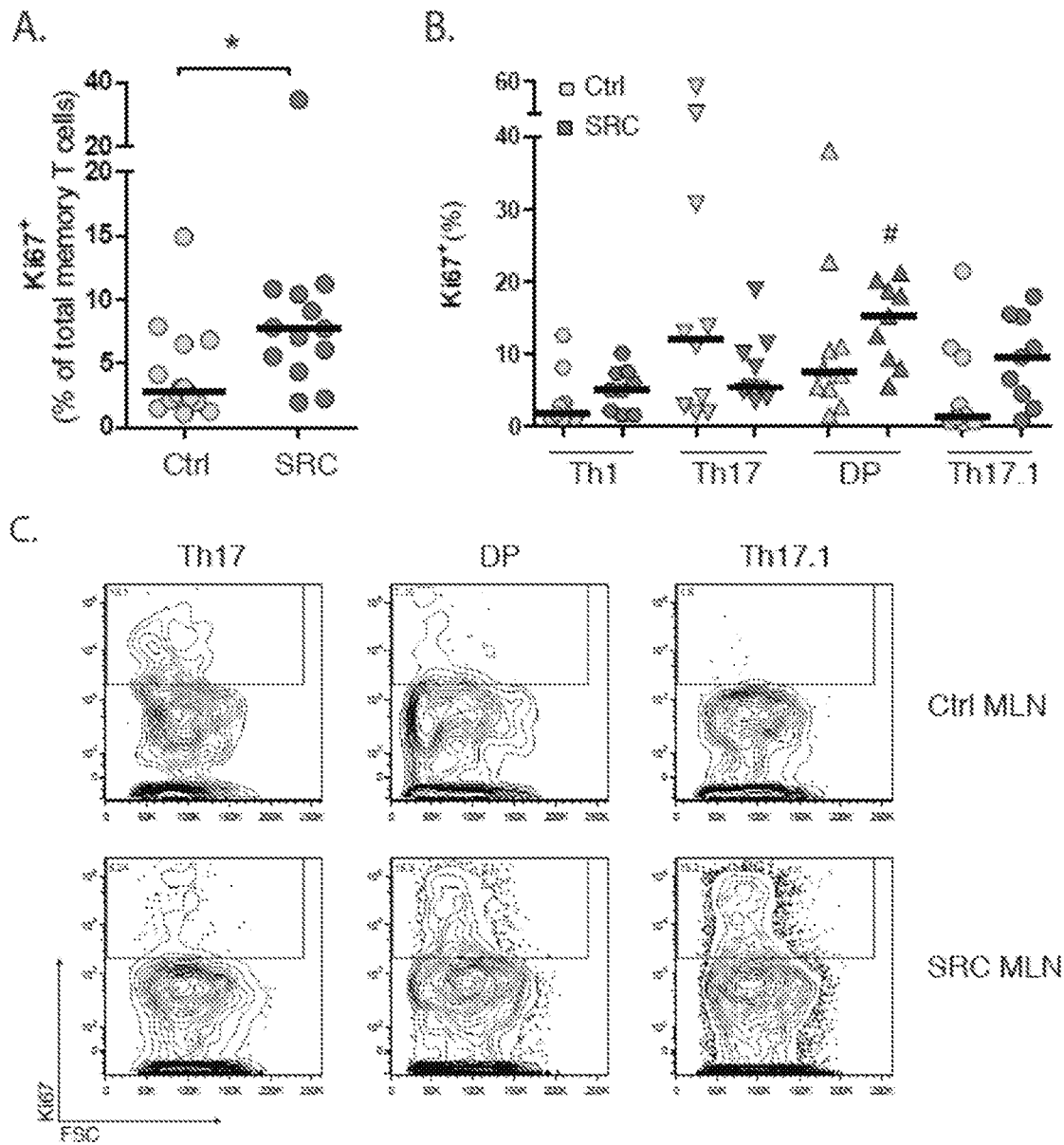


Figure 2



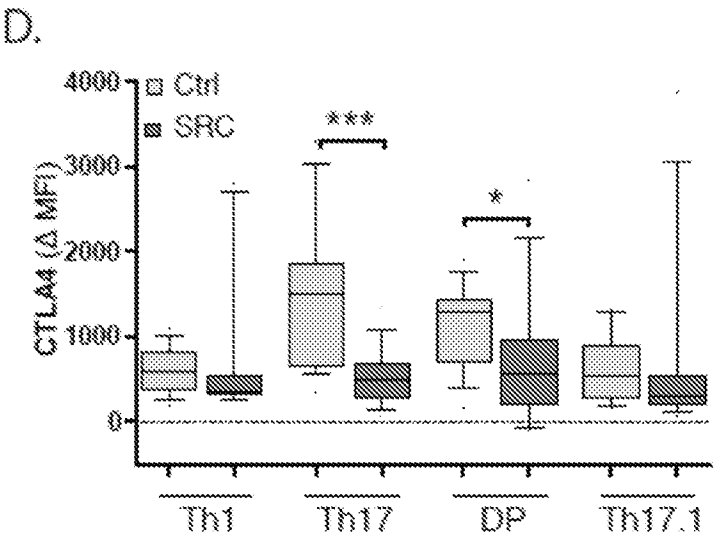


Figure 3

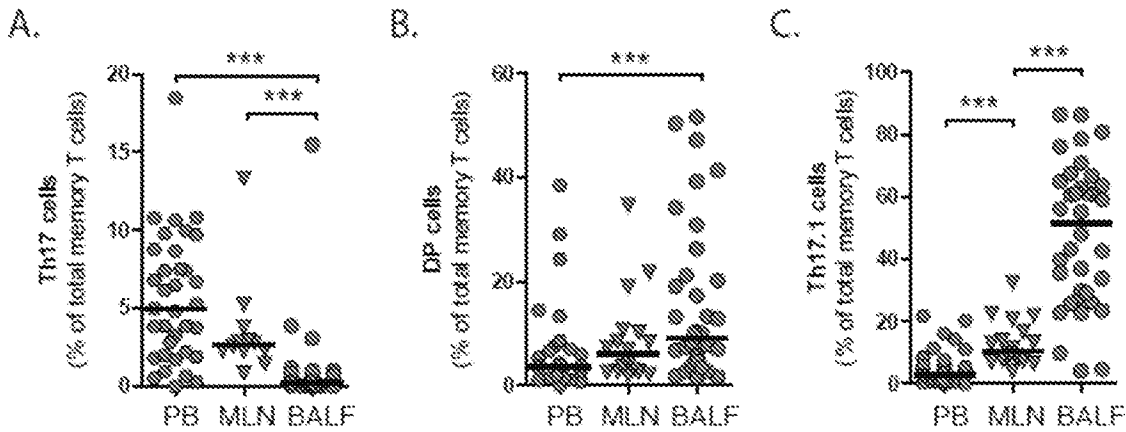


Figure 4

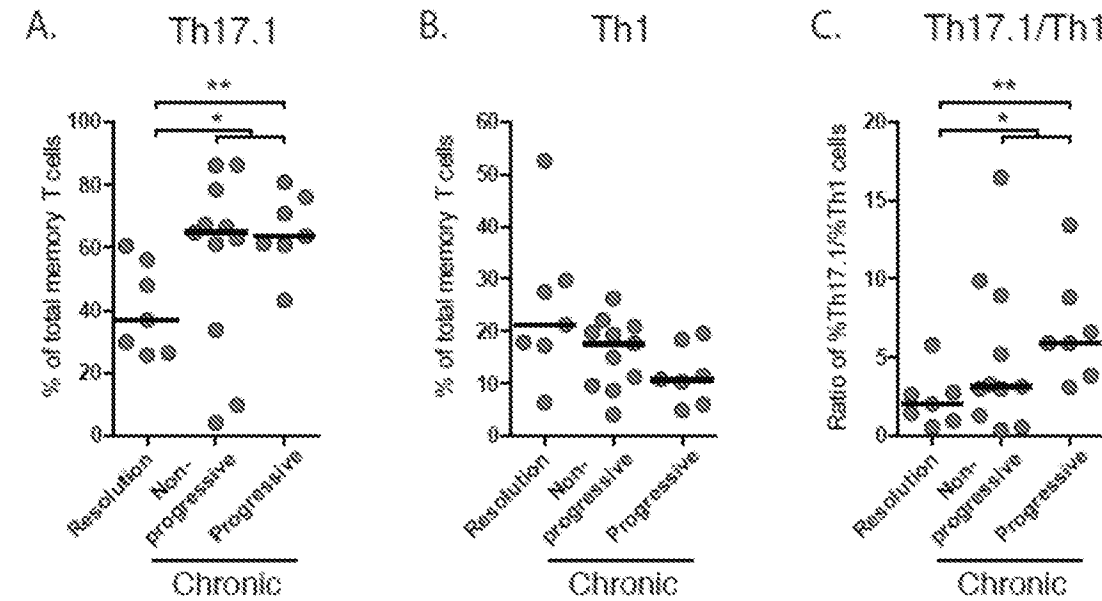


Figure 5

A.

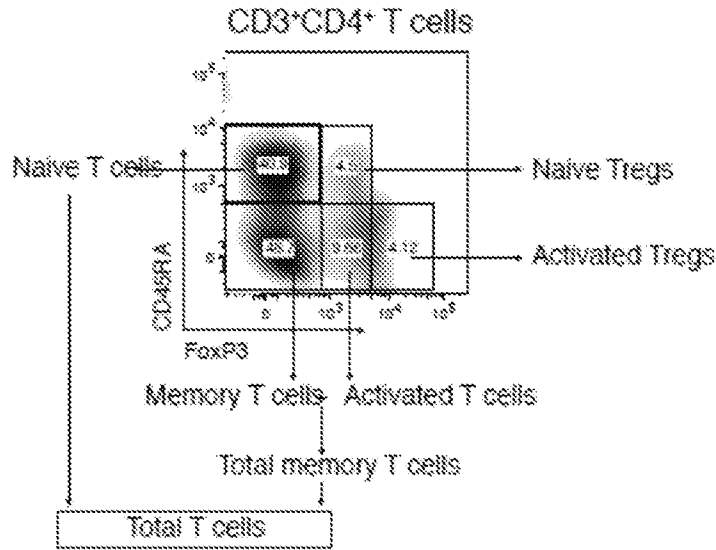


Figure 5

B.

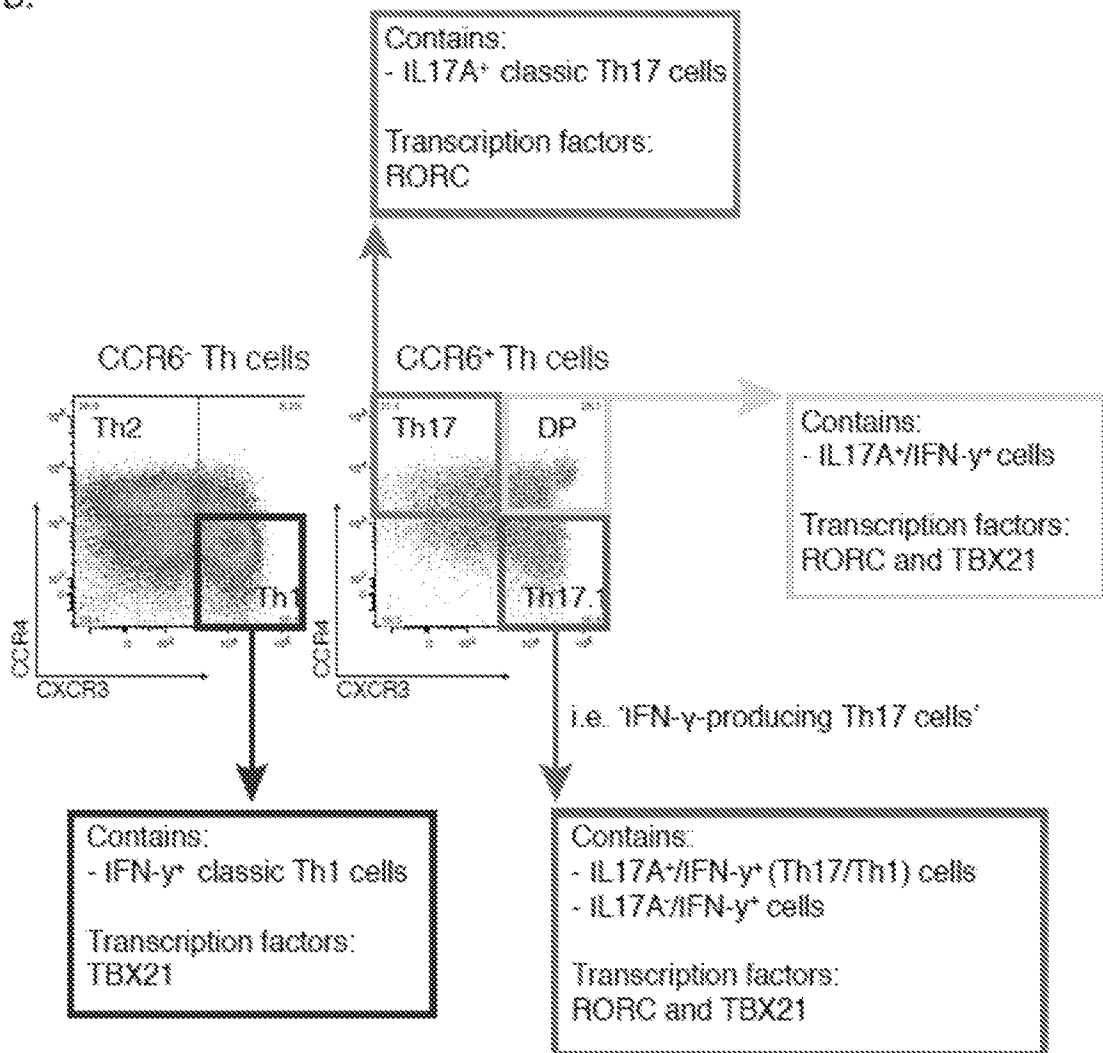


Figure 6

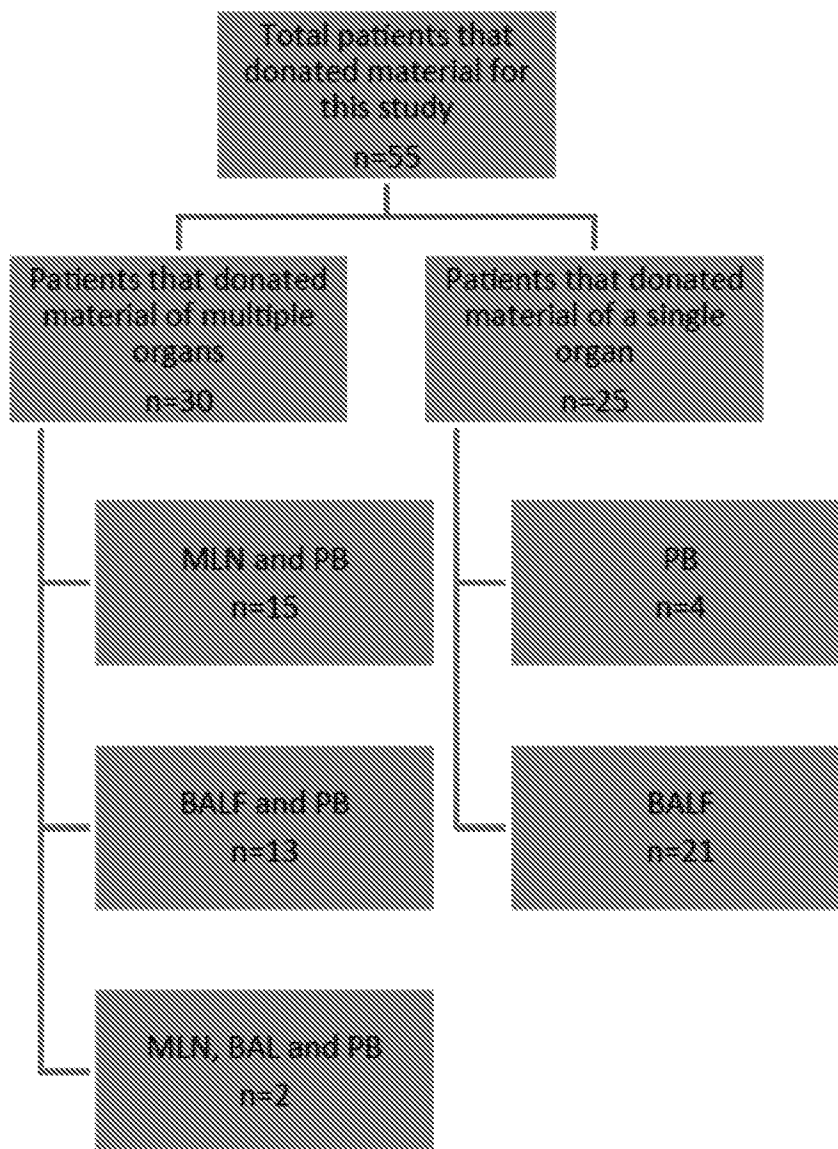
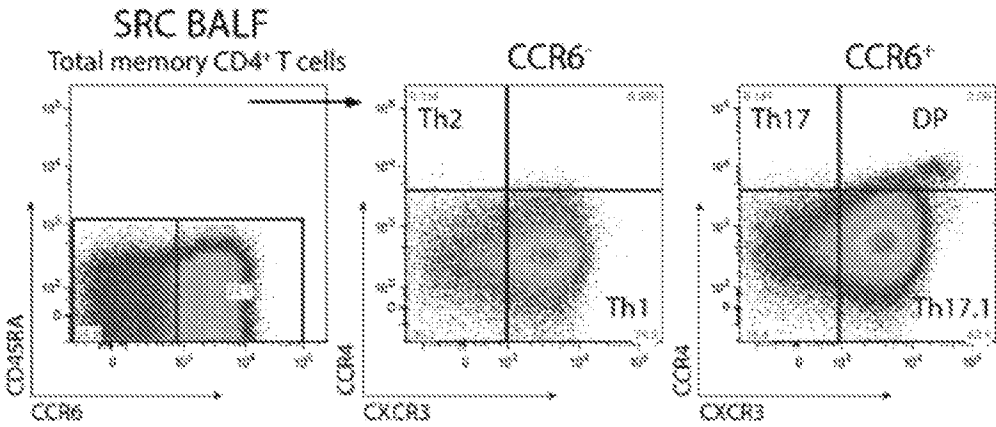


Figure 7

A.



B.

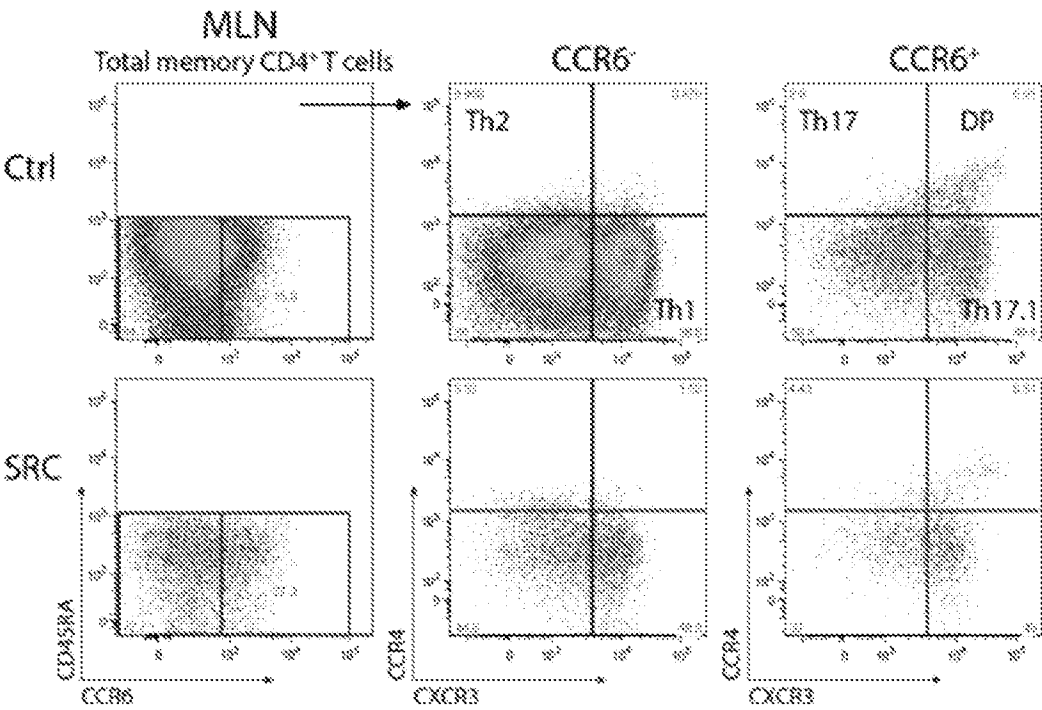


Figure 8

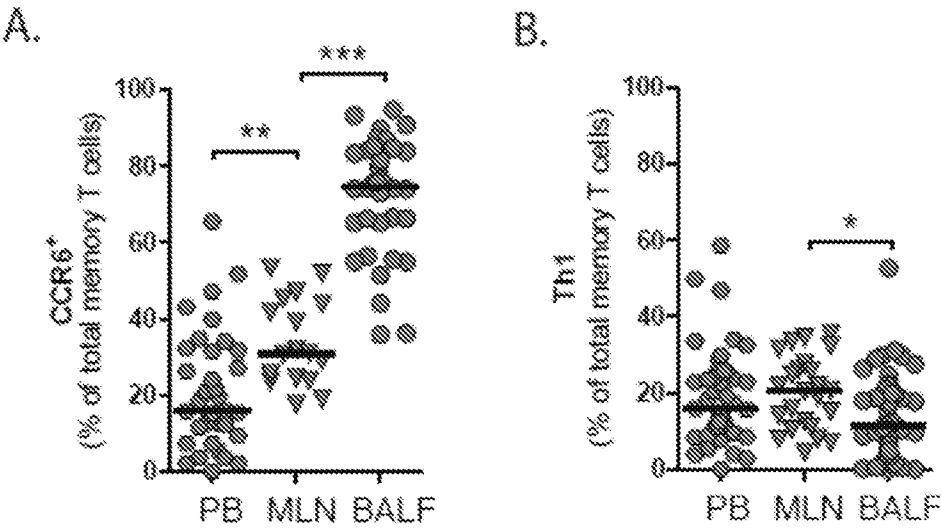


Figure 9

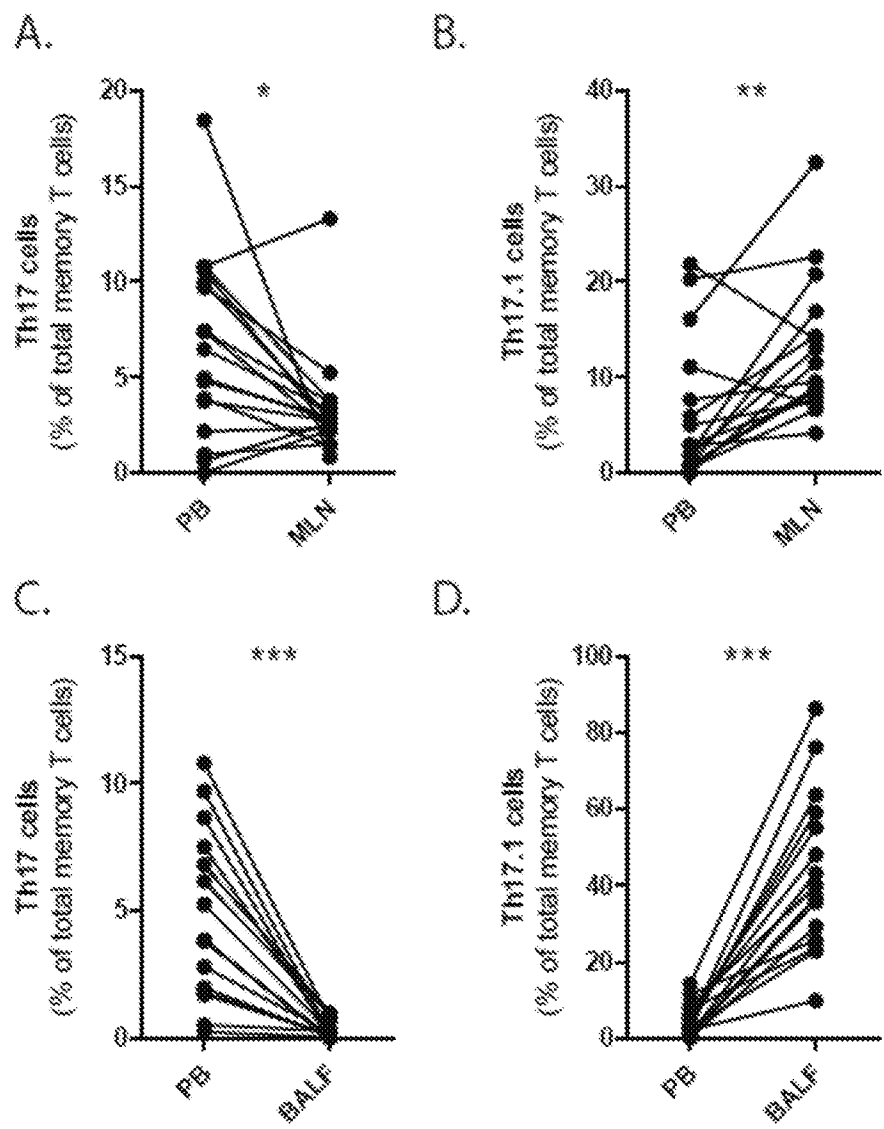


Figure 10

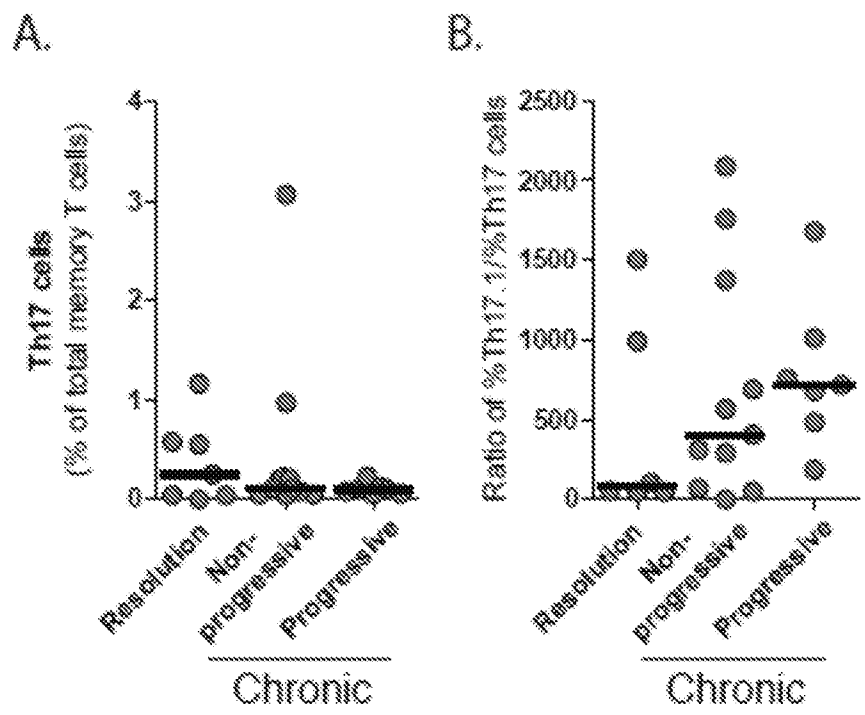


Figure 11

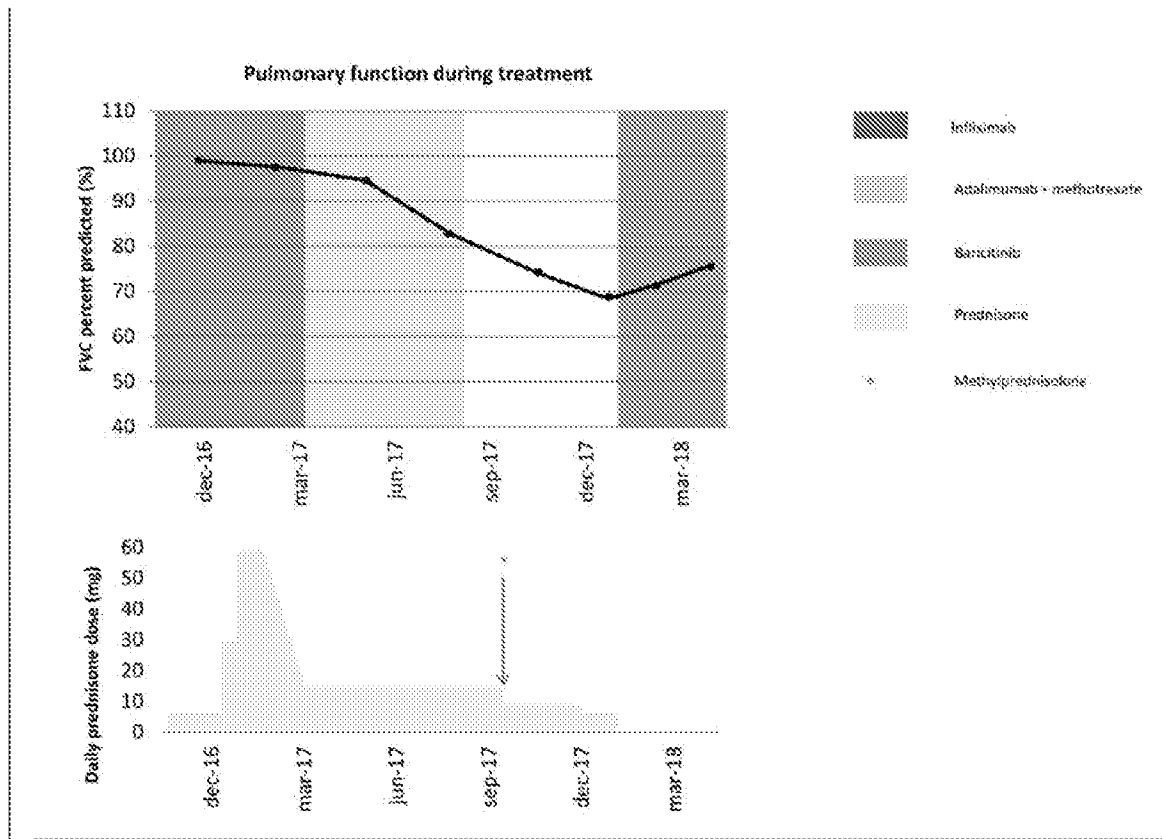


Figure 12

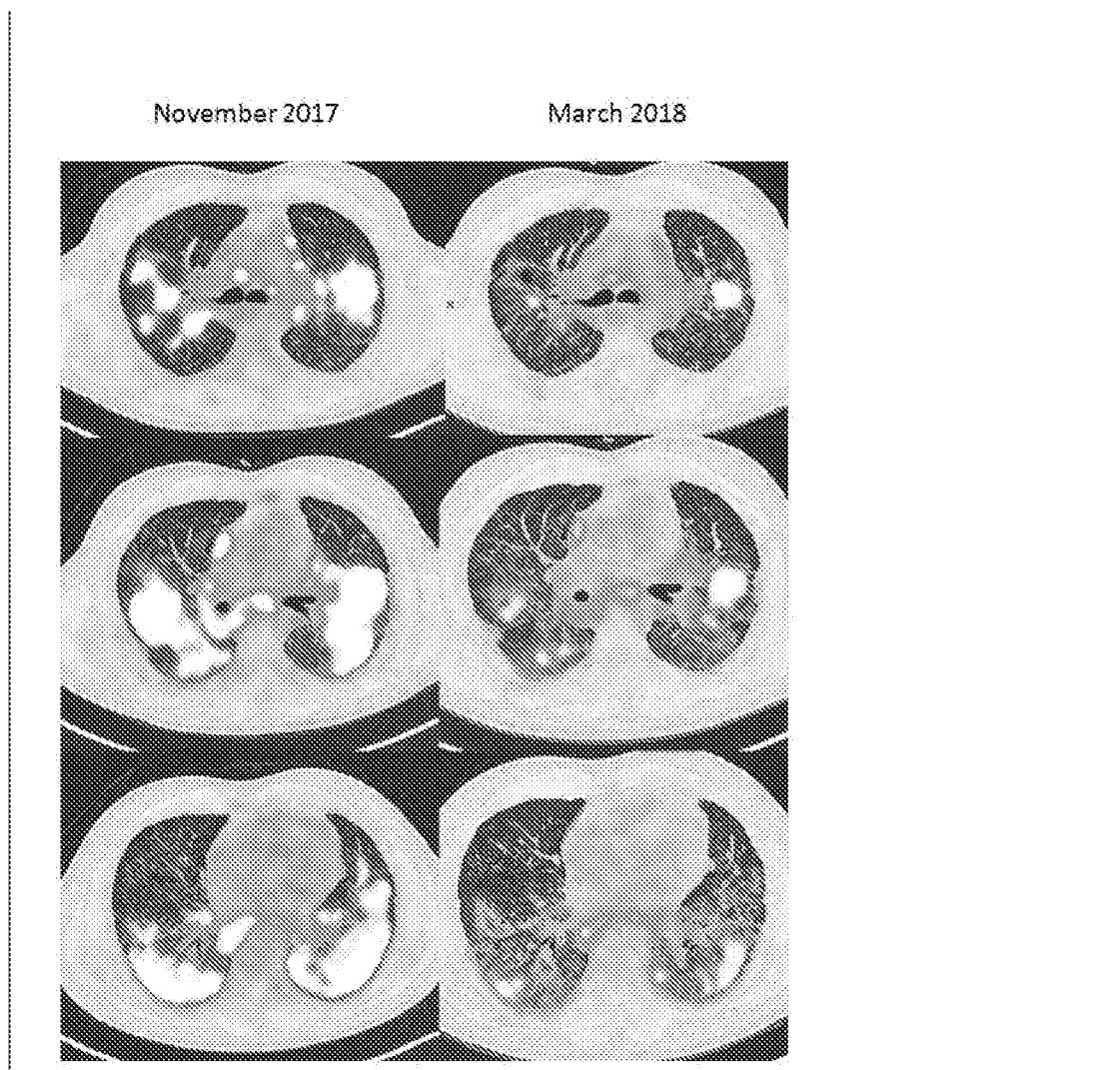


Figure 13

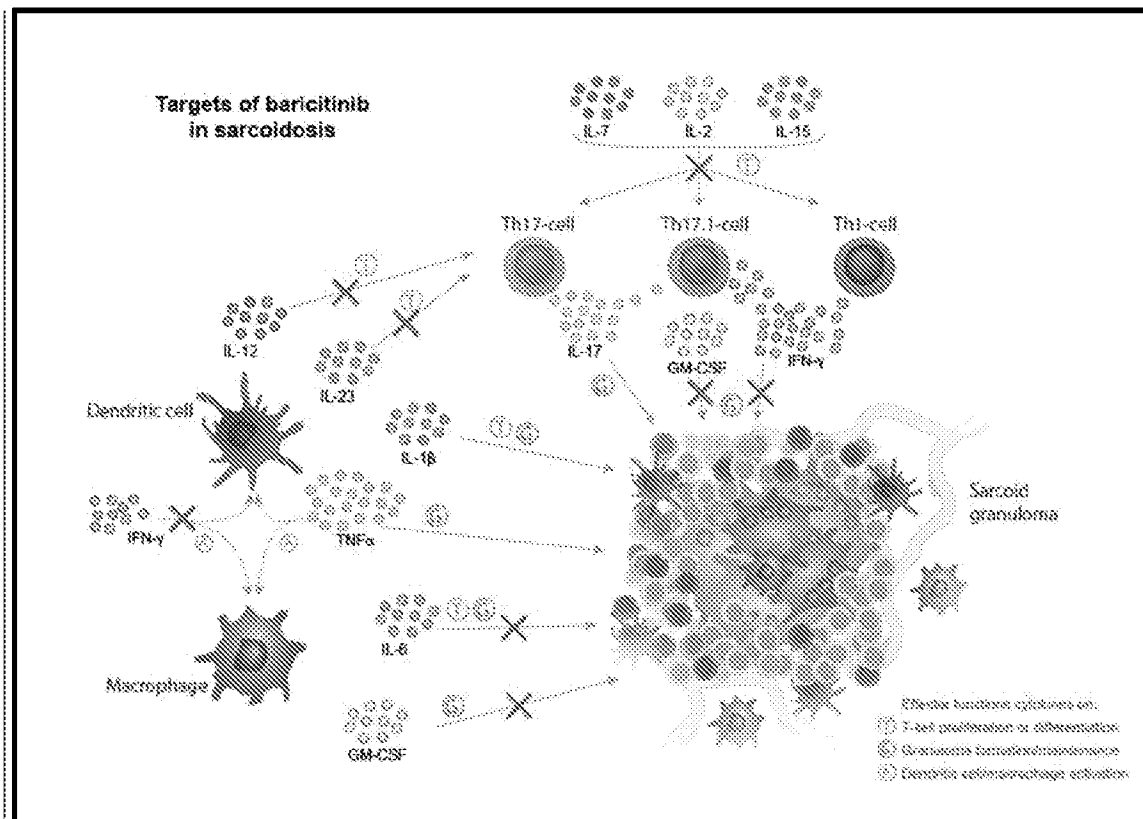


Figure 14

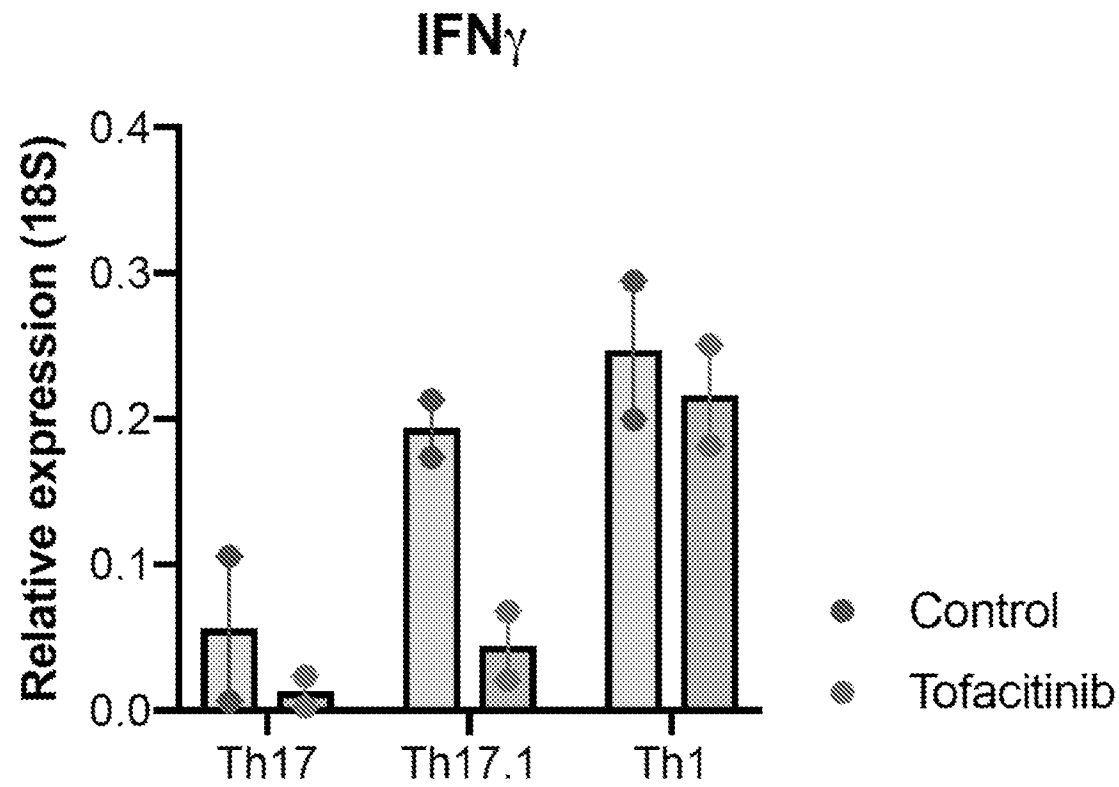
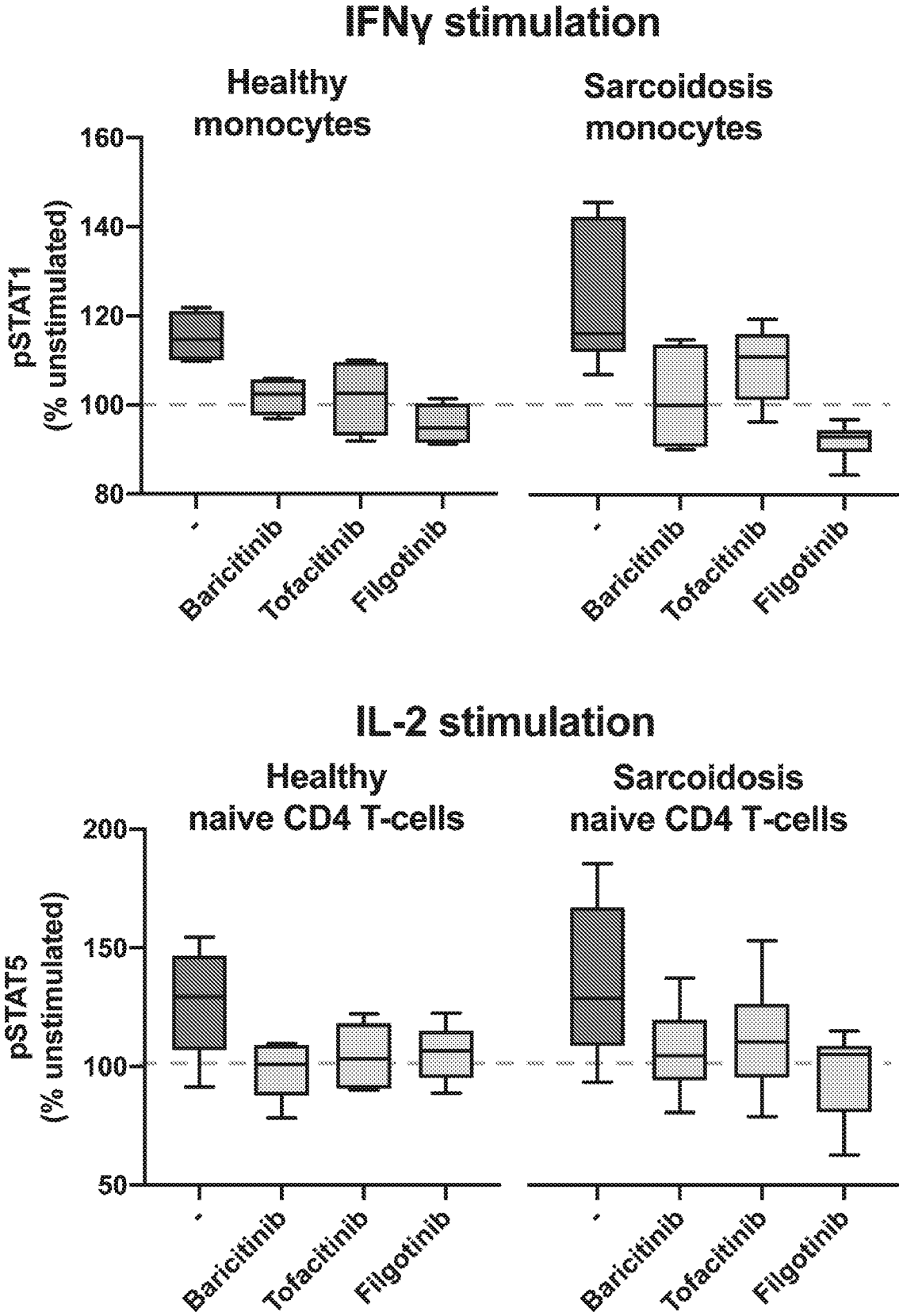


Figure 15



INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2019/050394

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/519

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/110259 A1 (VERTEX PHARMA [US]) 17 July 2014 (2014-07-17) Whole document, in particular paragraph 5 -----	1-14
A	WO 2015/032423 A1 (SAREUM LTD [GB]) 12 March 2015 (2015-03-12) whole document, in particular page 37, line18-page 38, line 10 -----	1-14
X	WO 2018/087202 A1 (GALAPAGOS NV [BE]) 17 May 2018 (2018-05-17) whole document, in particular paragraphs 1, 29, 41, 42, 60, 61, claims 1-9 and 75-89 ----- -/-	1-3,5, 7-10,12, 14



Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

22 October 2019

Date of mailing of the international search report

11/11/2019

Name and mailing address of the ISA/

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Authorized officer

Vanmontfort, D

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2019/050394

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TONG ZHOU ET AL: "Identification of Jak-STAT signaling involvement in sarcoidosis severity via a novel microRNA-regulated peripheral blood mononuclear cell gene signature", SCIENTIFIC REPORTS, vol. 7, no. 1, 26 June 2017 (2017-06-26), XP055504535, DOI: 10.1038/s41598-017-04109-6 whole document, in particular abstract, Figure 2, Table 3 -----	1-14
A	ROSENBAUM J T ET AL: "Hypothesis: Sarcoidosis is a STAT1-mediated disease", CLINICAL IMMUNOLOGY, ACADEMIC PRESS, US, vol. 132, no. 2, 1 August 2009 (2009-08-01), pages 174-183, XP026301931, ISSN: 1521-6616, DOI: 10.1016/J.CLIM.2009.04.010 [retrieved on 2009-05-22] whole document, in particular abstract; Tables 3 and 4 -----	1-14
A	SCHISCHMANOFF PIERRE OLIVIER ET AL: "Progressive pulmonary sarcoidosis is associated with over-expression of TYK2 and p21Waf1/Cip1.", SARCOIDOSIS, VASCULITIS, AND DIFFUSE LUNG DISEASES : OFFICIAL JOURNAL OF WASOG JUN 2006, vol. 23, no. 2, June 2006 (2006-06), pages 101-107, XP9507820, ISSN: 1124-0490 whole document, in particular abstract; Figure 1B and Table IV -----	1-14
A	ROBERT P. BAUGHMAN ET AL: "A Concise Review of Pulmonary Sarcoidosis", AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE., vol. 183, no. 5, 1 March 2011 (2011-03-01), pages 573-581, XP055464428, US ISSN: 1073-449X, DOI: 10.1164/rccm.201006-0865CI whole document, in particular paragraph "Therapy" on pages 577-578 ----- -/--	1-14

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2019/050394

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	DANIELLA M. SCHWARTZ ET AL: "JAK inhibition as a therapeutic strategy for immune and inflammatory diseases", NATURE REVIEWS. DRUG DISCOVERY, vol. 16, no. 12, 6 November 2017 (2017-11-06), pages 843-862, XP055504546, GB ISSN: 1474-1776, DOI: 10.1038/nrd.2017.201 the whole document -----	1-14
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Information on patent family members

International application No

PCT/NL2019/050394

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