

WO2012098407A1 is directed to agents comprising a binding moiety, such as antibodies, with specificity for IL1RAP for use in inducing cell death and/or inhibiting growth and/or proliferation of cells associated with solid tumors that express IL1RAP. WO2012098407A1 discloses a mouse IgG2a monoclonal antibody to human IL1RAP, “mAb 81.2,” that when administered *in vivo* resulted in statistically significant delay of tumor growth in a melanoma mouse model.

WO2015132602A1 is directed to antibodies with specificity for human IL1RAP and their use for treatment of solid tumors. WO2015132602A1 discloses a specific mouse-derived antibody “CAN04” that binds specifically to domain 2 of human IL1RAP with a KD of 200 pM, cross-reacts with cynomolgus monkey IL1RAP, capable of inducing ADCC in one or more cancer cell lines (such as CML) and has some inhibitory effect on IL-1 α , IL-1 β , and IL-33 stimulated signaling.

WO2016020502A1 discloses two specific mouse-derived antibodies “CAN01” and “CAN03” that bind specifically to domain 3 of human IL1RAP with a KD of 1.4 and 0.9 nM, respectively, cross-react with cynomolgus monkey IL1RAP, and are capable of inducing ADCC in one or more cancer cell lines (such as CML). CAN03 was determined to have some inhibitory effect on IL-1 α , IL-1 β , and IL-33 stimulated signaling, whereas CAN01 was found to lack appreciable inhibitory action on IL-1 α , IL-1 β , and IL-33 signaling.

WO2016207304A1 is directed to rabbit-derived antibodies that specifically bind human IL-1RAcP and have some inhibitory effect on NFkB activity stimulated by IL-1 α , IL-1 β , IL-33, and/or IL-36 β .

WO2017191325A9 is directed to humanized IgG1 antibodies that specifically bind human IL-1R3 and have some inhibitory effect on NFkB activity stimulated by IL-1 α , IL-1 β , IL-33, and/or IL-36 β .

WO2020037154A1 is directed to is directed to humanized antibodies that specifically bind human IL-1Rap and have some inhibitory effect in limited *in vitro* models.

There remains a need for therapies to treat, ameliorate, or prevent inflammatory, autoimmune, immune regulatory, degenerative, and cell proliferative diseases or disorders associated with inappropriate signaling through the IL-1 family of cytokine ligands and receptors.

SUMMARY

In one aspect, provided herein is an anti-IL1RAP antibody comprising a first heavy chain CDR region (CDR-H1), a second heavy chain CDR region (CDR-H2), and a third heavy chain CDR region (CDR-H3), wherein:

(a) CDR-H1 comprises an amino acid sequence SEQ ID NOs: 128;

(b) CDR-H2 comprises an amino acid sequence SEQ ID NOs: 188;

(c) CDR-H3 comprises an amino acid sequence SEQ ID NOs: 248.

and wherein said anti-IL1RAP antibody comprises a light chain variable region comprising SEQ ID NO: 268.

In another aspect, provided herein is an anti-IL1RAP antibody that specifically binds to the same epitope as said antibody as described herein.

- 5 In another aspect, provided herein is an anti-IL1RAP, wherein the antibody specifically binds to one or more amino acid residues within domain 2 of IL1RAP.

In another aspect, provided herein is a pharmaceutical composition comprising an antibody as described herein and a pharmaceutically acceptable carrier.

- 10 In another aspect, provided herein is use of the antibody or the pharmaceutical composition as described herein in the manufacture of a medicament for treating an IL1RAP mediated disease.

- In another aspect, provided herein is use of the antibody or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease selected from the group comprising: acne, pancreatitis, age-related macular degeneration (AMD), airway hyper responsiveness, airway inflammation, allergic conjunctivitis, amyotrophic lateral sclerosis (ALS), allergic rhinitis, allergy, Alzheimer's
 15 disease/dementia, amyotrophic lateral sclerosis (ALS), neutrophilic dermatoses, Hydradenitis suppurativa, Ichthyosis, anaphylaxis, arthritis, asthma/atopy/nasal polyps, atherosclerosis, atopic dermatitis, autoimmune/autoinflammatory vasculitides (including but not limited to giant cell arteritis, Takayasu's arteritis, Kawasaki disease), Behcet's disease (including neuro-Bechet's), bone cancer, brain cancer, breast cancer, cachexia/anorexia, cartilage inflammation, cerebral ischemia, chronic fatigue syndrome, chronic
 20 obstructive pulmonary disease, Clostridium associated illnesses, colon cancer, congestive heart failure, conjunctivitis, coronary artery inflammation, coronary restenosis, diabetes, diabetic macular edema, diabetic retinopathy, dry eye disease, endometriosis, eosinophil-associated gastrointestinal disorder, eosinophilic esophagitis, familial cold auto-inflammatory syndrome, familial Mediterranean fever, fibromyalgia, fibrotic disorder, food allergy, generalized pustular psoriasis, glaucoma, glomerulonephritis,
 25 gouty arthritides, graft versus host disease, helminth infection, hemorrhagic shock, hidradenitis suppurativa, hyperalgesia, hyper-IgD syndrome, hyperuricemia, idiopathic pulmonary fibrosis (IPF), cancer-related pain, infection, inflammatory bowel disease (IBD, including but not limited to ulcerative colitis and Crohn's disease), inflammatory conditions resulting from strain, inflammatory eye disease associated with corneal transplant, inflammatory pain, influenza-related sequelae, intestinal cancer, ischemia, juvenile arthritis,
 30 Kawasaki's disease, kidney cancer, Leber's congenital amaurosis, liver cancer, liver disease, lung cancer, macrophage activation syndrome (MAS), macular degeneration, Muckle-Wells syndrome, multiple myeloma, multiple sclerosis, musculoskeletal pain, myelogenous and other leukemias, myelodysplastic syndromes (MDS), myocardial dysfunction, myopathies, nasal polyp, neonatal onset multisystem

inflammatory disease, neurotoxicity, neutrophilic skin diseases (including palmoplantar pustulosis, pyoderma gangrenosum, psoriasis, Sweet's syndrome, non-infectious conjunctivitis, non-infectious uveitis, non-small cell lung cancer, orthopedic surgery, osteoarthritis, osteoporosis, pain, pancreas cancer, Parkinson's disease, periodontal disease, peripheral vascular disease, polymyalgia rheumatica, polypoidal choroidal vasculopathy (PCV), pre-eclampsia or eclampsia, pre-term labor, prostate cancer, protozoan infection, psoriasis, psoriatic arthritis, pyoderma gangrenosum, reperfusion injury, respiratory syncytial virus (RSV), restenosis in particular after angioplasty and stenting, retinal detachment, retinitis pigmentosa, retinopathy of prematurity (ROP), rheumatoid arthritis, systemic sclerosis, eosinophilic fasciitis, septic shock, sickle-cell anemia, side effects from radiation therapy, SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, sinusitis, skin cancer, sleep disturbance, inflammation resulting from sprain, Still's disease, stomach cancer, systemic lupus erythematosus (including lupus nephritis), temporomandibular joint disease, TNF receptor associated periodic syndrome and other genetic febrile syndromes, transplant rejection, trauma, traumatic eye injury, type-2 diabetes, and vitiligo.

In yet another aspect, provided herein is the antibody or the pharmaceutical composition as described herein for use in therapy.

The present disclosure provides antibodies that specifically bind human IL1RAP with high affinity. The antibodies are capable of decreasing, inhibiting, and/or fully-blocking IL-1, IL-33, and/or IL-36 signaling pathways, including signaling stimulated by binding of one or more of the following agonists: IL-1 α , IL-1 β , IL-33, IL-36 α , IL-36 β , and IL-36 γ . The present disclosure also provides methods of treating diseases and conditions responsive to inhibition of IL-1, IL-33, and/or IL-36 signaling.

Claims

~~1. An anti-IL 1 RAP antibody comprising a first heavy chain CDR region (CDR-H1), a second heavy chain CDR region (CDR-H2), and a third heavy chain CDR region (CDR-H3) selected from the group;~~

~~(a) CDR-H1 comprises an amino acid sequence GFXXXXXXXX (SEQ ID NO: 265), wherein X at position 3 can be anyone of amino acids I, T, P; X at position 4 can be anyone of amino acids L, F, Y; X at position 5 can be anyone of amino acids A, S, P, E, D; X at position 6 can be anyone of amino acids V, G, T, H, Q, E, N, D. X at position 7 can be anyone of amino acids F, A, S, Y; X at position 8 can be anyone of amino acids A, G, S, P; X at position 9 can be anyone of amino acids L, M, A; X at position 10 can be anyone of amino acids G, T, S, N;~~

~~(b) CDR-H2 comprises an amino acid sequence AISYDGEGTL (SEQ ID NO: 266);~~

~~(c) CDR-H3 comprises an amino acid sequence ARFXYYXAFDY (SEQ ID NO: 267), wherein X at position 4 can be anyone of amino acids R, H; X at position 6 can be anyone of amino acids Y, R; X at position 7 can be anyone of amino acids T, S; or~~

~~(d) CDR-H1 comprises an amino acid sequence GXXXXXXAIX (SEQ ID NO: 262), wherein X at position~~

~~2 can be anyone of amino acids V, G, S, P, E; X at position 3 can be anyone of I, L, A, G, T, S, P, H, K, R; X at position 4 can be anyone of L, F, A, S, W, H, N, R; X at position 5 can be anyone of G, T, S, Y, P, H, E, N, R. X at position 6 be anyone of amino acids V, A, S, P, Q, N, D; X at position 7 be anyone of amino acids Y, H; X at position 10 be anyone of amino acids H, Q;~~

~~(e) CDR-H2 comprises an amino acid sequence YIIPXXGXXD (SEQ ID NO: 263), wherein X at position 5 can be anyone of amino acids T, S; X at position 6 can be anyone of amino acids V, L; X at position 8 can be anyone of amino acids G, Q; X at position 9 can be anyone of amino acids F, Y;~~

~~(f) CDR-H3 comprises an amino acid sequence ARGQTLYXXGRQFDI (SEQ ID NO: 264), X at position 8 can be anyone of amino acids A, E, D. X at position 9 can be anyone of amino acids A, T, S;~~

~~and wherein said anti-IL1 RAP antibody comprises a light chain variable region comprising SEQ ID NO: 268.~~

21. The antibody of claim 1 An anti-IL1RAP antibody comprising a first heavy chain CDR region (CDR-H1), a second heavy chain CDR region (CDR-H2), and a third heavy chain CDR region (CDR-H3), wherein:

- (a) CDR-H1 comprises an amino acid sequence SEQ ID NOs: 128;
- (b) CDR-H2 comprises an amino acid sequence SEQ ID NOs: 188;
- (c) CDR-H3 comprises an amino acid sequence SEQ ID NOs: 248.

and wherein said anti-IL1RAP antibody comprises a light chain variable region comprising SEQ ID NO: 268.

32. The antibody of claim 1-or 2, wherein said antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

43. The antibody of any one of claims 1 to 32, wherein said antibody binds to human IL1RAP with a binding affinity of 1×10^8 M or less, 1×10^9 M or less, 1×10^{10} M or less, or 1×10^{11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (KD) to human IL1RAP polypeptide of SEQ ID NO: 1 or 6.

54. The antibody of any one of claims 1 to 43, wherein said antibody decreases an IL-1 stimulated signal, an IL-33 stimulated signal, and/or an IL-36 stimulated signal by at least 90%, at least 95%, at least 99%, or 100%; wherein the decrease in signal is measured by a cell-based blocking assay.

65. The antibody of any one of claims 1 to 46, wherein said antibody cross-reacts with a cynomolgus monkey IL1RAP polypeptide of SEQ ID NO: 2.

76. The antibody of any one of claims 1 to 65, wherein said antibody cross-reacts with a mouse IL1RAP polypeptide of SEQ ID NO: 261.

87. The antibody of any one of claims 1 to 76, wherein said antibody is a full-length antibody of class IgG and in particular wherein the class IgG antibody has an isotype selected from IgG1, IgG2, IgG3 and IgG4.

89. The antibody of any one of claims 1 to 87, wherein said antibody is a multispecific antibody.

~~109~~. An anti-IL1RAP antibody that specifically binds to the same epitope as said antibody of any one of claims 1 to ~~98~~.

~~1110~~. An anti-IL1RAP, wherein the antibody specifically binds to one or more amino acid residues within domain 2 of IL1RAP.

~~1211~~. A pharmaceutical composition comprising an antibody of any one of claims 1 to ~~98~~ and a pharmaceutically acceptable carrier.

~~1312~~. Use of ~~T~~the antibody according to anyone of claims 1-~~12~~ 10 or the pharmaceutical composition according to claim 11 in the manufacture of a medicament for treating an IL1RAP mediated disease.

~~1413~~. Use of ~~T~~the antibody according to anyone of claims 1-~~12~~ 10 or the pharmaceutical composition according to claim 11 ~~for use in the manufacture of a medicament for in~~ treating a disease selected from the group comprising: acne, pancreatitis, age-related macular degeneration (AMD), airway hyper responsiveness, airway inflammation, allergic conjunctivitis, amyotrophic lateral sclerosis (ALS), allergic rhinitis, allergy, Alzheimer's disease/dementia, amyotrophic lateral sclerosis (ALS), neutrophilic dermatoses, Hidradenitis suppurativa, Ichthyosis, anaphylaxis, arthritis, asthma/atopy/nasal polyps, atherosclerosis, atopic dermatitis, autoimmune/autoinflammatory vasculitides (including but not limited to giant cell arteritis, Takayasu's arteritis, Kawasaki disease), Behcet's disease (including neuro-Bechet's), bone cancer, brain cancer, breast cancer, cachexia/anorexia, cartilage inflammation, cerebral ischemia, chronic fatigue syndrome, chronic obstructive pulmonary disease, Clostridium associated illnesses, colon cancer, congestive heart failure, conjunctivitis, coronary artery inflammation, coronary restenosis, diabetes, diabetic macular edema, diabetic retinopathy, dry eye disease, endometriosis, eosinophil-associated gastrointestinal disorder, eosinophilic esophagitis, familial cold auto-inflammatory syndrome, familial Mediterranean fever, fibromyalgia, fibrotic disorder, food allergy, generalized pustular psoriasis, glaucoma, glomerulonephritis, gouty arthritides, graft versus host disease, helminth infection, hemorrhagic shock, hidradenitis suppurativa, hyperalgesia, hyper-IgD syndrome, hyperuricemia, idiopathic pulmonary fibrosis (IPF), cancer-related pain, infection, inflammatory bowel disease (IBD, including but not limited to ulcerative colitis and Crohn's disease), inflammatory conditions resulting from strain, inflammatory eye disease associated with corneal transplant, inflammatory pain, influenza-related sequelae, intestinal cancer, ischemia, juvenile arthritis, Kawasaki's disease, kidney cancer, Leber's congenital amaurosis, liver cancer, liver disease, lung cancer, macrophage activation syndrome (MAS), macular degeneration, Muckle-Wells syndrome, multiple myeloma,

multiple sclerosis, musculoskeletal pain, myelogenous and other leukemias, myelodysplastic syndromes (MDS), myocardial dysfunction, myopathies, nasal polyp, neonatal onset multisystem inflammatory disease, neurotoxicity, neutrophilic skin diseases (including palmoplantar pustulosis, pyoderma gangrenosum, psoriasis, Sweet's syndrome, non-infectious conjunctivitis, non-infectious uveitis, non-small cell lung cancer, orthopedic surgery, osteoarthritis, osteoporosis, pain, pancreas cancer, Parkinson's disease, periodontal disease, peripheral vascular disease, polymyalgia rheumatica, polypoidal choroidal vasculopathy (PCV), pre-eclampsia or eclampsia, pre-term labor, prostate cancer, protozoan infection, psoriasis, psoriatic arthritis, pyoderma gangrenosum, reperfusion injury, respiratory syncytial virus (RSV), restenosis in particular after angioplasty and stenting, retinal detachment, retinitis pigmentosa, retinopathy of prematurity (ROP), rheumatoid arthritis, systemic sclerosis, eosinophilic fasciitis, septic shock, sickle-cell anemia, side effects from radiation therapy, SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, sinusitis, skin cancer, sleep disturbance, inflammation resulting from sprain, Still's disease, stomach cancer, systemic lupus erythematosus (including lupus nephritis), temporomandibular joint disease, TNF receptor associated periodic syndrome and other genetic febrile syndromes, transplant rejection, trauma, traumatic eye injury, type-2 diabetes, and vitiligo.

[14. The antibody according to anyone of claims 1-10 or the pharmaceutical composition according to claim 11 for use in therapy.](#)