

Summary

The inventors of the present **inventiondisclosure** have generated an antibody, and variants thereof, binding to IL-1RAP domain 2 with the capability of inhibiting the signaling downstream of six IL1RAP dependent ligands; IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ . Due to this superior property, this antibody can be used for the prevention, treatment, alleviation, detection and/or diagnosis of diseases and disorders associated with signaling of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ , thereby simultaneously targeting several downstream pathways associated with these cytokines. Consequently, this antibody can be used in targeting several aspects and processes of diseases and disorders associated with signaling of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ , for example inflammatory and fibrotic aspects in inflammatory or fibrotic diseases or disorders, or inflammatory, fibrotic or proliferative aspects in neoplastic diseases or disorders. The antibody described here allows for simultaneous targeting of multiple cytokine pathways, for example targeting pathways of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and IL-36 γ , which is a clinical advantage when treating diseases or disorders where blocking only one or a few cytokines would not be effective enough to treat or prevent a disease or disorder. Further disclosed is the optimization of this antibody by humanization and de-immunization procedures, resulting in antibody variants with fine-tuned properties.

A first aspectexample of the **inventiondisclosure** relates to an antibody or antigen-binding fragment thereof with binding specificity for interleukin-1 receptor accessory protein (IL1RAP), wherein the antibody or antigen-binding fragment comprises:

a light chain variable region comprising

- a) a CDR-L1 comprising or consisting of an amino acid sequence selected from the group consisting of ESISTA (SEQ ID NO: 1), QASESISTALA (SEQ ID NO: 7) and QASESISTALA (SEQ ID NO: 13);
- b) a CDR-L2 comprising or consisting of an amino acid sequence selected from the group consisting of KAS, KASTLPS (SEQ ID NO: 8) and KASTLPS (SEQ ID NO: 14); and
- c) a CDR-L3 comprising or consisting of an amino acid sequence selected from the group consisting of QQGFSSGNVHNA (SEQ ID NO: 3), QQGFSSGNVHNA (SEQ ID NO: 9) and QQGFSSGNVHNA (SEQ ID NO: 15);

and / or

a heavy chain variable region comprising

- 5 d) a CDR-H1 comprising or consisting of an amino acid sequence selected from the group consisting of GPSLSHFD (SEQ ID NO: 4), HFDIT (SEQ ID NO: 10) and GPSLSHFDIT (SEQ ID NO: 16);
- e) a CDR-H2 comprising or consisting of an amino acid sequence selected from the group consisting of ISPGVST (SEQ ID NO: 5), TISPGVSTYYASWAKS (SEQ ID NO: 11) and TISPGVSTYYASWAKS (SEQ ID NO: 17); and
- 10 f) a CDR-H3 comprising or consisting of an amino acid sequence selected from the group consisting of ARGGVGSSWKAFDL (SEQ ID NO: 6), GGVGSSWKAFDL (SEQ ID NO: 12) and ARGGVGSSWKAFDL (SEQ ID NO: 18).

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A second aspectexample of the inventiondisclosure relates to a polynucleotide encoding the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure, or a component polypeptide chain thereof

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A third aspectexample of the inventiondisclosure relates to a vector comprising the polynucleotide according to the second aspectexample of the inventiondisclosure.

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A fourth aspectexample of the inventiondisclosure relates to a recombinant host cell comprising the polynucleotide according to the second aspectexample of the inventiondisclosure or a vector according to the third aspectexample of the inventiondisclosure.

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A fifth aspectexample of the inventiondisclosure relates to a method for producing the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure, the method comprising culturing the host cell of the fourth aspectexample of the inventiondisclosure, comprising the polynucleotide of the second aspectexample of the inventiondisclosure or the vector of the third aspectexample of the inventiondisclosure, under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.

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A sixth aspectexample of the inventiondisclosure relates to a pharmaceutical composition comprising the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,

the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
the vector of the third [aspectexample](#) of the [inventiondisclosure](#), and/or
the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#),
in a pharmaceutical composition, wherein the composition further comprises a
pharmaceutically-acceptable diluent, carrier or excipient

A seventh [aspectexample](#) of the [inventiondisclosure](#) relates to
the antibody or antigen-binding fragment of the first [aspectexample](#) of the
[inventiondisclosure](#),
the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
the vector of the third [aspectexample](#) of the [inventiondisclosure](#),
the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#), and/or
the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#),
for use in medicine.

An eighth [aspectexample](#) of the [inventiondisclosure](#) relates to the antibody or
antigen-binding fragment of the first [aspectexample](#) of the [inventiondisclosure](#),
the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
the vector of the third [aspectexample](#) of the [inventiondisclosure](#),
the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#), and/or
the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#),
for use in the prevention and/or treatment and/or alleviation and/or detection and/or
diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-
1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or
wherein the disease or disorder is associated with cells expressing IL1RAP.

A ninth [aspectexample](#) of the [inventiondisclosure](#) relates to
the antibody or antigen-binding fragment of the first [aspectexample](#) of the
[inventiondisclosure](#),
the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
the vector of the third [aspectexample](#) of the [inventiondisclosure](#),
the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#), and/or
the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#),
for use in inducing cell death and/or inhibiting the growth and/or proliferation of
pathological cells associated with a neoplastic disorder in a subject, or stem cells or
progenitor cells thereof, wherein the cells express IL1RAP.

A tenth aspectexample of the inventiondisclosure relates to the use of the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,
 the polynucleotide of the second aspectexample of the inventiondisclosure,
 5 the vector of the third aspectexample of the inventiondisclosure,
 the host cell of the fourth aspectexample of the inventiondisclosure, and/or
 the composition of the sixth aspectexample of the inventiondisclosure,
 in the preparation of a medicament for the prevention, treatment, alleviation, detection
 and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of
 10 IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling,
 and/or wherein the disease or disorder is associated with cells expressing IL1RAP.

An eleventh aspectexample of the inventiondisclosure relates to the use of the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,
 15 the polynucleotide of the second aspectexample of the inventiondisclosure,
 the vector of the third aspectexample of the inventiondisclosure,
 the host cell of the fourth aspectexample of the inventiondisclosure, and/or
 the composition of the sixth aspectexample of the inventiondisclosure,
 20 in the preparation of a medicament for the detection and/or diagnosis of a disease or
 disorder associated with cells expressing IL1RAP.

A twelfth aspectexample of the inventiondisclosure relates to a method for the prevention and/or treatment and/or alleviation and/or detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling and/or wherein the disease or disorder is associated with cells expressing IL1RAP in a subject, comprising the step of administering to the subject an effective amount of
 25 -the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,
 30 -the polynucleotide of the second aspectexample of the inventiondisclosure,
 -the vector of the third aspectexample of the inventiondisclosure,
 -the host cell of the fourth aspectexample of the inventiondisclosure, and/or
 -the composition of the sixth aspectexample of the inventiondisclosure.

A thirteenth aspectexample of the inventiondisclosure relates to an *in vitro* method for the detection of cells expressing IL1RAP in a subject, the method comprising:

- (a) providing a sample of cells from a subject to be tested, such as biopsy tissue or blood sample;
- (b) optionally, extracting and/or purifying the cells present in the sample;
- (c) contacting the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure with cells present in the sample;
- (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells

wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expressing IL1RAP in the tissue of a subject.

A fourteenth aspectexample of the inventiondisclosure relates to an *in vitro* method for identifying a patient with a disease or disorder associated with cells expressing IL1RAP who would benefit from treatment with the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure, the method comprising:

- (a) providing a sample of cells, such as biopsy tissue or blood sample from a patient to be tested;
- (b) optionally, extracting and/or purifying the cells present in the sample;
- (c) contacting the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure with cells present in the sample;
- (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells

wherein the binding of the antibody or antigen-binding fragment thereof to cells expressing IL1RAP is indicative of a patient who would benefit from treatment with the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure.

A fifteenth aspectexample of the inventiondisclosure relates to a method for treating a patient with a disease or disorder associated with cells expression IL1RAP, the method comprising:

- a) selecting a patient identified as having a disease or disorder associated with cells expressing IL1RAP using a method according to the fourteenth aspectexample of the inventiondisclosure; and

- b) administering to said patient a therapeutic agent effective in the treatment of said disease or disorder.

A sixteenth aspectexample of the inventiondisclosure relates to a method for the detection of cells expressing IL1RAP, the method comprising:

- (a) contacting an antibody or antigen-binding fragment thereof according to the first aspectexample with cells to be analysed for their expression of IL1RAP;
 (b) determining whether the antibody or antigen-binding fragment thereof binds to the cells

wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expressing IL1RAP in the tissue of a subject.

A seventeenth aspectexample of the inventiondisclosure relates to a method for reducing inflammation in a subject with peritonitis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,
- the polynucleotide of the second aspectexample of the inventiondisclosure,
- the vector of the third aspectexample of the inventiondisclosure,
- the host cell of the fourth aspectexample of the inventiondisclosure, and/or
- the composition of the sixth aspectexample of the inventiondisclosure.

An eighteenth aspectexample of the inventiondisclosure relates to a method for reducing disease severity in a subject with psoriasis or psoriatic arthritis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first aspectexample of the inventiondisclosure,
- the polynucleotide of the second aspectexample of the inventiondisclosure,
- the vector of the third aspectexample of the inventiondisclosure,
- the host cell of the fourth aspectexample of the inventiondisclosure, and/or
- the composition of the sixth aspectexample of the inventiondisclosure.

A nineteenth aspectexample of the **inventiondisclosure** relates to a method for reducing atherosclerotic plaque inflammation in a subject with atherosclerosis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first **aspectexample** of the **inventiondisclosure**,
- the polynucleotide of the second **aspectexample** of the **inventiondisclosure**,
- the vector of the third **aspectexample** of the **inventiondisclosure**,
- the host cell of the fourth **aspectexample** of the **inventiondisclosure**, and/or
- the composition of the sixth **aspectexample** of the **inventiondisclosure**.

A twentieth aspectexample of the **inventiondisclosure** relates to a method for reducing atherosclerotic plaque volume and/or atherosclerotic plaque size in a subject with atherosclerosis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first **aspectexample** of the **inventiondisclosure**,
- the polynucleotide of the second **aspectexample** of the **inventiondisclosure**,
- the vector of the third **aspectexample** of the **inventiondisclosure**,
- the host cell of the fourth **aspectexample** of the **inventiondisclosure**, and/or
- the composition of the sixth **aspectexample** of the **inventiondisclosure**.

A twenty-first aspectexample of the **inventiondisclosure** relates to a method for reducing inflammation and/or fibrosis in a subject with myocarditis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first **aspectexample** of the **inventiondisclosure**,
- the polynucleotide of the second **aspectexample** of the **inventiondisclosure**,
- the vector of the third **aspectexample** of the **inventiondisclosure**,
- the host cell of the fourth **aspectexample** of the **inventiondisclosure**, and/or
- the composition of the sixth **aspectexample** of the **inventiondisclosure**.

A twenty-second aspectexample of the **inventiondisclosure** relates to a method for counteracting deterioration in cardiac function in a subject with myocarditis or autoimmune myocarditis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first **aspectexample** of the **inventiondisclosure**,
- the polynucleotide of the second **aspectexample** of the **inventiondisclosure**,
- the vector of the third **aspectexample** of the **inventiondisclosure**,
- the host cell of the fourth **aspectexample** of the **inventiondisclosure**, and/or

-the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#).

A twenty-third [aspectexample](#) of the [inventiondisclosure](#) relates to a method for reducing dermal fibrosis in a subject with systemic sclerosis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first [aspectexample](#) of the [inventiondisclosure](#),
- the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
- the vector of the third [aspectexample](#) of the [inventiondisclosure](#),
- the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#), and/or
- the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#).

A twenty-fourth [aspectexample](#) of the [inventiondisclosure](#) relates to a method for reducing pulmonary fibrosis in a subject with systemic sclerosis, the method comprising the step of administering to the subject an effective amount of

- the antibody or antigen-binding fragment of the first [aspectexample](#) of the [inventiondisclosure](#),
- the polynucleotide of the second [aspectexample](#) of the [inventiondisclosure](#),
- the vector of the third [aspectexample](#) of the [inventiondisclosure](#),
- the host cell of the fourth [aspectexample](#) of the [inventiondisclosure](#), and/or
- the composition of the sixth [aspectexample](#) of the [inventiondisclosure](#).

In one aspect, the present disclosure relates to an antibody or antigen-binding fragment thereof with binding specificity for interleukin-1 receptor accessory protein (IL1RAP), wherein the antibody or antigen-binding fragment comprises: a light chain variable region comprising a) a CDR-L1 comprising or consisting of an amino acid sequence selected from the group consisting of ESISTA (SEQ ID NO: 1), QASESISTALA (SEQ ID NO: 7) and QASESISTALA (SEQ ID NO: 13); b) a CDR-L2 comprising or consisting of an amino acid sequence selected from the group consisting of KAS, KASTLPS (SEQ ID NO: 8) and KASTLPS (SEQ ID NO: 14); and c) a CDR-L3 comprising or consisting of an amino acid sequence selected from the group consisting of QQGFSNGNVHNA (SEQ ID NO: 3), QQGFSNGNVHNA (SEQ ID NO: 9) and QQGFSNGNVHNA (SEQ ID NO: 15); and / or a heavy chain variable region comprising d) a CDR-H1 comprising or consisting of an amino acid sequence selected from the group consisting of GPSLSHFD (SEQ ID NO: 4), HFDIT (SEQ ID NO: 10) and GPSLSHFDIT (SEQ ID NO: 16); e) a CDR-H2 comprising or consisting of an amino acid sequence selected from the group consisting of ISPGVST (SEQ ID NO: 5), TISPGVSTYYASWAKS (SEQ ID NO: 11) and TISPGVSTYYASWAKS (SEQ ID NO: 17); and f) a CDR-H3 comprising or consisting of an amino acid sequence selected from the group consisting of ARGGVGSSWKAFDL (SEQ ID NO: 6), GGVGSSWKAFDL (SEQ ID NO: 12) and ARGGVGSSWKAFDL (SEQ ID NO: 18).

In another aspect, the present disclosure relates to a polynucleotide encoding an antibody or antigen-binding fragment thereof as disclosed herein or a component polypeptide chain thereof; optionally: (a) wherein the polynucleotide is a cDNA molecule; (b) encoding an antibody light chain or variable region thereof; and/or (c) encoding an antibody heavy chain or variable region thereof.

In another aspect, the present disclosure relates to a vector comprising a polynucleotide as disclosed herein, optionally wherein the vector is an expression vector.

In another aspect, the present disclosure relates to a recombinant host cell comprising a polynucleotide as disclosed herein or a vector as disclosed herein, optionally wherein the host cell is a bacterial cell, a yeast cell, a mammalian cell, or a human cell.

In another aspect, the present disclosure relates to a method for producing an antibody or antigen-binding fragment as disclosed herein, the method comprising culturing a host cell as disclosed herein comprising the polynucleotide as disclosed herein or the vector as disclosed herein, under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as disclosed herein, the polynucleotide as disclosed herein, the vector as disclosed herein the recombinant host cell as disclosed herein, in a pharmaceutical composition, wherein the composition further comprises a pharmaceutically-acceptable diluent, carrier or excipient; optionally: (a) wherein the composition comprises an effective amount of the antibody or antigen-binding fragment thereof, the polynucleotide, the vector, and/or the recombinant host cell; and/or (b) adapted for parenteral delivery, optionally wherein the parenteral delivery is intravenous delivery, topical delivery, subcutaneous delivery and/or intramuscular delivery.

In another aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof as disclosed herein, a polynucleotide as disclosed herein, a vector as disclosed herein, a recombinant host cell as disclosed herein, and/or a composition as disclosed herein, for use in medicine.

In another aspect, the present disclosure refers to use of an antibody or antigen-binding fragment thereof as disclosed herein, a polynucleotide as disclosed herein, a vector as disclosed herein, a recombinant host cell as disclosed herein, and/or a composition as disclosed herein, in the manufacture of a medicament for the prevention, treatment, alleviation, detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or wherein the disease or disorder is associated with cells expressing IL1RAP; wherein the disease or disorder: (a) is an inflammatory and/or fibrotic disease or disorder, optionally wherein the inflammatory and/or fibrotic disease or disorder is selected from the group consisting of myocarditis, systemic sclerosis, psoriasis, psoriatic arthritis, atherosclerosis, rheumatoid arthritis, all types of arthritis, all types of juvenile arthritis including systemic onset juvenile idiopathic arthritis (SOJIA), osteoarthritis, familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells disease, neonatal onset multi-system inflammatory disease (NOMID), familial Mediterranean fever (FMF), pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome, adult onset Still's disease, hyper IgD syndrome, type 2 diabetes mellitus, macrophage activation syndrome, TNF receptor-associated periodic syndrome, Blau disease, ankylosing spondylitis, Sweets disease, lupus arthritis, Alzheimer's disease, asthma, allergy, sarcoidosis, atopic dermatitis, systemic lupus erythematosus, bullous pemphigoid, type 1 diabetes mellitus, chronic obstructive pulmonary disease, Helicobacter pylori gastritis, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), hepatitis, hepatitis C, ischaemia-reperfusion injury, multiple sclerosis, Neisserial or pneumococcal meningitis, tuberculosis, Bechet's syndrome, septic shock, graft versus host disease, adult T cell leukaemia, multiple myeloma, periodontitis, obesity and obesity-related diseases (for example, metabolic syndrome,

cardiomegaly, congestive heart failure, myocardial infarction, varicose veins, polycystic ovarian syndrome, gastroesophageal reflux disease (GERD), fatty liver disease, colorectal cancer, breast cancer, uterine cancer, chronic renal failure, stroke and hyperuricemia), intervertebral disc disease, irritable bowel syndrome, Schnitzler syndrome, allergy/atopic dermatitis, acne inversa, Behcet's disease, cardiac fibrosis, cardiovascular diseases, cryopyrin-associated periodic syndromes, cystic fibrosis, Goodpasture's syndrome, Guillain-Barre syndrome, kidney fibrosis, liver fibrosis, lung fibrosis, skin fibrosis, autoimmune myocarditis, organ dysfunction associated with organ transplantation, pancreatitis, peritonitis, uveitis, vasculitis, pneumonia, pulmonary hypertension, sclerodermatous chronic graft-versus-host disease, sepsis, Sjögren's syndrome, Takayasu's arteritis and gout; (b) has an inflammatory and/or fibrotic component; and/or (c) is an autoimmune disease or disorder.

In another aspect, the present disclosure refers to use of an antibody or antigen-binding fragment thereof as disclosed herein, a polynucleotide as disclosed herein, a vector as disclosed herein, a recombinant host cell as disclosed herein, and/or a composition as disclosed herein in the manufacture of a medicament for the prevention, treatment, alleviation, detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or wherein the disease or disorder is associated with cells expressing IL1RAP; wherein the disease or disorder is a neoplastic disease or disorder, optionally wherein the neoplastic disease or disorder is: (a) a hematologic disease or disorder, or a solid tumour; (b) selected from the group consisting of chronic myeloid leukemia (CML), myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML); and/or (c) a solid tumour selected from the group consisting of prostate cancer, breast cancer, lung cancer, colon cancer, colorectal cancer, melanomas, bladder cancer, brain/CNS cancer, cancer of urinary organs, biliary tract cancer, cervical cancer, oesophageal cancer, gastric cancer, head/neck cancer, kidney cancer, liver cancer, lymphomas, ovarian cancer, pancreatic cancer, sarcomas, skin cancer and uterus cancer.

In yet another aspect, the present disclosure refers to use of an antibody or antigen-binding fragment thereof as disclosed herein, a polynucleotide as disclosed herein, a vector as disclosed herein, a recombinant host cell as disclosed herein, and/or a composition as disclosed herein, in the manufacture of a medicament for inducing cell death and/or inhibiting the growth and/or proliferation of pathological cells associated with a neoplastic disorder in a subject, or stem cells or progenitor cells thereof, wherein the cells express IL1RAP.

In yet another aspect, the present disclosure relates to an *in vitro* method for the detection of cells expressing IL1RAP in a subject, the method comprising: (a) providing a sample of cells from a subject to be tested, such as biopsy tissue or blood sample; (b) optionally, extracting and/or purifying the cells present in the sample; (c) contacting an antibody or antigen-binding fragment thereof as disclosed herein with cells present in the sample; (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expressing IL1RAP in the tissue of a subject.

In yet another aspect, the present disclosure relates to an *in vitro* method for identifying a patient with a disease or disorder associated with cells expressing IL1RAP who

would benefit from treatment with an antibody or antigen-binding fragment thereof as disclosed herein, the method comprising: (a) providing a sample of cells, such as biopsy tissue or blood sample from a patient to be tested; (b) optionally, extracting and/or purifying the cells present in the sample; (c) contacting an antibody or antigen-binding fragment thereof as disclosed herein with cells present in the sample; (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells wherein the binding of the antibody or antigen-binding fragment thereof to cells expressing IL1RAP is indicative of a patient who would benefit from treatment with an antibody or antigen-binding fragment thereof as disclosed herein

Description of Drawings

Figure 1: The anti-IL1RAP antibody mCAN10 reduces inflammation in a model for acute peritonitis

WT or KO mice were immunized with MSU crystals and 6 hrs after immunization, flow cytometry was performed on peritoneal lavages for quantification of infiltrating cells **(A)**. WT mice were treated with mCAN10, IL1RA, isotype control antibody (Isotype), or PBS only 1 hr prior to immunization with MSU crystals. Six hrs after immunization, peritoneal lavages were collected for flow cytometry for quantification of infiltrating cells **(B)**, or for quantification of cytokines and chemokines by a Luminex assay **(C)**.

Figure 2: The anti-IL1RAP antibody mCAN10 reduces disease severity in models for psoriasis and psoriatic arthritis

Psoriasis was induced in BALB/c mice by administration of Imiquimod on the shaved backs of mice for 7 days. During this period, mice were treated on three occasions with

CLAIMS

1. An antibody or antigen-binding fragment thereof with binding specificity for interleukin-1 receptor accessory protein (IL1RAP), wherein the antibody or antigen-binding fragment comprises:

a light chain variable region comprising

- a) a CDR-L1 comprising or consisting of an amino acid sequence selected from the group consisting of ESISTA (SEQ ID NO: 1), QASESISTALA (SEQ ID NO: 7) and QASESISTALA (SEQ ID NO: 13);
- b) a CDR-L2 comprising or consisting of an amino acid sequence selected from the group consisting of KAS, KASTLPS (SEQ ID NO: 8) and KASTLPS (SEQ ID NO: 14); and
- c) a CDR-L3 comprising or consisting of an amino acid sequence selected from the group consisting of QQGFSSGNVHNA (SEQ ID NO: 3), QQGFSSGNVHNA (SEQ ID NO: 9) and QQGFSSGNVHNA (SEQ ID NO: 15);

and / or

a heavy chain variable region comprising

- d) a CDR-H1 comprising or consisting of an amino acid sequence selected from the group consisting of GPSLSHFD (SEQ ID NO: 4), HFDIT (SEQ ID NO: 10) and GPSLSHFDIT (SEQ ID NO: 16);
- e) a CDR-H2 comprising or consisting of an amino acid sequence selected from the group consisting of ISPGVST (SEQ ID NO: 5), TISPGVSTYYASWAKS (SEQ ID NO: 11) and TISPGVSTYYASWAKS (SEQ ID NO: 17); and
- f) a CDR-H3 comprising or consisting of an amino acid sequence selected from the group consisting of ARGGVGSSWKAFDL (SEQ ID NO: 6), GGVGSSWKAFDL (SEQ ID NO: 12) and ARGGVGSSWKAFDL (SEQ ID NO: 18).

~~2. The antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment comprises: a light chain variable region comprising~~

a) ~~a CDR-L1 consisting of an amino acid sequence selected from the group consisting of ESISTA (SEQ ID NO: 1), QASESISTALA (SEQ ID NO: 7) and QASESISTALA (SEQ ID NO: 13);~~

b) ~~a CDR-L2 consisting of an amino acid sequence selected from the group consisting of KAS, KASTLPS (SEQ ID NO: 8) and KASTLPS (SEQ ID NO: 14); and~~

c) ~~a CDR-L3 consisting of an amino acid sequence selected from the group consisting of QQGFSSGNVHNA (SEQ ID NO: 3), QQGFSSGNVHNA (SEQ ID NO: 9) and QQGFSSGNVHNA (SEQ ID NO: 15);~~

and/or

a heavy chain variable region comprising

d) ~~a CDR-H1 consisting of an amino acid sequence selected from the group consisting of GPSLSHFD (SEQ ID NO: 4), HFDIT (SEQ ID NO: 10) and GPSLSHFDIT (SEQ ID NO: 16);~~

e) ~~a CDR-H2 consisting of an amino acid sequence selected from the group consisting of ISPGVST (SEQ ID NO: 5), TISPGVSTYYASWAKS (SEQ ID NO: 11) and TISPGVSTYYASWAKS (SEQ ID NO: 17); and~~

f) ~~a CDR-H3 consisting of an amino acid sequence selected from the group consisting of ARGGVGSSWKAFDL (SEQ ID NO: 6), GGVGSSWKAFDL (SEQ ID NO: 12) and ARGGVGSSWKAFDL (SEQ ID NO: 18).~~

~~32.~~ The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the IL1RAP is human IL1RAP; and/or

~~4.~~ The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the IL1RAP is expressed on the surface of a cell.

~~53.~~ The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment thereof binds to domain 2 of IL1RAP.

~~6.~~ The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the CDRs

~~comprising or consisting of an amino acid sequence selected from the group consisting of ESISTA (SEQ ID NO: 1), QASESISTALA (SEQ ID NO: 7) and QASESISTALA (SEQ ID NO: 13);~~

~~comprising or consisting of an amino acid sequence selected from the group consisting of KAS, KASTLPS (SEQ ID NO: 8) and KASTLPS (SEQ ID NO: 14); and/or~~

~~comprising or consisting of an amino acid sequence selected from the group consisting of QQGFSSGNVHNA (SEQ ID NO: 3), QQGFSSGNVHNA (SEQ ID NO: 9) and QQGFSSGNVHNA (SEQ ID NO: 15).~~

~~74.~~ The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a light chain variable region comprising or consisting of the amino acid sequence selected from the group consisting of: SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25 and SEQ ID NO: 31;

or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 19 SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25 or SEQ ID NO: 31, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.

optionally

~~8. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25;~~

~~or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24 or SEQ ID NO: 25, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~

~~9. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising or consisting of the amino acid sequence of SEQ ID NO: 31;~~

~~or an amino acid sequence having at least 70% sequence identity to SEQ ID~~

~~NO: 31, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~

5 ~~10. The antibody or antigen binding fragment thereof according to any one claims 7 to 9,~~ wherein any one of the amino acids of the framework region of the light chain variable region has been altered for another amino acid, with the proviso that no more than 5 amino acids have been so altered, such as 4 amino acids, no more than 3 amino acids, such as 2 amino acids or no more than 1 amino acid; and/or

10 (b)

~~11. The antibody or antigen binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the CDRs comprising or consisting of an amino acid sequence selected from the group consisting of GPSLSHFD (SEQ ID NO: 4), HFDIT (SEQ ID NO: 10) and GPSLSHFDT (SEQ ID NO: 16); comprising or consisting of an amino acid sequence selected from the group consisting of ISPGVST (SEQ ID NO: 5), TISPGVSTYYASWAKS (SEQ ID NO: 11) and TISPGVSTYYASWAKS (SEQ ID NO: 17); and/or comprising or consisting of an amino acid sequence selected from the group consisting of ARGGVGSSWKAFDL (SEQ ID NO: 6), GGVGSSWKAFDL (SEQ ID NO: 12) and ARGGVGSSWKAFDL (SEQ ID NO: 18).~~

25 ~~12. The antibody or antigen binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen binding fragment thereof comprises~~ a heavy chain variable region comprising or consisting of the amino acid sequence selected from the group consisting of: SEQ ID NO: 20, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34, ;
 30 or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 20, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity;.

35 optionally

- 5 ~~13. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30; or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO: 30, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~
- 10 ~~14. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34; or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~
- 15 ~~15. The antibody or antigen-binding fragment thereof according to any one of~~
- 20 ~~claims 12 to 14,~~ wherein any one of the amino acids of the framework region of the heavy chain variable region has been altered for another amino acid, with the proviso that no more than 5 amino acids have been so altered, such as 4 amino acids, no more than 3 amino acids, such as 2 amino acids or no more than 1 amino acid.
- 25 ~~16. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises:~~
- 30 ~~a light chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 19 and a heavy chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 20, or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 19 or SEQ ID NO: 20, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~

35

17. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment thereof comprises:~~

- ~~a) a light chain variable region which comprises or consists of SEQ ID NO: 21 and a heavy chain variable region which comprises or consists of SEQ ID NO: 26; _____~~
- ~~b) a light chain variable region which comprises or consists of SEQ ID NO: 21 and a heavy chain variable region which comprises or consists of SEQ ID NO: 27;~~
- ~~c) a light chain variable region which comprises or consists of SEQ ID NO: 21 and a heavy chain variable region which comprises or consists of SEQ ID NO: 28;~~
- ~~d) a light chain variable region which comprises or consists of SEQ ID NO: 21 and a heavy chain variable region which comprises or consists of SEQ ID NO: 29;~~
- ~~e) a light chain variable region which comprises or consists of SEQ ID NO: 21 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~
- ~~f) a light chain variable region which comprises or consists of SEQ ID NO: 22 and a heavy chain variable region which comprises or consists of SEQ ID NO: 26;~~
- ~~g) a light chain variable region which comprises or consists of SEQ ID NO: 22 and a heavy chain variable region which comprises or consists of SEQ ID NO: 27;~~
- ~~h) a light chain variable region which comprises or consists of SEQ ID NO: 22 and a heavy chain variable region which comprises or consists of SEQ ID NO: 28;~~
- ~~i) a light chain variable region which comprises or consists of SEQ ID NO: 22 and a heavy chain variable region which comprises or consists of SEQ ID NO: 29;~~
- ~~j) a light chain variable region which comprises or consists of SEQ ID NO: 22 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~
- ~~k) a light chain variable region which comprises or consists of SEQ ID NO: 23 and a heavy chain variable region which comprises or consists of SEQ ID NO: 26;~~

	~~l) a light chain variable region which comprises or consists of SEQ ID NO: 23 and a heavy chain variable region which comprises or consists of SEQ ID NO: 27;~~
5	~~m) a light chain variable region which comprises or consists of SEQ ID NO: 23 and a heavy chain variable region which comprises or consists of SEQ ID NO: 28;~~
	~~n) a light chain variable region which comprises or consists of SEQ ID NO: 23 and a heavy chain variable region which comprises or consists of SEQ ID NO: 29;~~
10	~~o) a light chain variable region which comprises or consists of SEQ ID NO: 23 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~
	~~p) a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 26;~~
15	~~q) a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 27;~~
	~~r) a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 28;~~
20	~~s) a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 29;~~
	~~t) a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~
25	~~u) a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 26;~~
30	~~v) a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 27;~~
	~~w) a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 28;~~
35	

x) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 29; or~~

y) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~

~~or an amino acid sequence having at least 70% sequence identity to any one of SEQ ID NO: 21 to SEQ ID NO: 30, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~

18. ~~The antibody or antigen binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen binding fragment thereof comprises:~~

a) ~~a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~

b) ~~a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 32;~~

c) ~~a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 33;~~

d) ~~a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 34;~~

e) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~

f) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 32;~~

g) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 33;~~

h) ~~a light chain variable region which comprises or consists of SEQ ID NO: 25 and a heavy chain variable region which comprises or consists of SEQ ID NO: 34;~~

i) ~~— a light chain variable region which comprises or consists of SEQ ID NO: 31 and a heavy chain variable region which comprises or consists of SEQ ID NO: 30;~~

j) ~~— a light chain variable region which comprises or consists of SEQ ID NO: 31 and a heavy chain variable region which comprises or consists of SEQ ID NO: 32;~~

k) ~~— a light chain variable region which comprises or consists of SEQ ID NO: 31 and a heavy chain variable region which comprises or consists of SEQ ID NO: 33; or~~

l) ~~— a light chain variable region which comprises or consists of SEQ ID NO: 31 and a heavy chain variable region which comprises or consists of SEQ ID NO: 34;~~

~~or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 31, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity.~~

19. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region which comprises or consists of SEQ ID NO: 24 and a heavy chain variable region which comprises or consists of SEQ ID NO: 34.~~

20. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region which comprises or consists of SEQ ID NO: 31 and a heavy chain variable region which comprises or consists of SEQ ID NO: 34.~~

21. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein any one of the amino acids of the framework region of the light chain variable region and/or the heavy chain variable region has been altered for another amino acid, with the proviso that no more than 5 amino acids have been so altered, such as 4 amino acids, no more than 3 amino acids, such as 2 amino acids or no more than 1 amino acid.~~

~~22~~5. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof:

(a) comprises a light chain constant region, or part thereof, optionally

5 23. ~~The antibody or antigen-binding fragment thereof according to claim 22,~~ wherein the light chain constant region is of a kappa or lambda light chain:

(b)

10 24. ~~The antibody or antigen-binding fragment thereof according to any one of claims 22 to 23, wherein the light chain constant region is of a kappa light chain.~~

15 25. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof~~ comprises a light chain constant region comprising or consisting of the amino acid sequence of SEQ ID NO: 35, or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 35, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity:

(c)

25 26. ~~The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof~~ comprises a heavy chain constant region, or part thereof, optionally

30 27. ~~The antibody or antigen-binding fragment thereof according to claim 26,~~ wherein the heavy chain constant region is of an immunoglobulin subclass selected from the group consisting of IgG1, IgG2, IgG3 and IgG4:

(d)

35 28. ~~The antibody or antigen-binding fragment thereof according to any one of claims 26 to 27, wherein the heavy chain constant region is of an immunoglobulin subclass IgG1.~~

~~29. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof~~ comprises or consists of a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 2, or an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 36 or SEQ ID NO: 2, for example at least 80%, 85%, 90%, 95%, 98% or 99% sequence identity; and/or

(e)

~~30. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein~~ any one of the amino acids of the light chain constant region and/or the heavy chain constant region has been altered for another amino acid, with the proviso that no more than 5 amino acids have been so altered, such as 4 amino acids, no more than 3 amino acids, such as 2 amino acids or no more than 1 amino acid.

~~31. The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment thereof comprises or consists of~~

~~-a light chain variable region according to any one of claims 6 to 10; and/or
-a heavy chain variable region according to any one of claims 11 to 15; and/or
-a light chain constant region according to any one of claims 22 to 25; and/or
-a heavy chain constant region according to any one of claims 26 to 30.~~

~~32~~6. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises:

(a) an Fc region; optionally

~~33. The antibody or antigen-binding fragment thereof according to claim 32,~~ wherein the Fc region is non-naturally occurring; and/or
(b)

~~34. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody comprises an~~ Fc region with a mutated IgG constant region; optionally

~~35.—The antibody or antigen-binding fragment thereof according to any one of claims 32 to 34, wherein:~~

~~(i) the Fc region comprises one or more of the mutations affecting the effector function of the antibody or antigen-binding fragment thereof;~~

~~(ii)~~

~~36.—The antibody or antigen-binding fragment thereof according to any one of claims 32 to 35, wherein the Fc region comprises one or more of the mutations selected from the group consisting of L234A, L235A, P329G, G237A, P238S, H269A, A330S and P331S as defined by the EU Index;~~ and/or

~~(iii)~~

~~37.—The antibody or antigen-binding fragment thereof according to any one of claims 32 to 36, wherein the glycan attached to the Fc region is lacking fucose;~~ or

~~38.—The antibody or antigen-binding fragment thereof according to any one of claims 32 to 36, wherein the glycan attached to the Fc region is low in fucose.~~

~~39~~7. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment is produced in a FUT8 negative cell line.

~~40~~8. The antibody or antigen-binding fragment thereof according to any one of the preceding claims comprising or consisting of:

~~(a) an intact antibody;~~ and/or

~~(b)~~

~~41.—The antibody or antigen-binding fragment thereof according to any one of the preceding claims comprising or consisting of an antigen-binding fragment selected from the group consisting of Fv fragments (e.g. single chain Fv and disulphide-bonded Fv), Fab-like fragments (e.g. Fab~~

fragments, Fab' fragments and F(ab)₂ fragments) and domain antibodies (e.g. single V_H variable domains or V_L variable domains).

429. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of:

(a) inhibiting signaling of interleukin-1 (IL-1) family cytokine ligands and/or receptors; and/or

(b)

~~43. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of at least one cytokine selected from the group consisting of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and IL-36 γ , or any combination thereof;~~

optionally

~~44. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-1 α .~~

~~45. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-1 β .~~

~~46. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-33.~~

~~47. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-36 α .~~

~~48. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-36 β .~~

~~49. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-36γ.~~

~~50. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is capable of inhibiting signaling of IL-1α, IL-1β, IL-33, IL-36α, IL-36β and IL-36γ.~~

~~51. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein inhibiting signaling is essentially complete inhibition of signaling-or~~

~~52. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein inhibiting signaling is partial inhibition of signaling.~~

~~53~~10. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment exhibits one or more of the following properties:

- a) a binding affinity (K_D) for IL1RAP characterized by a K_D -value of 3 nM or less;
- b) binding to domain 2 of IL1RAP, preferably binding to the H2 region of domain 2, wherein the H2 region comprises or consists of amino acids of SEQ ID NO: 39;
- c) cross-reactivity with IL1RAP from cynomolgus monkey or pig;
- d) an inhibitory action on IL-1α signaling;
- e) an inhibitory action on IL-1β signaling;
- f) an inhibitory action on IL-33 signaling;
- g) an inhibitory action on IL-36α signaling;
- h) an inhibitory action on IL-36β signaling;
- i) an inhibitory action on IL-36γ signaling;
- j) internalization by IL1RAP-expressing cells-~~;~~
- k)

~~54. The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment exhibits all of the following properties:~~

- ~~a) a binding affinity (K_D) for IL1RAP characterized by a K_D -value of 3 nM or less;~~
- ~~b) binding to domain 2 of IL1RAP, preferably binding to the H2 region of domain 2, wherein the H2 region comprises or consists of amino acids of SEQ ID NO: 39;~~
- ~~c) cross-reactivity with IL1RAP from cynomolgus monkey or pig;~~
- ~~d) an inhibitory action on IL-1 α signaling;~~
- ~~e) an inhibitory action on IL-1 β signaling;~~
- ~~f) an inhibitory action on IL-33 signaling;~~
- ~~g) an inhibitory action on IL-36 α signaling;~~
- ~~h) an inhibitory action on IL-36 β signaling;~~
- ~~i) an inhibitory action on IL-36 γ signaling;~~
- ~~j) internalization by IL1RAP-expressing cells.~~

~~55. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment is capable of inducing ADCC of cells expressing IL1RAP.~~

~~56. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 54, wherein the antibody or antigen-binding fragment is not capable of inducing ADCC of cells expressing IL1RAP.~~

~~57~~11. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof:

(a) further comprises a moiety for increasing the *in vivo* half-life of the agent, optionally

~~58. The antibody or antigen-binding fragment thereof according to claim 57, wherein the moiety for increasing the *in vivo* half-life is selected from the group consisting of polyethylene glycol (PEG), human serum albumin, glycosylation groups, fatty acids and dextran.~~

(b)

~~59.—The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is PEGylated; and/or~~

~~(c)~~

~~60.—The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment is covalently bound, directly or indirectly, to a functional moiety such as a cytotoxic or detectable moiety.~~

~~61. The antibody or antigen-binding fragment thereof according to any one of the preceding claims wherein the antibody or antigen-binding fragment comprises a cytotoxic moiety.~~

~~62. The antibody or antigen-binding fragment thereof according to any one of claims 60 to 61, wherein the cytotoxic moiety comprises or consists of a radioisotope.~~

~~63. The antibody or antigen-binding fragment thereof according to claim 62, wherein the radioisotope is selected from the group consisting of beta-emitters, auger emitters, conversion electron emitters, alpha emitters, and low photon energy emitters.~~

~~64. The antibody or antigen-binding fragment thereof according any one of claims 62 to 63, wherein the radioisotope has an emission pattern of locally absorbed energy that creates a high dose absorbance in the vicinity of the agent.~~

~~65. The antibody or antigen-binding fragment thereof according to any one of claims 62 to 64, wherein the radioisotope is selected from the group consisting of long-range beta-emitters, such as ^{90}Y , ^{32}P , ^{186}Re / ^{186}Re , ^{166}Ho , ^{76}As / ^{77}As , ^{153}Sm ; medium range beta-emitters, such as ^{131}I , ^{177}Lu , ^{67}Cu , ^{164}Tb ; low-energy beta-emitters, such as ^{45}Ca , ^{35}S or ^{14}C ; conversion or auger-emitters, such as ^{51}Cr , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I , ^{125}I , ^{201}Tl ; and alpha-emitters, such as ^{212}Bi , ^{213}Bi , ^{223}Ac , and ^{224}At .~~

66. The antibody or antigen-binding fragment thereof according to any one of claims 62 to 65 wherein the radioisotope is ^{177}Lu .

67. The antibody or antigen-binding fragment thereof according to any one of claims 60 to 66, wherein the cytotoxic moiety comprises or consists of a cytotoxic drug.

68. The antibody or antigen-binding fragment thereof according to claim 67, wherein the cytotoxic drug is selected from the group consisting of a cytostatic drug; an anti-androgen drug; cortisone and derivatives thereof; a phosphonate; a testosterone $5\text{-}\alpha$ -reductase inhibitor; a boron addend; a cytokine; thapsigargin and its metabolites; a toxin (such as saporin or calicheamicin); a chemotherapeutic agent (such as an antimetabolite); or any other cytotoxic drug useful in the treatment of neoplastic disorders.

69. The antibody or antigen-binding fragment thereof according to any one of claims 67 or 68, wherein the cytotoxic drug is suitable for use in activation therapy, such as photon activation therapy, neutron activation therapy, neutron induced Auger electron therapy, synchrotron irradiation therapy, or low energy X-ray photon activation therapy.

70. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises a detectable moiety.

71. The antibody or antigen-binding fragment thereof according to claim 70, wherein the detectable moiety comprises or consists of a radioisotope.

72. The antibody or antigen-binding fragment thereof according to claim 71 wherein the radioisotope is selected from the group consisting of $^{99\text{m}}\text{Tc}$, ^{111}In , ^{67}Ga , ^{68}Ga , ^{72}As , ^{89}Zr , ^{123}I and ^{201}Tl .

73. The antibody or antigen-binding fragment thereof according to any one of claims 71 to 72, wherein the radioisotope is ^{89}Zr .

74. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment

~~comprises a pair of detectable and cytotoxic radioisotopes, such as $^{86}\text{Y}/^{90}\text{Y}$ or $^{124}\text{I}/^{211}\text{At}$.~~

5 ~~75. The antibody or antigen-binding fragment thereof according to any one of claims 60 to 74, wherein the radioisotope is capable of simultaneously acting in a multi-modal manner as a detectable moiety and as a cytotoxic moiety.~~

10 ~~76. The antibody or antigen-binding fragment thereof according to any one of claims 60 to 75, wherein the detectable moiety comprises or consists of a paramagnetic isotope.~~

15 ~~77. The antibody or antigen-binding fragment thereof according to claim 76 wherein the paramagnetic isotope is selected from the group consisting of ^{157}Gd , ^{55}Mn , ^{162}Dy , ^{52}Cr and ^{56}Fe .~~

~~78. The antibody or antigen-binding fragment thereof according to any of claims 60 to 77, wherein the detectable moiety is detectable by an imaging technique such as SPECT, PET, MRI, optical or ultrasound imaging.~~

20 ~~79. The antibody or antigen-binding fragment thereof according to any of claims 60 to 78, wherein the cytotoxic moiety and/or detectable moiety is joined to the antibody or antigen-binding fragment thereof indirectly, via a linking moiety.~~

25 ~~80. The antibody or antigen-binding fragment thereof according to claim 79, wherein the linking moiety is a chelator.~~

30 ~~81. The antibody or antigen-binding fragment thereof according to claim 80, wherein the chelator is selected from the group consisting of derivatives of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), deferoxamine (DFO), derivatives of diethylenetriaminepentaacetic acid (DTPA), derivatives of S-2-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and derivatives of 1,4,8,11-tetraazacyclododecan-1,4,8,11-tetraacetic acid (TETA).~~

35

~~82. The antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody or antigen-binding fragment does not comprise a cytotoxic moiety.~~

5 ~~83~~12. A polynucleotide encoding an antibody or antigen-binding fragment thereof according to any one of the preceding claims or a component polypeptide chain thereof;

optionally:

(a)

10 ~~84. The polynucleotide according to claim 83, wherein the polynucleotide is a cDNA molecule;~~

(b)

15 ~~85. The polynucleotide according to any one of claims 83 to 84, encoding an antibody light chain or variable region thereof;~~ and/or

(c)

20 ~~86. The polynucleotide according to any one of claims 83 to 84 encoding an antibody heavy chain or variable region thereof.~~

~~87~~13. A vector comprising a polynucleotide according to ~~any one of claims 12~~83 to 86, optionally

25 ~~88. The vector according to claim 87~~ wherein the vector is an expression vector.

~~89~~14. A recombinant host cell comprising a polynucleotide according to ~~any one of claims 12~~83 to 86 or a vector according to ~~any one of claims 87 to 88~~13, optionally

30 ~~90. The host cell according to claim 89, wherein the host cell is a bacterial cell;~~

~~91. The host cell according to claim 89, wherein the host cell is a yeast cell;~~

35 ~~92. The host cell according to claim 89, wherein the host cell is a mammalian cell;~~ or

~~93. The host cell according to claim 89, wherein the host cell is~~ a human cell.

~~94~~¹⁵. A method for producing an antibody or antigen-binding fragment according to any one of claims 1 to ~~11~~⁸², the method comprising culturing a host cell according to ~~any of claims 14~~^{89 to 93} comprising the polynucleotide according to ~~any one of claims 12~~^{83 to 86} or the vector according to ~~any one of claims 87 to 88~~¹³, under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.

~~95~~¹⁶. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~⁸², the polynucleotide according to ~~any one of claims 83 to 86~~¹², the vector according to ~~any one of claims 87 to 88~~¹³, and/or the recombinant host cell according to ~~any one of claims 89 to 93~~¹⁴, in a pharmaceutical composition, wherein the composition further comprises a pharmaceutically-acceptable diluent, carrier or excipient;

optionally:

(a)

~~96. The composition according to claim 95,~~ wherein the composition comprises an effective amount of the antibody or antigen-binding fragment thereof, the polynucleotide, the vector, and/or the recombinant host cell; and/or

(b)

~~97. The composition according to any one of claims 95 to 96~~ adapted for parenteral delivery; optionally

~~98. The composition according to claim 97,~~ wherein the parenteral delivery is intravenous delivery, topical delivery, subcutaneous delivery and/or intramuscular delivery.

~~99~~¹⁷. An antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~⁸², a polynucleotide according to ~~any one of claims 83 to 86~~¹², a vector according to ~~any one of claims 87 to 88~~¹³, a recombinant host cell according to ~~any one of claims 89 to 93~~¹⁴, and/or a composition according to ~~any one of claims 95 to 98~~¹⁵, for use in medicine.

~~100~~18. Use of Aan antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82, a polynucleotide according to ~~any one of claims 83 to 86~~12, a vector according to ~~any one of claims 87 to 88~~13, a recombinant host cell according to ~~any one of claims 89 to 93~~14, and/or a composition according to ~~any one of claims 95 to 98~~15, in the manufacture of a medicament for ~~use in~~ the prevention, treatment, alleviation, detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or wherein the disease or disorder is associated with cells expressing IL1RAP~~;~~:

~~101.~~ ~~The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to claim 100,~~ wherein the disease or disorder:

(a) is an inflammatory and/or fibrotic disease or disorder~~;~~, optionally

~~102.~~ ~~The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according any one of claims 100 to 101,~~

wherein the inflammatory and/or fibrotic disease or disorder is selected from the group consisting of myocarditis, systemic sclerosis, psoriasis, psoriatic arthritis, atherosclerosis, rheumatoid arthritis, all types of arthritis, all types of juvenile arthritis including systemic onset juvenile idiopathic arthritis (SOJIA), osteoarthritis, familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells disease, neonatal onset multi-system inflammatory disease (NOMID), familial Mediterranean fever (FMF), pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome, adult onset Still's disease, hyper IgD syndrome, type 2 diabetes mellitus, macrophage activation syndrome, TNF receptor-associated periodic syndrome, Blau disease, ankylosing spondylitis, Sweets disease, lupus arthritis, Alzheimer's disease, asthma, allergy, sarcoidosis, atopic dermatitis, systemic lupus erythematosus, bullous pemphigoid, type I diabetes mellitus, chronic obstructive pulmonary disease, Helicobacter pylori gastritis, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), hepatitis, hepatitis C, ischaemia-reperfusion injury, multiple sclerosis, Neisserial or pneumococcal meningitis, tuberculosis,

Bechet's syndrome, septic shock, graft versus host disease, ~~an~~ adult T cell leukaemia, multiple myeloma, periodontitis, obesity and obesity-related diseases (for example, metabolic syndrome, cardiomegaly, congestive heart failure, myocardial infarction, varicose veins, polycystic ovarian syndrome, gastroesophageal reflux disease (GERD), fatty liver disease, colorectal cancer, breast cancer, uterine cancer, chronic renal failure, stroke and hyperuricemia), intervertebral disc disease, irritable bowel syndrome, Schnitzler syndrome, allergy/atopic dermatitis, acne inversa, Behcet's disease, cardiac fibrosis, cardiovascular diseases, cryopyrin-associated periodic syndromes, cystic fibrosis, Goodpasture's syndrome, Guillain-Barre syndrome, kidney fibrosis, liver fibrosis, lung fibrosis, skin fibrosis, autoimmune myocarditis, organ dysfunction associated with organ transplantation, pancreatitis, peritonitis, uveitis, vasculitis, pneumonia, pulmonary hypertension, sclerodermatous chronic graft-versus-host disease, sepsis, Sjögren's syndrome, Takayasu's arteritis and gout;

(b)

~~103. The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to any one of claims 100 to 102, wherein the disease or disorder~~ has an inflammatory and/or fibrotic component; and/or

(c)

~~104. The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to any one of claims 100 to 103, wherein the disease or disorder~~ is an autoimmune disease or disorder.

~~105~~ 19. Use of an antibody or antigen-binding fragment thereof according to any one of claims 1 to 11, a polynucleotide according to claim 12, a vector according to claim 13, a recombinant host cell according to claim 14, and/or a composition according to claim 15, in the manufacture of a medicament for the prevention, treatment, alleviation, detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or wherein the disease or disorder is associated with cells expressing IL1RAP;

~~The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to claim 100,~~ wherein the disease or disorder is a neoplastic disease or disorder, optionally

~~106.—The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use according to any one of claims 100 or 105,~~ wherein the neoplastic disease or disorder is:

(a) a hematologic disease or disorder, or a solid tumour;

(b)

~~107.—The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to any one of claims 105 to 106,~~ wherein the neoplastic hematologic disease or disorder is selected from the group consisting of chronic myeloid leukemia (CML), myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML);

and/or

(c) a

~~108.—The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to any one of claims 105 to 107,~~ wherein the solid tumour is selected from the group consisting of prostate cancer, breast cancer, lung cancer, colon cancer, colorectal cancer, melanomas, bladder cancer, brain/CNS cancer, cancer of urinary organs, biliary tract cancer, cervical cancer, oesophageal cancer, gastric cancer, head/neck cancer, kidney cancer, liver cancer, lymphomas, ovarian cancer, pancreatic cancer, sarcomas, skin cancer and uterus cancer.

~~109.—The antibody, the antigen-binding fragment thereof, the polynucleotide, the vector, the host cell or the composition for use, according to any one of claims 100 to 108,~~ wherein the disease or disorder is associated with cells expressing IL1RAP.

~~110~~20. Use of Aan antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82, a polynucleotide according to ~~any one of claims~~

~~83 to 86~~¹², a vector according to ~~any one of claims 87 to 88~~¹³, a recombinant host cell according to ~~any one of claims 89 to 93~~¹⁴, and/or a composition according to ~~any one of claims 95 to 98~~¹⁵, in the manufacture of a medicament for ~~use in~~-inducing cell death and/or inhibiting the growth and/or proliferation of pathological cells associated with a neoplastic disorder in a subject, or stem cells or progenitor cells thereof, wherein the cells express IL1RAP.

~~111. — Use of an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82, a polynucleotide according to any one of claims 83 to 86, a vector according to any one of claims 87 to 88, a recombinant host cell according to any one of claims 89 to 93, and/or a composition according to any one of claims 95 to 98, in the preparation of a medicament for the prevention, treatment, alleviation, detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling, and/or wherein the disease or disorder is associated with cells expressing IL1RAP.~~

~~112. — Use of antibody or antigen-binding fragment thereof according to any one of claims 1 to 82, a polynucleotide according to any one of claims 83 to 86, a vector according to any one of claims 87 to 88, a recombinant host cell according to any one of claims 89 to 93, and/or a composition according to any one of claims 95 to 98, in the preparation of a medicament for the detection and/or diagnosis of a disease or disorder associated with cells expressing IL1RAP.~~

~~113. — A method for the prevention and/or treatment and/or alleviation and/or detection and/or diagnosis of a disease or disorder susceptible to treatment with an inhibitor of IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β and/or IL-36 γ signaling and/or wherein the disease or disorder is associated with cells expressing IL1RAP in a subject, comprising the step of administering to the subject an effective amount of~~

- ~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
- ~~-a polynucleotide according to any one of claims 83 to 86,~~
- ~~-a vector according to any one of claims 87 to 88,~~

~~a recombinant host cell according to any one of claims 89 to 93, and/or a composition according to any one of claims 95 to 98.~~

~~414~~21. An *in vitro* method for the detection of cells expressing IL1RAP in a subject, the method comprising:

- (a) providing a sample of cells from a subject to be tested, such as biopsy tissue or blood sample;
- (b) optionally, extracting and/or purifying the cells present in the sample;
- (c) contacting an antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82 with cells present in the sample;
- (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells

wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expressing IL1RAP in the tissue of a subject.

~~415~~22. An *in vitro* method for identifying a patient with a disease or disorder associated with cells expressing IL1RAP who would benefit from treatment with an antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82, the method comprising:

- (a) providing a sample of cells, such as biopsy tissue or blood sample from a patient to be tested;
- (b) optionally, extracting and/or purifying the cells present in the sample;
- (c) contacting an antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82 with cells present in the sample;
- (d) determining whether the antibody or antigen-binding fragment thereof binds to the cells

wherein the binding of the antibody or antigen-binding fragment thereof to cells expressing IL1RAP is indicative of a patient who would benefit from treatment with an antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~11~~82.

~~116. — A method for treating a patient with a disease or disorder associated with cells expressing IL1RAP, the method comprising:~~

- ~~a) selecting a patient identified as having a disease or disorder associated with cells expressing IL1RAP according to any one of claims 114 to 115;~~
- ~~b) administering to said patient a therapeutic agent effective in the treatment of said disease or disorder.~~

~~117. — A method for the detection of cells expressing IL1RAP, the method comprising:~~

- ~~(a) contacting an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82 with cells to be analysed for their expression of IL1RAP;~~
- ~~(b) determining whether the antibody or antigen-binding fragment thereof binds to the cells~~

~~wherein the binding of the antibody or antigen-binding fragment thereof to the cells is indicative of the presence of a disease or disorder associated with cells expressing IL1RAP in the tissue of a subject.~~

~~118. — The method according to claim 117, wherein the method is an *in vivo* method, an *ex vivo* method or an *in vitro* method.~~

~~119. — A method for reducing inflammation in a subject with peritonitis, the method comprising the step of administering to the subject an effective amount of~~

- ~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
- ~~-a polynucleotide according to any one of claims 83 to 86,~~
- ~~-a vector according to any one of claims 87 to 88,~~
- ~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
- ~~-composition according to any one of claims 95 to 98.~~

~~120. — A method for reducing disease severity in a subject with psoriasis or psoriatic arthritis, the method comprising the step of administering to the subject an effective amount of~~

~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~

121. ~~— A method for reducing atherosclerotic plaque inflammation in a subject with atherosclerosis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~

122. ~~— A method for reducing atherosclerotic plaque volume and/or atherosclerotic plaque size in a subject with atherosclerosis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~

123. ~~— A method for reducing inflammation and/or fibrosis in a subject with myocarditis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~

124. ~~— A method for counteracting deterioration in cardiac function in a subject with myocarditis or autoimmune myocarditis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~
125. ~~— A method for reducing dermal fibrosis in a subject with systemic sclerosis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~
126. ~~— A method for reducing pulmonary fibrosis in a subject with systemic sclerosis, the method comprising the step of administering to the subject an effective amount of~~
~~-an antibody or antigen-binding fragment thereof according to any one of claims 1 to 82,~~
~~-a polynucleotide according to any one of claims 83 to 86,~~
~~-a vector according to any one of claims 87 to 88,~~
~~-a recombinant host cell according to any one of claims 89 to 93, and/or a~~
~~-composition according to any one of claims 95 to 98.~~