There is a need for further optimisation of treatment of the diseases described above with such antibodies.

Summary

The present inventors have identified particularly effective dosages of antibodies or binding fragments that specifically bind to a citrullinated epitope on deiminated human histone 2A and/or histone 4 for use in a method of treating or preventing diseases associated with extracellular trap release from cells, such as Neutrophil Extracellular Trap (NET)-associated pathologies or Eosinophil Extracellular Trap (EET) -associated pathologies in a subject in need thereof. The dosage of antibody or binding fragment is in the range of 0.01 mg/kg to 0.6 mg/kg. In one particularly preferred example the dosages provided results in not just a desired impact on NETs and/or EETs, but also particular cytokine levels which differ from when higher dosages of antibody or binding fragment are employed. For example, in one example the dosages may result in increased IL-10 release in the subject. In another example, the dosage result in a reduced level of at least one of calprotectin, P-selectin, CXCL10, TNF-alpha, and VCAM in the subject.

In one aspect, the present disclosure refers to use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating or preventing a disease associated with extracellular trap release from cells, such as a Neutrophil Extracellular Trap (NET)-associated pathology (NET associated pathology) or an Eosinophil Extracellular Trap (EET) -associated pathology (EET-associated pathology) in a subject in need thereof, wherein the use comprises that at least one dose of the antibody or binding fragment thereof is to be administered at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises: (a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and (b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

In another aspect, the present disclosure refers to use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating a Neutrophil Extracellular Trap associated pathology (a NET-associated pathology) in a subject in need thereof, the use comprises that at least one dose the antibody or binding fragment thereof is to be administered to the subject, wherein each dose of the antibody or binding fragment thereof is at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises: (a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and (b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

In another aspect, the present disclosure refers to use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating an Eosinophil Extracellular Trap (EET) -associated pathology (EET-associated pathology) in a subject in need thereof, wherein the use comprises that at least one dose the antibody or binding fragment thereof is to be administered to the subject, wherein each dose of the antibody or binding fragment thereof is at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises: (a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and (b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

Accordingly, the present disclosure provides an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 for use in a method of treating or preventing a disease associated with extracellular trap release from cells, such as a Neutrophil Extracellular

Trap (NET)-associated pathology or an Eosinophil Extracellular Trap (EET) -associated pathology in a subject in need thereof, wherein the antibody or binding fragment thereof is administered at a dosage of about 0.01 mg/kg to about 0.6 mg/kg.

The present disclosure also provides a method for treating a Neutrophil Extracellular Trap associated pathology (a NET-associated pathology) in a subject in need thereof, the method comprising administering an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 to the subject, wherein the antibody or binding fragment thereof is administered at a dosage of about 0.01 mg/kg to about 0.6 mg/kg.

The present disclosure also provides a method for treating an Eosinophil Extracellular Trap (EET) -associated pathology (an EET-associated pathology) in a subject in need thereof,

CLAIMS

1. Use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating or preventing a disease associated with extracellular trap release from cells, such as a Neutrophil Extracellular Trap (NET)-associated pathology (NET associated pathology) or an Eosinophil Extracellular Trap (EET) -associated pathology (EET-associated pathology) in a subject in need thereof, wherein the use comprises that at least one dose of the antibody or binding fragment thereof is to be administered at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises:

(a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and

(b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

2. The use of claim 1, wherein the antibody or binding fragment thereof is to be administered at a dosage of:

(a) from about 0.02 mg/kg to about 0.5 mg/kg;

(b) from about 0.05 mg/kg to about.0.4 mg/kg; or

(c) from about 0.1 mg/kg to about 0.3 mg/kg.

3. The use of claim 1, wherein the antibody or binding fragment thereof is to be administered at a dosage of about 0.3 mg/kg.

4. The use of any one of claims 1 to 3, wherein:

(a) the antibody or binding fragment thereof is to be administered to the subject intravenously or subcutaneously; and/or

(b) the administration of the antibody or binding fragment thereof increases the level of IL-10 in the subject; and/or

(c) the administration of the antibody or binding fragment thereof suppresses the level of at least one of calprotectin, P-selectin, CXCL10, TNF-alpha, and VCAM in the subject.

5. The use of any one of claims 1 to 4, wherein:

(a) 1 to 10 doses of the antibody are to be administered;

(b) 2 to 8 doses of the antibody are to be administered; or

(c) 4 to 6 doses of the antibody or binding fragment are to be administered, optionally wherein a plurality of doses are to be administered at intervals of:

(i) 1 week to 3 months;

(ii) 1 week to 3 weeks; or

(iii) about 2 weeks.

6. The use of any one of claims 1 to 5, wherein the antibody or binding fragment thereof comprises:

i) VL CDR1 of SEQ ID NO: 9;

ii) VL CDR2 of SEQ ID NO:4 and VL CDR3 of SEQ ID NO:5; and

iii) the heavy chain variable domain amino acid sequence of SEQ ID NO: 11 or 12.

7. The use of any one of claims 1 to 5, wherein the antibody or binding fragment thereof comprises:

a) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 11 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 16;

b) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 16;

c) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 11; and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 17;

d) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 17;

e) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 11 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 13;

f) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 11 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 14;

g) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 11 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 15;

h) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 13;

i) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable domain amino acid sequence set forth in SEQ ID NO: 14; or

j) the heavy chain variable domain amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable domain amino acid sequence of SEQ ID NO: 15.

8. The use of any one of claims 1 to 7, wherein the NET-associated pathology is a tauopathy, systemic lupus erythematosus (SLE), lupus, sepsis, vasculitis, inflammatory arthritis, rheumatoid arthritis and osteoarthritis, psoriasis, hidradenitis suppurativa, Alzheimer's disease, autoimmune hepatitis, juvenile idiopathic arthritis, myositis (polymyositis and dermatomyositis), Sjögren’s disease, Anti-phospholipid Syndrome, Bechet’s disease, spondylitis, spondyloarthropathy, multiple system atrophy, Parkinson's disease, Lewy body dementia asthma, allergic rhinovirus exacerbated asthma, allergic asthma, acute respiratory distress syndrome, cystic fibrosis, fibrosis and idiopathic pulmonary fibrosis, heart failure, atherosclerosis, dry eye disease, uveitis, nongranulomatous uveitis, granulomatous uveitis, dermatitis, atopic dermatitis, COPD, bronchitis, thrombotic diseases, cardiovascular diseases or another NET-associated pathology such as wound healing in diabetes, cancer, cancer metastasis, and transplant organ health *in vivo* or *ex vivo*.

9. The use of any one of claims 1 to 8, wherein the NET-associated pathology is Parkinson's disease.

10. The use of any one of claims 1 to 7, wherein the EET-associated pathology is an eosinophilic disease or condition, such as eosinophilic disease or condition of the skin; a respiratory eosinophilic disease or condition; a gastro-intestinal eosinophilic disease or condition; an allergic disease or condition; or a helminth, fungal, viral, or bacterial infection; or an eosinophilic disease or condition disease or condition such as Bullous Pemphigoid, Atopic dermatitis, allergic contact dermatitis, Eosinophilic Asthma, Chronic RhinoSinusitis with Nasal Polyposis (CRSwNP), Allergic sinusitis, Allergic bronchopulmonary aspergillosis, Eosinophilic chronic rhinosinusitis, Eosinophilic

Esophagitis (EoE), HyperEosinophilic Syndrome (HES), Eosinophilic Granulomatosis with PolyAngitis (EGPA), Eosinophilic otitis media (EOM), and Drug Reaction with Eosinophilic & Systemic Symptoms (DRESS), arteriosclerosis, and vasculitis.

11. Use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating a Neutrophil Extracellular Trap associated pathology (a NET-associated pathology) in a subject in need thereof, the use comprises that at least one dose the antibody or binding fragment thereof is to be administered to the subject, wherein each dose of the antibody or binding fragment thereof is at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises:

(a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and

(b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

12. The use of claim 11, wherein:

(a) the dosage of the antibody or binding fragment thereof to be administered is as defined in claim 2 or 3;

(b) the route of administration of the antibody or binding fragment thereof is as defined in claim 4;

(c) the administration of the antibody or binding fragment thereof increases the level of IL-10 in the subject;

(d) the administration of the antibody or binding fragment thereof suppresses the level of at least one of calprotectin, P-selectin, CXCL10, TNF-alpha, and VCAM in the subject;

(e) the sequence of the antibody is as defined in claim 6 or 7; and/or

(f) the NET-associated pathology is as defined in claim 8 or 9.

13. Use of an antibody or binding fragment thereof that specifically binds to a citrullinated epitope on deiminated human histone 2A and/or histone 4 in the manufacture of a medicament for treating an Eosinophil Extracellular Trap (EET) -associated pathology (EET-associated pathology) in a subject in need thereof, wherein the use comprises that at

least one dose the antibody or binding fragment thereof is to be administered to the subject, wherein each dose of the antibody or binding fragment thereof is at a dosage of from about 0.01 mg/kg to about 0.6 mg/kg, wherein the antibody or binding fragment thereof comprises:

(a) the VL CDR 1 of SEQ ID NO: 9 (QSLLDADGKTY) or SEQ ID NO: 10 (QSLLDNDGKTY) or SEQ ID NO: 6 (QSLLDTDGKTY) or SEQ ID NO: 7 (QSLLDSDAKTY) or SEQ ID NO: 8 (QSLLDTDAKTY); and

(b) the VH CDR 1 of SEQ ID NO: 1 (GYTFTNYG), the VH CDR 2 of SEQ ID NO: 2 (INTYSGEA), the VH CDR 3 of SEQ ID NO: 3 (LRGYTYQSFDEGGDY), the VL CDR 2 of SEQ ID NO: 4 (LVS) and the VL CDR 3 of SEQ ID NO: 5 (WQGTHFPYT).

14. The use of claim 13, wherein:

(a) the dosage of the antibody or binding fragment thereof to be administered is as defined in claim 2 or 3;

(b) the route of administration of the antibody or binding fragment thereof is as defined in claim 4;

(c) the administration of the antibody or binding fragment thereof increases the level of IL-10 in the subject;

(d) the administration of the antibody or binding fragment thereof suppresses the level of at least one of calprotectin, P-selectin, CXCL10, TNF-alpha, and VCAM in the subject;

(e) the sequence of the antibody is as defined in claim 6 or 7; and/or

(f) the EET-associated pathology is as defined in claim 10.