

patterns of LCs or responding T cells are altered (13-15). Furthermore, CD1a has been linked to other systemic disorders including inflammatory bowel disease, multiple sclerosis, Guillain-Barre syndrome, thyroiditis, and neurodegeneration (Al-amodi Inflammatory Bowel Diseases 2018 24: 1225–1236; Caporale J Neuroimmunol 2006 177:112-8; Jamshidian Immunological Investigations 2010 3:874-889; Roura-Mir J Immunol 2005 174:3773-80; Wang Aging 2019 11: 4521–4535). In addition, CD1a can be expressed by certain malignancies including Langerhans cell histiocytosis, subsets of T cell lymphomas, subsets of thymomas and rare descriptions of other malignancies, such as subsets of mastocytosis.

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It is an object of the invention to provide anti-CD1a antibodies. Such antibodies are particularly useful in treating or preventing inflammatory diseases or disorders of the skin or mucosa, such as psoriasis, dermatitis, lupus erythematosus or drug reactions which manifest as an inflammatory skin or mucosal disease or disorder. Such antibodies may also be beneficial in treating or preventing associated systemic diseases or disorders, or inflammatory drug reactions which manifest systemically or in the treatment of CD1a-expressing malignancies.

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SUMMARY

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In one aspect, the present disclosure provides an antibody or antigen binding fragment thereof which binds to CD1a, for use in the treatment or prevention of one or more inflammatory skin or mucosal disease or disorder, or one or more associated systemic disease or disorder, or one or more inflammatory drug reaction which manifests systemically, or one or more CD1a-expressing malignancies. In another aspect, the present disclosure provides antibody or antigen binding fragment thereof, comprising:

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a) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 35 or a sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 38 or a sequence having at least 80% identity thereto; or

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b) a heavy chain variable region comprising a complementarity determining region CDR3 of SEQ ID NO: 3 or a sequence having at least 80% thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 6 or a sequence having at least 80% identity thereto; or

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c) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 11 or a sequence having at least 80% identity thereto, and/or a light chain variable region

comprising a CDR3 of SEQ ID NO: 14 or a sequence having at least 80% identity thereto; or

5 d) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 19 or a sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 22 or a sequence having at least 80% identity thereto; or

10 e) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 27 or a sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 30 or a sequence having at least 80% identity thereto.

In another aspect, the present disclosure provides an antibody or antigen binding fragment thereof, comprising:

a) a heavy chain variable region comprising:

15 a CDR1 of SEQ ID NO: 33,
a CDR2 of SEQ ID NO: 34, and
a CDR3 of SEQ ID NO: 35,
or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 36,
20 a CDR2 of SEQ ID NO: 37, and
a CDR3 of SEQ ID NO: 38,
or sequences having at least 80%, identity thereto; or

b) a heavy chain variable region comprising:

25 a CDR1 of SEQ ID NO: 1,
a CDR2 of SEQ ID NO: 2, and
a CDR3 of SEQ ID NO: 3,
or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 4,
30 a CDR2 of SEQ ID NO: 5, and
a CDR3 of SEQ ID NO: 6,
or sequences having at least 80%, identity thereto; or

c) a heavy chain variable region comprising:

35 a CDR1 of SEQ ID NO: 9,
a CDR2 of SEQ ID NO: 10, and

- a CDR3 of SEQ ID NO: 11,
 or sequences having at least 80% identity thereto, and/or
 a light chain variable region comprising:
 a CDR1 of SEQ ID NO: 12,
 5 a CDR2 of SEQ ID NO: 13, and
 a CDR3 of SEQ ID NO: 14,
 or sequences having at least 80%, identity thereto; or
 d) a heavy chain variable region comprising:
 a CDR1 of SEQ ID NO: 17,
 10 a CDR2 of SEQ ID NO: 18, and
 a CDR3 of SEQ ID NO: 19,
 or sequences having at least 80% identity thereto, and/or
 a light chain variable region comprising:
 a CDR1 of SEQ ID NO: 20,
 15 a CDR2 of SEQ ID NO: 21, and
 a CDR3 of SEQ ID NO: 22,
 or sequences having at least 80%, identity thereto; or
 e) a heavy chain variable region comprising:
 a CDR1 of SEQ ID NO: 25,
 20 a CDR2 of SEQ ID NO: 26, and
 a CDR3 of SEQ ID NO: 27,
 or sequences having at least 80% identity thereto, and/or
 a light chain variable region comprising:
 a CDR1 of SEQ ID NO: 28,
 25 a CDR2 of SEQ ID NO: 29, and
 a CDR3 of SEQ ID NO: 30,
 or sequences having at least 80%, identity thereto.

In another aspect, the present disclosure provides an antibody or antigen binding fragment thereof, comprising:

- 30 a) a heavy chain variable region comprising or consisting of SEQ ID NO: 39;
 and/or a light chain variable region comprising or consisting of SEQ ID NO: 40
 or sequences having at least 80% identity thereto; or
 b) a heavy chain variable region comprising or consisting of SEQ ID NO: 7;
 and/or a light chain variable region comprising or consisting of SEQ ID NO: 8
 35 or sequences having at least 80% identity thereto; or

- c) a heavy chain variable region comprising or consisting of SEQ ID NO: 15; and/or a light chain variable region comprising or consisting of SEQ ID NO: 16 or sequences having at least 80% identity thereto; or
- d) a heavy chain variable region comprising or consisting of SEQ ID NO: 23; and/or a light chain variable region comprising or consisting of SEQ ID NO: 24 or sequences having at least 80% identity thereto; or
- e) a heavy chain variable region comprising or consisting of SEQ ID NO: 31; and/or a light chain variable region comprising or consisting of SEQ ID NO: 32 or sequences having at least 80% identity thereto.
- 10 In another aspect, the present disclosure provides an antibody or antigen binding fragment thereof, comprising:
- a) a heavy chain comprising or consisting of SEQ ID NO: 49; and/or a light chain comprising or consisting of SEQ ID NO: 50 or sequences having at least 80% identity thereto; or
- 15 b) a heavy chain comprising or consisting of SEQ ID NO: 41; and/or a light chain comprising or consisting of SEQ ID NO: 42 or sequences having at least 80% identity thereto; or
- c) a heavy chain comprising or consisting of SEQ ID NO: 43; and/or a light chain comprising or consisting of SEQ ID NO: 44 or sequences having at least 80% identity thereto; or
- 20 d) a heavy chain comprising or consisting of SEQ ID NO: 45; and/or a light chain comprising or consisting of SEQ ID NO: 46 or sequences having at least 80% identity thereto; or
- e) a heavy chain comprising or consisting of SEQ ID NO: 47; and/or a light chain comprising or consisting of SEQ ID NO: 48 or sequences having at least 80% identity thereto.
- In an example, the description provides an antibody or antigen binding fragment thereof which is capable of binding to CD1a. The antibody or antigen binding fragment thereof may specifically bind to CD1a. The antibody or antigen binding fragment thereof may preferentially bind to CD1a. The antibody or antigen binding fragment thereof may induce cell death of cells expressing CD1a. The antibody or antigen binding fragment thereof may block the binding of ligands to CD1a.

The antibody or antigen binding fragment thereof may comprise a **heavy** chain variable region comprising a complementarity determining region (CDR) 3 (**CDR3**) of SEQ ID

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NO: 3 or a sequence having at least 80%, 90%, 95%, 98%, 99% or 100% identity thereto;
and/or

the antibody or antigen binding fragment thereof may comprise a **light** chain variable
region comprising a **CDR3** of SEQ ID NO:6 or a sequence having at least 80%, 90%,

5 95%, 98%, 99% or 100% identity thereto.

The antibody or antigen binding fragment thereof may consist of:

- a) a heavy chain comprising or consisting of SEQ ID NO: 49; and
- b) a light chain comprising or consisting of SEQ ID NO: 50.

5 An antibody or antigen binding fragment thereof of the description may be isolated.

In any example, “an antibody or antigen binding fragment thereof” may refer to one more, such as two of the recited antibodies or antigen binding fragments thereof. For example, in any example, two antibodies or antigen binding fragments thereof may be envisioned, each comprising or consisting of:

- a) a first antibody or antigen binding fragment thereof having a heavy chain variable region comprising:
 - a CDR1 of SEQ ID NO: 33, a CDR2 of SEQ ID NO: 34, and a CDR3 of SEQ ID NO: 35, or sequences having at least 80% identity thereto, and
 - 15 a light chain variable region comprising:
 - a CDR1 of SEQ ID NO: 36, a CDR2 of SEQ ID NO: 37, and a CDR3 of SEQ ID NO: 38, or sequences having at least 80%, identity thereto; and
 - a second antibody or antigen binding fragment thereof having a heavy chain variable region comprising:
 - 20 a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 2, and a CDR3 of SEQ ID NO: 3, or sequences having at least 80% identity thereto, and
 - a light chain variable region comprising:
 - a CDR1 of SEQ ID NO: 4, a CDR2 of SEQ ID NO: 5, and a CDR3 of SEQ ID NO: 6, or sequences having at least 80%, identity thereto; or
 - 25 b) a first antibody or antigen binding fragment thereof having a heavy chain variable region comprising or consisting of SEQ ID NO: 39; and a light chain variable region comprising or consisting of SEQ ID NO: 40, or sequences having at least 80% identity thereto; and
 - a second antibody or antigen binding fragment thereof having a heavy chain variable region comprising or consisting of SEQ ID NO: 7; and a light chain variable region comprising or consisting of SEQ ID NO: 8, or sequences having at least 80% identity thereto; or
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c) a first antibody or antigen binding fragment thereof having a heavy chain comprising or consisting of SEQ ID NO: 49; and a light chain comprising or consisting of SEQ ID NO: 50, or sequences having at least 80% identity thereto; and

5 a second antibody or antigen binding fragment thereof having a heavy chain comprising or consisting of SEQ ID NO: 41; and a light chain comprising or consisting of SEQ ID NO: 42, or sequences having at least 80% identity thereto.

For example, in any therapeutic application disclosed herein, and/or in any method of monitoring disclosed herein, any combination of antibodies or antigen-binding
10 fragments may be utilised. Preferably, Ab 116 and 16 are used in combination.

In another example, Ab 116 may be used in any therapeutic application disclosed herein, and Ab 16 may be used in monitoring of the same subject. Alternatively, Ab 16 may be used in any therapeutic application disclosed herein, and Ab 116 may be used in
15 monitoring of the same subject.

The term "antibody" as referred to herein refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (V_H) and a heavy chain constant region. Each light chain is comprised of a light chain variable region (V_L) and a light chain constant region. The variable regions of the heavy and light chains contain
20 a binding domain that interacts with an antigen. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). The constant regions of the antibodies may mediate the binding of the
25 immunoglobulin to host tissues or factors, including various cells of the immune system (e.g effector cells) and the first component (C1q) of the classical complement system.

The term "antigen-binding fragment thereof" of an antibody refers to one or more
30 fragments of an antibody that retain the ability to selectively bind to an antigen. Antigen-binding fragments thereof may be, but are not limited to Fab, modified Fab, Fab', modified Fab', $F(ab')_2$, Fv, single domain antibodies (e.g. V_H or V_L or VHH), scFv, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope-binding fragments of any of the above (Holliger and Hudson, 2005, Nature
35 Biotech. 23(9): 1126-1136; Adair and Lawson, 2005, Drug Design Reviews - Online

2(3), 209-217). The methods for creating and manufacturing these antigen-binding fragments are well known in the art (see for example Verma et al., 1998, Journal of Immunological Methods, 216, 165-181).

- 5 The antibody or antigen binding fragment thereof may be a monoclonal antibody, bispecific antibody, multi-specific antibody, ScFv or other single chain or modified format, Fab, (Fab')₂, Fv, dAb, Fd, nanobody, camelid antibody or a diabody. Preferably, the antibody or antigen binding fragment thereof is a monoclonal antibody.
- 10 The inventors have targeted CD1a and its potential role in inflammatory skin and mucosal diseases and disorders, or associated systemic diseases or disorders, or inflammatory drug reactions which manifest systemically, by generating effective monoclonal antibodies. As CD1a is highly expressed in the skin and mucosae, use of such antibodies provides an opportunity to selectively treat inflammatory skin and
- 15 mucosal diseases and disorders whilst minimising off target effects. CD1a is not expressed by mice but is expressed by other mammals. Human CD1a (UniProtKB/Swiss-Prot: P06126-CD1A_HUMAN) is expressed from a dominant allele worldwide, with a variant that is present in some Chinese ethnic groups (18). Targeting CD1a antigen presentation also intercepts the inflammatory pathway upstream of other
- 20 cytokine-directed antibody therapies such as anti-IL17 therapies, or other immune therapies, and therefore provides a powerful means to modulate proinflammatory disorders early in the immune cascade. Furthermore, utilising the specificity of CD1a to the skin may provide the means to direct additional therapies to the skin, for example by use of bi-specific, or multi-specific or conjugate antibody technology, to specifically
- 25 target small molecule, drug, nucleic acid, peptide, antibody, or cell conjugate therapies. Further still, as CD1a is relatively non-polymorphic, the description provides universal potential in the prevention and/or treatment of inflammatory skin and mucosal diseases such as atopic dermatitis and psoriasis, where the frequency of CD1a-expressing dendritic cell subsets is increased, and migratory patterns of LCs are altered (13-15), or
- 30 CD1a-expressing malignancies.

By modifying the number and function of CD1a-expressing cells, the antibodies will have effects beyond lipid reactivity and influence all roles of CD1a-expressing cells, including antigen presentation to peptide-specific T cells and innate pathways (for example

35 neutrophils). The antibodies of the description are able to reduce Langerhans

cells despite their murine IgG1 nature. Such reduction offers a means of controlling broad inflammatory pathways in the absence of complement/ADCC-associated inflammation, which may offer therapeutic benefit. This is shown in the imiquimod model described herein, where antibodies according to the description for example reduce inflammation including to levels significantly below the wild-type mouse, demonstrating a profound anti-inflammatory effect on pathways beyond CD1a-expressing cells, including innate pathways such as neutrophils and eosinophils. The antibodies of the description also inhibit the production of diverse cytokines including IFN-gamma and IL-22 which are relevant to a broad range of clinical diseases.

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In another aspect, the description provides a nucleic acid encoding an antibody or antigen binding fragment thereof of the description. Such nucleic acids may be provided by any of SEQ ID Nos: 51-90. The skilled person will understand that due to codon redundancy, a number of DNA sequences may be used to encode an antibody or antigen binding fragment thereof of the description. Alternatively, codon optimization of the nucleotide sequence can be used to improve the efficiency of translation in expression systems for the production of an antibody or antigen binding fragment thereof of the description.

20 In another aspect, the description provides a vector comprising a nucleic acid of the description. Suitable vectors can be chosen or constructed, containing appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Vectors may be for example plasmids or viral. For further details see, for example, (Sambrook, J., E. F. Fritsch, and T. Maniatis. (1989), *Molecular cloning: a laboratory manual*, 2nd ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). Many known techniques and protocols for manipulation of nucleic acid, for example in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into cells and gene expression, and analysis of proteins, are described in detail in (Ausubel et al., *Current protocols in molecular biology*. New York: Greene Publishing Association; Wiley-Interscience, 1992). The vector may be an expression vector. The vector or expression vector may be a plasmid.

35 A nucleic acid molecule or vector of the description may be expressed using any suitable expression system, for example in a suitable host cell or in a cell-free system.

In another aspect, the description provides a host cell comprising an antibody or antigen binding fragment thereof, nucleic acid, and/or vector of the description. The host cell may be selected from bacterial host cells (prokaryotic systems) such as *E. Coli*, or eukaryotic cells such as those of yeasts, fungi, insect cells or mammalian cells.

5 Preferably a host cell of the description is capable of producing the antibody or antigen binding fragment thereof of the description. The produced antibody or antigen binding fragment thereof may be enriched by means of selection and/or isolation.

An antibody or antigen binding fragment thereof of the description may also be

10 produced by chemical synthesis. The obtained antibody or antigen binding fragment thereof may be enriched by means of selection and/ or isolation.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising one or more antibody or antigen binding fragment thereof as described

15 herein, nucleic acid as described herein, vector as described herein, and/or host cell as described herein. In yet another aspect, the present disclosure provides the antibody or antigen binding fragment thereof as described herein, the nucleic acid as described herein, the vector as described herein, the host cell as described herein, or the pharmaceutical composition as described herein, for use in medicine. According to a

20 further example, the description provides a pharmaceutical composition comprising an antibody or antigen binding fragment thereof, nucleic acid, vector and/or host cell of the description, optionally together with one or more pharmaceutically acceptable excipients or diluents.

25 Antibodies or antigen binding fragments thereof, nucleic acids, vectors or host cells of the description can be formulated into pharmaceutical compositions using established methods of preparation (Gennaro, A.L. and Gennaro, A.R. (2000) Remington: The Science and Practice of Pharmacy, 20th Ed., Lippincott Williams & Wilkins, Philadelphia, PA). To prepare the pharmaceutical compositions, pharmaceutically inert

30 inorganic or organic excipients can be used. To prepare for example pills, powders, gelatin capsules or suppositories, lactose, talc, stearic acid and its salts, fats, waxes, solid or liquid polyols, natural and hardened oils are examples of pharmaceutically acceptable excipients which can be used. Suitable excipients for the production of solutions, suspensions, emulsions, aerosol mixtures or powders for

reconstitution into solutions or aerosol mixtures prior to use include water, alcohols, glycerol, polyols, and suitable mixtures thereof as well as vegetable oils.

5 A pharmaceutical composition of the description may be administered via any parenteral or non-parenteral (enteral) route that is therapeutically effective. Parenteral application methods include, for example, intracutaneous, subcutaneous, intramuscular, intratracheal, intranasal, intravitreal or intravenous injection and infusion techniques, e.g. in the form of injection solutions, infusion solutions or mixtures, as well as aerosol

installation and inhalation, e.g. in the form of aerosol mixtures, sprays or powders. A pharmaceutical composition of the description can be administered systemically or topically in formulations containing conventional non-toxic pharmaceutically acceptable excipients or carriers, additives and vehicles as desired. A combination of
5 intravenous and subcutaneous infusion and /or injection might be most convenient in case of compounds with a relatively short or long serum half-life or needing rapid onset of action. Preferably, the pharmaceutical composition is administered subcutaneously or intravenously. The pharmaceutical composition may be an aqueous solution, an oil-in water emulsion or a water-in-oil emulsion.

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For intravenous injection, or injection at the site of affliction, or other site of administration, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using for
15 example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

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The compositions are preferably administered to an individual in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The optimal dosage will depend on the biodistribution of the antibody or antigen binding fragment thereof, the mode of administration, the severity of the disease/disorder being treated as well as the medical condition of the patient. If desired, the antibody or antigen binding fragment thereof may be given in a sustained release formulation, for example
25 liposomal dispersions or hydrogel-based polymer microspheres, like PolyActive™ or OctoDEX™ (cf. Bos et al., Business Briefing: Pharmatech 2003: 1-6). Other sustained release formulations available are for example PLGA based polymers (PR pharmaceuticals), PLA-PEG based hydrogels (Medincell) and PEA based polymers (Medivas). Prescription of treatment, e.g., decisions on dosage etc, is within the
30 responsibility of a medical practitioner, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners.

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The pharmaceutical composition may also contain additives, such as, for example, fillers, binders, wetting agents, glidants, stabilizers, preservatives, emulsifiers, and

furthermore solvents or solubilizers or agents for achieving a depot effect. The latter is that fusion proteins may be incorporated into slow or sustained release or targeted delivery systems, such as liposomes and microcapsules.

- 5 In another example, an antibody or antigen binding fragment thereof, nucleic acid, vector, host cell or pharmaceutical composition of the description may be for use in the treatment or prevention of one or more disease or disorder in a subject.

10 In an example, there is provided a method of treating or preventing one or more disease or disorder in a subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment thereof, nucleic acid, vector, host cell or composition of the description.

15 In a further aspect, the present disclosure provides a use of one or more antibody or antigen binding fragment thereof as described herein, one or more nucleic acid as described herein, one or more vector as described herein, one or more host cell as described herein, or one or more pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment or prevention of one or more inflammatory skin or mucosal disease or disorder, or one or more associated systemic
20 diseases or disorders, or one or more inflammatory drug reaction which manifests systemically, or a CD1a-expressing malignancy. In an example, there is provided the use of an antibody or antigen binding fragment thereof, nucleic acid, vector, host cell or pharmaceutical composition of the description in the manufacture of a medicament for the treatment or prevention of one or more diseases or disorders in a subject.

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In any example, the subject may be a mammal. The mammal may express a CD1a orthologue. Preferably, the subject is a human.

30 The one or more disease or disorder may be one or more inflammatory skin or mucosal disorder, or disease or one or more associated systemic disease or disorder, or one or more inflammatory drug reaction which manifests systemically, or a CD1a-expressing malignancy.

An inflammatory skin or mucosal disease or disorder may be selected from:

- 5 a) a predominantly neutrophilic skin disease, such as acne, generalized pustular psoriasis, plaque psoriasis, guttate psoriasis, palmoplantar pustulosis, SAPHO syndrome, acute febrile neutrophilic dermatosis (Sweet syndrome), histiocytoid neutrophilic dermatitis, neutrophilic dermatosis of the dorsal hands, pyoderma gangrenosum, neutrophilic eccrine hidradenitis, hidradenitis suppurativa, erythema elevatum diutinum, Behcet disease, bowel-associated dermatitis-arthritis syndrome, other infection-associated inflammation, neutrophilic urticarial dermatosis, palisading neutrophilic granulomatous dermatitis,

An associated systemic disease or disorder as used herein may refer to any non-cutaneous site involvement that may be associated with an inflammatory skin or mucosal disease or disorder as defined herein. This may include non-cutaneous lupus erythematosus.

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An inflammatory drug reaction which manifests systemically, may be at a non-cutaneous site such as the spleen. An associated systemic disease or disorder, or inflammatory drug reaction which manifests systemically, may be as a result of an inflammatory response. The inflammatory response may be for example to a drug such as Aldara (5% imiquimod cream).

10 The inflammatory response may result in increased numbers or activity of CD4 T-cells, CD8 T-cells, neutrophils or eosinophils, and/or increased levels of IL-23, IL-12, IL-1 β and/or MCP-1, and/or decreased IL-10 and/or IL-27.

15 Furthermore, an antibody or antigen binding fragment thereof, nucleic acid, vector, host cell or pharmaceutical composition of the description may be administered alone or in combination with one or more other therapeutic agent, either simultaneously, sequentially or separately, dependent upon the condition to be treated. The one or more other therapeutic agent may be selected from the group comprising cytotoxic agents, immune activation agents such as checkpoint inhibitors or TLR agonists, anti-inflammatory agents such as
20 steroids, CAR-T cells such as regulatory or cytolytic CAR-T cells, or other cells expressing or presenting one or more antibody or antigen binding fragment of the description.

In another aspect, there is provided a method of monitoring treatment efficacy or disease status in a subject diagnosed with a CD1a-expressing malignancy, comprising:

- 25 i. providing a biological sample obtained from the subject;
- ii. determining the level of binding of one or more antibodies or antigen binding fragments of the description to CD1a-expressing cells in the sample obtained from the subject before treatment, or at intervals between treatments, or at time intervals in the absence of treatment;
- 30 iii. determining that the treatment is effective, or that the disease status is improving, if the tumour volume, or level of binding of one or more antibodies or antigen binding fragments of the description to CD1a-expressing cells, is reduced after treatment or between treatment intervals or at time intervals in the absence of treatment,

A biological sample may be a blood or serum sample, tissue biopsy, cerebrospinal fluid, saliva, or urine sample. Preferably, the biological sample may be a blood or serum sample.

- 5 The level of binding of one or more antibodies or antigen binding fragments of the description to CD1a-expressing cells in the sample may be determined using any method known to the skilled person. One such method is for example using flow cytometry or any other technique utilising a detectable label, to be able to determine the number of CD1a expressing cells in the sample.

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Tumour volume may be determined by any suitable technique known to the skilled person.

- 15 The reduction in tumour volume or level of binding of one or more antibodies or antigen binding fragments of the description to CD1a-expressing cells may be by 10% or more, such as 25% or more, 50% or more, 75% or more, or 90% or more.

- 20 The treatment intervals or time intervals in the absence of treatment may be two weeks or more, such as four weeks or more, 8 weeks or more, 12 weeks or more, six months or more, or 12 months or more.

- 25 Techniques for the production of antibodies and antigen binding fragments thereof are well known in the art. The term "antibody" also includes immunoglobulins (Ig's) of different classes (i.e. IgA, IgG, IgM, IgD and IgE) and subclasses (such as IgG1, IgG2 etc.). Illustrative examples of an antibodies or antigen binding fragments thereof include Fab fragments, F(ab')₂, Fv fragments, single-chain Fv fragments (scFv), diabodies, domain antibodies or bispecific antibodies (Holt LJ et al., Trends Biotechnol. 21(11), 2003, 484-490). Examples also include a dAB fragment which consists of a single CH domain or VL domain which alone is capable of binding an antigen. An antibody or
- 30 antigen binding fragment thereof may be chimeric, a nanobody, single chain and/or humanized. The antibody or antigen binding fragment thereof may be a human IgG1 isotype or a human IgG4 isotype or other natural or modified isotype. Antibodies may be monoclonal (mAb) or polyclonal.

The antibody or antigen binding fragment thereof may be modified to change in vivo stability and/or half-life. The modification for example may be PEGylation.

5 The antibody or antigen binding fragment thereof may be an antibody-like molecule which includes the use of CDRs separately or in combination in synthetic molecules such as SMIPs and small antibody mimetics.

10 The percent identity of two amino acid sequences or of two nucleic acid sequences is generally determined by aligning the sequences for optimal comparison purposes (e.g., gaps can be introduced in the first sequence for best alignment with the second sequence) and comparing the amino acid residues or nucleotides at corresponding positions. The "best alignment" is an alignment of two sequences that results in the highest percent identity. The percent identity is determined by comparing the number of identical amino acid residues or nucleotides within the sequences (i.e., % identity =
15 number of identical positions/total number of positions x 100).

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and
20 Altschul, 1990, PNAS, 87(6):2264-8, modified as in Karlin and Altschul, 1993, PNAS, 90(12):5873-5877. The NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol., 215:403-10 have incorporated such an algorithm. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, word length = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the description. BLAST protein
25 searches can be performed with the XBLAST program, score = 50, word length = 3 to obtain amino acid sequences homologous to a protein molecules of the description. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997). Alternatively, PSI-Blast can be used to perform an iterated search that detects distant relationships between molecules (Id.). When utilizing
30 BLAST, GappedBLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>. Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller. The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other
35 algorithms for sequence analysis known in the

art include ADVANCE and ADAM as described in Torellis and Robotti (1994); and FASTA described in Pearson and Lipman (1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

- 5 An antibody or antigen binding fragment thereof of the description may comprise one or more mutated amino acid residues. The terms "mutated", "mutant" and "mutation" in reference to a nucleic acid or an antibody or antigen binding fragment thereof of the description refers to the substitution, deletion, or insertion of one or more nucleotides or amino acids, respectively, compared to the "naturally" occurring nucleic acid or
10 polypeptide, i.e. to a reference sequence that can be taken to define the wild-type.

The amino acid variations in the CDR sequences may be conservative amino acid substitutions.

- 15 A mutation may be a substitution wherein the substitution is a conservative substitution. Conservative substitutions are generally the following substitutions, listed according to the amino acid to be mutated, each followed by one or more replacement(s) that can be taken to be conservative: Ala → Gly, Ser, Val; Arg → Lys; Asn → Gln, His; Asp → Glu; Cys → Ser; Gln → Asn; Glu → Asp; Gly → Ala; His → Arg, Asn, Gln; Ile → Leu, Val; Leu →
20 Ile, Val; Lys → Arg, Gln, Glu; Met → Leu, Tyr, He; Phe → Met, Leu, Tyr; Ser → Thr; Thr → Ser; Trp → Tyr; Tyr → Trp, Phe; Val → He, Leu. Other substitutions are also permissible and can be determined empirically or in accord with other known conservative or non-conservative substitutions.
- 25 1, 2 or 3 conservative substitutions may be made in the CDRs of the antibody or antigen binding fragment thereof of the description.

- Methods of making an antibody or antigen binding fragment thereof are well known in the art. The skilled person may use hybridoma technology for example, or may use recombinant
30 DNA technology to clone the respective antibody sequence into a vector, such as an expression vector. Methods of making a bispecific antibody molecule are known in the art, e.g. recombinant DNA technology, chemical conjugation of two different monoclonal antibodies or for example, also chemical conjugation of two antibody fragments, for example, of two Fab fragments. Alternatively, bispecific antibody molecules are made by
35 quadroma technology, which is by fusion of the

hybridomas producing the parental antibodies. Because of the random assortment of H and L chains, a potential mixture of ten different antibody structures are produced of which only one has the desired binding specificity. A bispecific antibody molecule of the description can act as a monoclonal antibody (mAb) with respect to each target. The antibody or antigen binding fragment thereof may be chimeric, humanized or fully human. The antibody or antigen binding fragment thereof may be a human IgG1 isotype or a human IgG4 isotype or other natural or modified isotype. A bispecific antibody molecule or multi-specific antibody may for example be a bispecific tandem single chain Fv, a bispecific Fab2, or a bispecific diabody.

All of the features disclosed in this specification may be combined in any combination, including with any example or any example.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 – shows the inhibition of polyclonal T cell responses by a panel of anti-CD1a antibodies. A. Dose titration curve of polyclonal T cell IFN γ response with increasing concentration of anti-CD1a antibody (0.01-10 μ g/ml) (n=6 donors). **B.** IC50 values calculated for the panel of newly generated anti-CD1a antibodies and commercial antibodies (OKT6, HI149 and SK9, n=6 donors)

Figure 2 – demonstrates the inhibition of CD1a-restricted enriched T cell line responses by a panel of anti-CD1a antibodies. A-B. Cytokine secretion response of CD1a-restricted enriched T cell lines induced by empty vector (EV) or CD1a transfected K562 presenting endogenous ligands. Inhibition of IFN γ (A.) or IL-22 (B.) was assessed for the panel of newly generated anti-CD1a antibodies by flow cytometry. **C.** IFN γ secretion response of CD1a-restricted enriched T cell lines induced by CD1a coated beads presenting endogenous ligands. Inhibition was assessed for the panel of newly generated anti-CD1a antibodies by flow cytometry. Inhibition was assessed for the panel of newly generated anti-CD1a antibodies by flow cytometry. (N=4-19 enriched T cell lines, 2-way-ANOVA with Tukey's test, *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001 where * indicates significance on comparison to "CD1a").

Figure 3 – demonstrates the characterisation of CD1a transgenic mouse. A. Representative flow cytometry plots and **B.** graphical summary of CD1a protein expression by cells of wild-type (WT) and CD1a transgenic (CD1a) mice. CD1a protein

CLAIMS

1. An antibody or antigen binding fragment thereof which binds to CD1a, for use in the
5 treatment or prevention of one or more inflammatory skin or mucosal disease or disorder, or one or more associated systemic disease or disorder, or one or more inflammatory drug reaction which manifests systemically, or one or more CD1a-expressing malignancies.
- 10 2. An antibody or antigen binding fragment thereof, comprising:
 - a) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 35 or a sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 38 or a sequence having at least 80% identity thereto; or
 - 15 b) a heavy chain variable region comprising a complementarity determining region CDR3 of SEQ ID NO: 3 or a sequence having at least 80% thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 6 or a sequence having at least 80% identity thereto; or
 - c) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 11 or a
20 sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 14 or a sequence having at least 80% identity thereto; or
 - d) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 19 or a
25 sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 22 or a sequence having at least 80% identity thereto; or
 - e) a heavy chain variable region comprising a CDR3 of SEQ ID NO: 27 or a
30 sequence having at least 80% identity thereto, and/or a light chain variable region comprising a CDR3 of SEQ ID NO: 30 or a sequence having at least 80% identity thereto.
3. An antibody or antigen binding fragment thereof, comprising:
 - a) a heavy chain variable region comprising:
 - a CDR1 of SEQ ID NO: 33,
 - 35 a CDR2 of SEQ ID NO: 34, and
 - a CDR3 of SEQ ID NO: 35,

- or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 36,
a CDR2 of SEQ ID NO: 37, and
5 a CDR3 of SEQ ID NO: 38,
or sequences having at least 80%, identity thereto; or
b) a heavy chain variable region comprising:
a CDR1 of SEQ ID NO: 1,
a CDR2 of SEQ ID NO: 2, and
10 a CDR3 of SEQ ID NO: 3,
or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 4,
a CDR2 of SEQ ID NO: 5, and
15 a CDR3 of SEQ ID NO: 6,
or sequences having at least 80%, identity thereto; or
c) a heavy chain variable region comprising:
a CDR1 of SEQ ID NO: 9,
a CDR2 of SEQ ID NO: 10, and
20 a CDR3 of SEQ ID NO: 11,
or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 12,
a CDR2 of SEQ ID NO: 13, and
25 a CDR3 of SEQ ID NO: 14,
or sequences having at least 80%, identity thereto; or
d) a heavy chain variable region comprising:
a CDR1 of SEQ ID NO: 17,
a CDR2 of SEQ ID NO: 18, and
30 a CDR3 of SEQ ID NO: 19,
or sequences having at least 80% identity thereto, and/or
a light chain variable region comprising:
a CDR1 of SEQ ID NO: 20,
a CDR2 of SEQ ID NO: 21, and
35 a CDR3 of SEQ ID NO: 22,

- or sequences having at least 80%, identity thereto; or
- e) a heavy chain variable region comprising:
- a CDR1 of SEQ ID NO: 25,
 - a CDR2 of SEQ ID NO: 26, and
 - 5 a CDR3 of SEQ ID NO: 27,
- or sequences having at least 80% identity thereto, and/or
- a light chain variable region comprising:
- a CDR1 of SEQ ID NO: 28,
 - a CDR2 of SEQ ID NO: 29, and
 - 10 a CDR3 of SEQ ID NO: 30,
- or sequences having at least 80%, identity thereto.
4. An antibody or antigen binding fragment thereof, comprising:
- e) a heavy chain variable region comprising or consisting of SEQ ID NO: 39;
 - 15 and/or a light chain variable region comprising or consisting of SEQ ID NO: 40
- or sequences having at least 80% identity thereto; or
- b) a heavy chain variable region comprising or consisting of SEQ ID NO: 7;
- and/or a light chain variable region comprising or consisting of SEQ ID NO: 8
- or sequences having at least 80% identity thereto; or
- 20 c) a heavy chain variable region comprising or consisting of SEQ ID NO: 15;
- and/or a light chain variable region comprising or consisting of SEQ ID NO: 16
- or sequences having at least 80% identity thereto; or
- d) a heavy chain variable region comprising or consisting of SEQ ID NO: 23;
- and/or a light chain variable region comprising or consisting of SEQ ID NO: 24
- 25 or sequences having at least 80% identity thereto; or
- e) a heavy chain variable region comprising or consisting of SEQ ID NO: 31;
- and/or a light chain variable region comprising or consisting of SEQ ID NO: 32
- or sequences having at least 80% identity thereto.
- 30 5. An antibody or antigen binding fragment thereof, comprising:
- a) a heavy chain comprising or consisting of SEQ ID NO: 49; and/or a
- light chain comprising or consisting of SEQ ID NO: 50
- or sequences having at least 80% identity thereto; or
- b) a heavy chain comprising or consisting of SEQ ID NO: 41; and/or a light
 - 35 chain comprising or consisting of SEQ ID NO: 42

- or sequences having at least 80% identity thereto; or
- c) a heavy chain comprising or consisting of SEQ ID NO: 43; and/or a light chain comprising or consisting of SEQ ID NO: 44
- or sequences having at least 80% identity thereto; or
- 5 d) a heavy chain comprising or consisting of SEQ ID NO: 45; and/or a light chain comprising or consisting of SEQ ID NO: 46
- or sequences having at least 80% identity thereto; or
- e) a heavy chain comprising or consisting of SEQ ID NO: 47; and/or a light chain comprising or consisting of SEQ ID NO: 48
- 10 or sequences having at least 80% identity thereto.
6. The antibody or antigen binding fragment thereof of any of claims 1-5, wherein the antibody or antigen binding fragment thereof includes an ScFv or other modified format.
- 15 7. The antibody or antigen binding fragment thereof of any of claims 1-6, wherein the antibody or antigen binding fragment thereof is modified to stabilise and/or extend the half-life; optionally wherein the modification is PEGylation.
8. The antibody or antigen binding fragment thereof of any of claims 1-7, wherein the antibody or antigen binding fragment thereof is humanized.
- 20 9. The antibody or antigen binding fragment thereof of any of claims 1-8, wherein the antibody or antigen binding fragment thereof is a human IgG1 isotype or a human IgG4 isotype or other natural or modified isotype.
- 25 10. The antibody or antigen binding fragment thereof of any of claims 1-9, wherein the antibody or antigen binding fragment thereof is bispecific or multispecific.
11. A nucleic acid encoding the antibody or antigen binding fragment thereof of any of claims 1-10.
- 30 12. A vector comprising the nucleic acid of claim 11.
13. The vector of claim 12, wherein the vector is an expression vector, plasmid, or viral vector.
- 35

14. A host cell comprising the antibody or antigen binding fragment thereof of any of claims 1-10, the nucleic acid of claim 11, and/or the vector of claim 12 or claim 13.

15. The host cell of claim 14, wherein the host cell is a bacterial cell or mammalian cell.

16. A pharmaceutical composition comprising one or more antibody or antigen binding fragment thereof of any of claims 1-10, nucleic acid of claim 11, vector of claim 12 or claim 13, and/or host cell of claim 14 or claim 15.

10

17. The antibody or antigen binding fragment thereof of any of claims 2-10, the nucleic acid of claim 11, the vector of claim 12 or claim 13, the host cell of claim 14 or claim 15, or the pharmaceutical composition of claim 16, for use in medicine.

18. Use of one or more antibody or antigen binding fragment thereof of any of claims 2-10, one or more nucleic acid of claim 11, one or more vector of claim 12 or claim 13, one or more host cell of claim 14 or claim 15, or one or more pharmaceutical composition of claim 16, in the manufacture of a medicament for the treatment or prevention of one or more inflammatory skin or mucosal disease or disorder, or one or more associated systemic diseases or disorders, or one or more inflammatory drug reaction which manifests systemically, or a CD1a-expressing malignancy.

19. The use according to claim 18, wherein the one or more one or more antibody or antigen binding fragment thereof comprise or consist of two antibodies or antigen binding fragments thereof, each comprising or consisting of:

a) a first antibody or antigen binding fragment thereof having a heavy chain variable region comprising:

a CDR1 of SEQ ID NO: 33, a CDR2 of SEQ ID NO: 34, and a CDR3 of SEQ ID NO: 35, or sequences having at least 80% identity thereto, and

30

a light chain variable region comprising:

a CDR1 of SEQ ID NO: 36, a CDR2 of SEQ ID NO: 37, and a CDR3 of SEQ ID NO: 38, or sequences having at least 80%, identity thereto; and

a second antibody or antigen binding fragment thereof having a heavy chain variable region comprising:

a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 2, and a CDR3 of SEQ ID NO: 3, or sequences having at least 80% identity thereto, and

a light chain variable region comprising:

a CDR1 of SEQ ID NO: 4, a CDR2 of SEQ ID NO: 5, and a CDR3 of
5 SEQ ID NO: 6, or sequences having at least 80%, identity thereto; or

b) a first antibody or antigen binding fragment thereof having a heavy chain variable region comprising or consisting of SEQ ID NO: 39; and a light chain variable region comprising or consisting of SEQ ID NO: 40, or sequences having at least 80% identity thereto; and

10 a second antibody or antigen binding fragment thereof having a heavy chain variable region comprising or consisting of SEQ ID NO: 7; and a light chain variable region comprising or consisting of SEQ ID NO: 8, or sequences having at least 80% identity thereto; or

c) a first antibody or antigen binding fragment thereof having a heavy chain
15 comprising or consisting of SEQ ID NO: 49; and a light chain comprising or consisting of SEQ ID NO: 50, or sequences having at least 80% identity thereto; and

a second antibody or antigen binding fragment thereof having a heavy chain comprising or consisting of SEQ ID NO: 41; and a light chain comprising or consisting of SEQ ID NO: 42, or sequences having at least 80% identity thereto.

20

20. The use according to claim 18 or claim 19, wherein

a) the one or more inflammatory skin or mucosal disease or disorder is one or more of:

i) a predominantly neutrophilic skin disease such as acne,
25 generalized pustular psoriasis, plaque psoriasis, guttate psoriasis, palmoplantar pustulosis, SAPHO syndrome, acute febrile neutrophilic dermatosis (Sweet syndrome), histiocytoid neutrophilic dermatitis, neutrophilic dermatosis of the dorsal hands, pyoderma gangrenosum, neutrophilic eccrine hidradenitis, hidradenitis suppurativa, erythema elevatum diutinum, Behcet disease, bowel-associated dermatitis-arthritis syndrome, other infection-associated
30 inflammation, neutrophilic urticarial dermatosis, palisading neutrophilic granulomatous dermatitis, erythema gyratum repens, neutrophilic annular erythema, acute generalised exanthematous pustulosis (AGEP), vasculitis and others;

ii) an autoimmune disorder such as connective tissue disease (eg lupus, dermatomyositis, scleroderma/systemic sclerosis, Churg Strauss syndrome), panniculitis, vasculitides, autoimmune blistering conditions (eg bullous pemphigoid, pemphigus, linear IgA disease), dermatitis herpetiformis, coeliac disease, some auto-inflammatory disease, vitiligo, alopecia areata, alopecia universalis, alopecia totalis, panniculitis, lichen planus, erythema multiforme, lichen sclerosis, other lichenoid and erythema multiforme-like diseases, psoriatic arthritis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome, transverse myelitis, thyroiditis, neurodegeneration and others;

iii) mast cell disorders and eosinophilic disorders, such as Muckle Wells syndrome, eosinophilia and systemic symptoms syndrome, urticaria, angioedema, keratoconjunctivitis, food allergy, other allergy or atopy including atopic dermatitis, rhinitis, conjunctivitis, asthma, eosinophilic oesophagitis and other eosinophilic mucosal diseases, contact dermatitis and others;

iv) Graft vs host disease; and

v) Other drug reactions which manifest as an inflammatory skin or mucosal disease or disorder including Stevens Johnsons syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) and acute generalised exanthematous pustulosis (AGEP), erythema multiforme, bullous, fixed drug, and other drug reactions which manifest as an inflammatory skin or mucosal disease or disorder; or

(b) the one or more associated systemic disease or disorder, or one or more inflammatory drug reaction which manifests systemically, is an inflammatory reaction to Aldara (imiquimod); or

(c) the CD1a-expressing malignancy is one or more of Langerhans cell histiocytosis, a T cell lymphoma or a thymoma.

21. The use according to claim 20, wherein the one or more inflammatory skin or mucosal disease or disorder is one or more of psoriasis, dermatitis, lupus erythematosus, or drug reactions which manifest as an inflammatory skin or mucosal disease or disorder.

22. The use according to any of claims 18-21, wherein the antigen binding fragment thereof, nucleic acid, vector, host cell, or pharmaceutical composition is intended to be administered alone or in combination with one or more other therapeutic agent.

5 23. The use according to claim 22, wherein the one or more other therapeutic agent is selected from the group comprising cytotoxic agents, anti-inflammatory agents such as steroids, and CAR-T cells such as regulatory or cytolytic CAR-T cells, or other cells expressing or presenting one or more antibody or antigen binding fragment of any of claims 1-10.

10

24. A method of monitoring treatment efficacy or disease status in a subject diagnosed with a CD1a-expressing malignancy, comprising:

- i. providing a biological sample obtained from the subject;
- ii. determining the level of binding of one or more antibodies or antigen binding
15 fragments of any of claims 1-10 to CD1a-expressing cells in the sample obtained from the subject before treatment, or at intervals between treatments, or at time intervals in the absence of treatment;
- iii. determining that the treatment is effective, or that the disease status is improving, if the tumour volume, or level of binding of one or more antibodies
20 or antigen binding fragments of the invention to CD1a-expressing cells, is reduced after treatment or between treatment intervals or at time intervals in the absence of treatment, optionally wherein the reduction in tumour volume or level of binding of one or more antibodies or antigen binding fragments of any of claims 2-10 to CD1a-expressing cells is by 25% or more.

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