(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 January 2020 (02.01.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/006199 A3

(51) International Patent Classification:
A61K 38/43 (2006.01) *G01N 33/92* (2006.01)
A61K 38/20 (2006.01) *A61P 3/04* (2006.01)
A61K 31/7076 (2006.01) *A61P 3/10* (2006.01)
A61K 31/197 (2006.01) *C12Q 1/25* (2006.01)
G01N 33/573 (2006.01)

(21) International Application Number:
PCT/US2019/039454

(22) International Filing Date:
27 June 2019 (27.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/690,732 27 June 2018 (27.06.2018) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: METHODS AND AGENTS FOR MODULATING INFLAMMATION

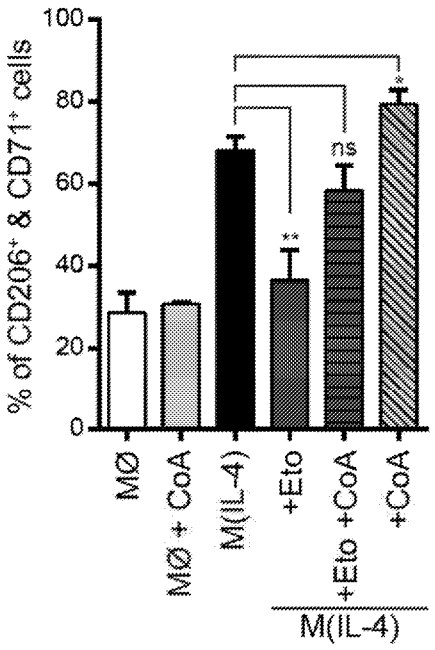

FIG. 10B

(57) Abstract: Methods and agents for modulating intracellular coenzyme A levels are described for therapeutic purposes. Increasing intracellular coenzyme A increases alternate macrophage activation resulting in suppression or resolution of an immune response for benefit in treating inflammatory diseases. Decreasing intracellular coenzyme A levels decreases alternate macrophage activation which is beneficial in treating NASH/NAFLD and various fibrotic diseases as well as reversing immune suppressing activity of tumor-associated immune cells such as macrophages for the treatment of cancer.

WO 2020/006199 A3

[Continued on next page]

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
13 February 2020 (13.02.2020)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/39454

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 38/43, 38/20, 31/7076, 31/197; G01N 33/573, 33/92; A61P 3/04, 3/10; C12Q 1/25 (2019.01)

CPC - A61K 38/43, 38/2026, 38/20, 31/7076, 31/197; G01N 33/5735, 33/573, 33/92; A61P 3/04, 3/10, 3/08; C12Q 1/25

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	(STIENSTRA, R et al.) Peroxisome Proliferator-Activated Receptor [gamma] Activation Promotes Infiltration of Alternatively Activated Macrophages Into Adipose Tissue. The Journal of Biological Chemistry. 15 August 2008, Vol. 283, No. 33; pages 22620-22627; abstract; page 22620, second column, third paragraph to page 22621, first column, second paragraph; page 22621, first column, fifth paragraph to second column, first paragraph; page 22622, second column, fourth paragraph to page 22623, second column, first paragraph; page 22624, second column, second paragraph; page 22626, second column, third paragraph; DOI: 10.1074/jbc.M710314200	1-3, 9 ------- 6
X -- Y	US 2010/0028319 A1 (SAKAMOTO, H et al.) 4 February 2010; paragraphs [0004], [0013]-[0015], [0023], [0028]-[0029], [0037], [0041]-[0042], [0044]-[0045], [0076], [0087]-[0088], [0094]	10-11, 16-17, 21-22, 27, 32, 34 -------- 6, 37, 41, 43
X -- Y	(MUSSELMAN, L et al.) CoA Protects Against the Deleterious Effects of Caloric Overload In Drosophila. Journal of Lipid Research. 24 January 2016, Vol. 57, pages 380-387; abstract; ; page 380, second column, second paragraph; page 381, first column, second and fourth paragraphs; page 384, first column, second paragraph-second column, first paragraph; page 386, first column, first paragraph; page 386, second column, second paragraph; doi: 10.1194/jlr.M062976	10, 12-13, 16, 18, 21, 23-24, 27-29, 35-36, 39-40 -------- 37, 41, 43
X	US 3,819,830 A (YOSHIMURA, Y et al.) 25 June 1974; entire document	10-11, 16-17, 21-22, 27, 32, 34

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 2019 (05.11.2019)	07 JAN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/39454

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/007728 A1 (KANEKA CORPORATION) 17 January 2008; entire document	10-11, 16-17, 21-22, 27, 32, 34
Y	(ROBERTS, L et al.) The Contrasting Roles of PPAR [delta] and PPAR [gamma] In Regulating the Metabolic Switch Between Oxidation And Storage Of Fats In White Adipose Tissue. Genome Biology. 11 August 2011, Vol. 12, No. 8; pages 1-19; page 10, first column, second paragraph to second column, first paragraph; page 12, second column, third paragraph; DOI: 10.1186/gb-2011-12-8-r75	1-3, 6, 9
A	(MAUER, J. et al.) Interleukin-6 Signaling Promotes Alternative Macrophage Activation to Limit Obesity-Associated Insulin Resistance and Endotoxemia. Nature Immunology. May 2014, Epub 30 March 2014, Vol. 15, No. 5, pages 423-430; DOI: 10.1038/ni.2865	1-3, 6, 9-13, 16-18, 21-24, 27-29, 32, 34-37, 39-41, 43
A	(ODEGAARD, J. et al.) Mechanisms of Macrophage Activation in Obesity-Induced Insulin Resistance. Nature Clinical Practice: Endocrinology and Metabolism. November 2008, Epub 7 October 2008, Vol. 4, No. 11; pages 619-626; DOI: 10.1038/ncpendmet0976	1-3, 6, 9-13, 16-18, 21-24, 27-29, 32, 34-37, 39-41, 43
A	(COVARRUBIAS, A. et al.) Akt-mTORC1 Signaling Regulated Acly to Integrate Metabolic Input to Control of Macrophage Activation. eLife. 19 February 2016, Vol. 5; pages 1-19; DOI: 10.7554/eLife.11612	1-3, 6, 9-13, 16-18, 21-24, 27-29, 32, 34-37, 39-41, 43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/39454

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2, 3 (in-part), 6 (in-part), 9-10, 11 (in-part), 12, 13 (in-part), 16, 17-18 (each in-part), 21, 22 (in-part), 23, 24 (in-part), 27-28, 29 (in-part), 32 (in-part), 34, 35 (in-part), 36, 37 (in-part), 39, 40-41 (in-part), 43 (in-part); diet-induced obesity (disease) and coenzyme A (agent)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/39454

-***-Continued from Box No. III: Observations where unity of invention is lacking: -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-43, diet-induced obesity (disease), and coenzyme A (agent) are directed toward methods and compositions for increasing alternative macrophage activation in a subject by administering an agent that increases intracellular coenzyme A levels resulting in suppression or resolution of an immune response for benefit in treating inflammatory diseases.

The methods and compositions will be searched to the extent that they encompass diet-induced obesity (first exemplary disease) and coenzyme A (first exemplary agent). Applicant is invited to elect additional disease(s) and/or agent(s), to be searched. Additional disease (s) and/or agent(s) will be searched upon the payment of additional fees. It is believed that claims 1-2, 3 (in-part), 6 (in-part), 9-10, 11 (in-part), 12, 13 (in-part), 16, 17-18 (each in-part), 21, 22 (in-part), 23, 24 (in-part), 27-28, 29 (in-part), 32 (in-part), 34, 35 (in-part), 36, 37 (in-part), 39, 40-41 (in-part), and 43 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass diet-induced obesity (disease) and coenzyme A (agent). Applicants must specify the claims that encompass any additionally elected disease(s) and/or agent(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be inflammation-related metabolic disorders (disease).

Groups II+, Claims 44-70, non-alcoholic steatohepatitis(disease) and hopantenate (pantothenate kinase inhibitor) are directed toward methods and compositions for decreasing alternative macrophage activation in a subject by administering an agent that decreases intracellular coenzyme A levels resulting in decreased alternate macrophage activation for benefit in treating various fibrotic diseases as well as revering immune suppressing activity of tumor-associated immune cells such as macrophages for the treatment of cancer.

The methods and compositions can be searched to the extent that they encompass non-alcoholic steatohepatitis (first exemplary disease) and hopantenate (first exemplary pantothenate kinase inhibitor). Applicant is invited to elect additional disease(s) and/or inhibitor (s), to be searched. Additional disease(s) and/or inhibitor(s) can be searched upon the payment of additional fees. It is believed that claims 44, 45 (in-part), 46-49, 50 (in-part), 51-54, 55-56 (each in-part), 57-59, and 60-70 (each in-part) encompass this first named invention and thus these claims can be searched without fee to the extent that they encompass non-alcoholic steatohepatitis(disease) and hopantenate (pantothenate kinase inhibitor). Applicants must specify the claims that encompass any additionally elected disease(s) and/or inhibitor(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention to be searched/examined. An exemplary election would be non-alcoholic fatty liver disease (disease) and alpha-methyl-N-phenethyl-pantothenamide (pantothenate kinase inhibitor).

Group III, Claims 71-73 are directed toward a method for modulating alternative macrophage activation in a subject, comprising determining the level of alternative macrophage activation by measuring a biomarker.

The inventions listed as Groups I+, II+, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include increasing alternative macrophage activation, not present in any of Groups II+ or III; the special technical features of Groups II+ include decreasing alternative macrophage activation, not present in any of Groups I+ or III: the special technical features of Groups III include biomarker measurement, not present in any of Groups I+ or II+.

Groups I+, II+, and III share the technical features including: modulating alternative macrophage activation in a subject.

However, these shared technical features are previously disclosed by the publication entitled 'Cell-Intrinsic Lysosomal Lipolysis is Essential for Macrophage Alternative Activation' by Huang, et al. (hereinafter 'Huang').

Huang discloses a method for modulating alternative macrophage activation in a subject (administering IL-4 to a subject (a method for modulating alternative macrophage activation in a subject); abstract; page 2, first paragraph; page 8, second paragraph).

Groups I+, II+, and III share the technical features including: modulating alternative macrophage activation in a subject, modulating intracellular coenzyme A levels, and treating a condition in a subject.

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box -***-

These technical features are previously disclosed by Huang, as above, as evidenced by the publication entitled 'Akt-mTORC1 Signaling Regulates Acly to Integrate Metabolic Input to Control of Macrophage Activation' by Covarrubias, et al. (hereinafter 'Covarrubias').

Huang discloses modulating alternative macrophage activation in a subject (administering IL-4 to a subject (a method for modulating alternative macrophage activation in a subject); abstract; page 2, first paragraph; page 8, second paragraph), by administering an agent that increases intracellular coenzyme A levels (by administering IL-4 (by administering an agent that increases intracellular coenzyme A levels); abstract; page 2, first paragraph; page 8, second paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A); and a method for treating a parasitic infection in a subject (method for suppressing a helminth (parasitic) infection in a subject; page 7, third paragraph - page 8, second paragraph).

No technical features are shared between the diseases and/or agents of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a method for increasing alternative macrophage activation in a subject by administering an agent that increases intracellular coenzyme A levels; a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels for administration to a subject to increase alternative macrophage activation; a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels for administration to a subject to suppress or resolve an immune response; use of an agent that increases intracellular coenzyme A levels for administering to a subject to increase alternative macrophage activation; a method for suppressing or resolving an immune response in a subject by administering to said subject an agent that increases alternative macrophage activation; method for treating diet-induced obesity, inflammation-related metabolic disorders, metabolic syndrome, sepsis, rheumatoid arthritis, eczemas, allergic or atopic dermatitis, an inflammatory condition of the eye, or promoting tissue repair, wound healing, repair of skin damage from burns, sunburn or radiation damage, or suppressing or treating a parasitic infection in a subject comprising administering to the subject an agent that increases alternative macrophage activation; a method for treating diet-induced obesity, inflammation-related metabolic disorders, metabolic syndrome, sepsis, rheumatoid arthritis, eczemas, allergic or atopic dermatitis, an inflammatory condition of the eye, or promoting tissue repair, wound healing, repair of skin damage from burns, sunburn or radiation damage, or suppressing or treating a parasitic infection in a subject comprising administering to the subject an agent that increases intracellular levels of coenzyme A; these shared technical features are previously disclosed by Huang, as evidenced by Covarrubias, as above.

Huang discloses a method for increasing alternative macrophage activation in a subject (administering IL-4 to a subject (a method for increasing alternative macrophage activation in a subject); abstract; page 2, first paragraph; page 8, second paragraph) by administering an agent that increases intracellular coenzyme A levels (by administering IL-4 (by administering an agent that increases intracellular coenzyme A levels); abstract; page 2, first paragraph; page 8, second paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A); a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels for administration to a subject to increase alternative macrophage activation (i.p. injection of IL-4 (a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels) for administration to a subject to increase alternative macrophage activation; abstract; page 2, first paragraph; page 8, second paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A); a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels for administration to a subject to suppress or resolve an immune response (i.p. injection of IL-4 (a pharmaceutical composition comprising an agent that increases intracellular coenzyme A levels) for administration to a subject to suppress or resolve an immune response; abstract; page 2, first paragraph; page 8, second paragraph; page 9, third paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A); use of an agent that increases intracellular coenzyme A levels for administering to a subject to increase alternative macrophage activation (use of IL-4 (an agent that increases intracellular coenzyme A levels) for administering to a subject to increase alternative macrophage activation; abstract; page 2, first paragraph; page 8, second paragraph; page 9, third paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A); a method for suppressing or resolving an immune response in a subject by administering to said subject an agent that increases alternative macrophage activation (a method for suppressing or resolving an immune response in a subject by administering to said subject IL-4 (an agent) that increases alternative macrophage activation; abstract; page 2, first paragraph; page 8, second paragraph; page 9, third paragraph); a method for treating diet-induced obesity, inflammation-related metabolic disorders, metabolic syndrome, sepsis, rheumatoid arthritis, eczemas, allergic or atopic dermatitis, an inflammatory condition of the eye, or promoting tissue repair, wound healing, repair of skin damage from burns, sunburn or radiation damage, or suppressing or treating a parasitic infection in a subject (method for suppressing a helminth (parasitic) infection in a subject; page 7, third paragraph - page 8, second paragraph) comprising administering to the subject an agent that increases alternative macrophage activation (comprising administering to the subject IL-4 (an agent that increases alternative macrophage activation); page 7, third paragraph – page 8, second paragraph); a method for treating diet-induced obesity, inflammation-related metabolic disorders, metabolic syndrome, sepsis, rheumatoid arthritis, eczemas, allergic or atopic dermatitis, an inflammatory condition of the eye, or promoting tissue repair, wound healing, repair of skin damage from burns, sunburn or radiation damage, or suppressing or treating a parasitic infection in a subject (method for suppressing a helminth (parasitic) infection in a subject; page 7, third paragraph - page 8, second paragraph) comprising administering to the subject an agent that increases intracellular levels of coenzyme A (comprising administering to the subject IL-4 (an agent that increases intracellular levels of coenzyme A); page 7, third paragraph – page 8, second paragraph; as further indicated by the Covarrubias evidentiary reference that IL-4 increases coenzyme A levels; abstract; page 2, third paragraph; figure 3A).

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

No technical features are shared between the diseases and/or inhibitors of Groups II+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups II+ were considered to share the technical features including: a method for decreasing alternative macrophage activation in a subject by administering an agent that decreases intracellular coenzyme A levels; a pharmaceutical composition comprising an agent that decreases intracellular coenzyme A levels for administration to a subject to decrease alternative macrophage activation; Use of an agent that decreases intracellular coenzyme A levels for administering to a subject to decrease alternative macrophage activation; a method for suppressing or treating non-alcoholic steatohepatitis, nonalcoholic fatty liver disease, pulmonary fibrosis, cardiac hypertrophy, fibrosis and fibrotic diseases and disorders, and suppresses tumorigenesis or cancer growth comprising administering to a subject an agent that decreases alternative macrophage activation; a method for suppressing or treating non-alcoholic steatohepatitis, nonalcoholic fatty liver disease, pulmonary fibrosis, cardiac hypertrophy, fibrosis and fibrotic diseases and disorders, and suppresses tumorigenesis or cancer growth comprising administering to a subject an agent that decreases intracellular levels of coenzyme A; these shared technical features are previously disclosed by WO 2017/048322 A1 (TOBIRA THERAPEUTICS, INC.) (hereinafter 'Tobira') as evidenced by Huang, as above.

Tobira discloses a method for decreasing alternative macrophage activation in a subject by administering an agent that decreases intracellular coenzyme A levels (administering TOFA to a subject (method for decreasing alternative macrophage activation in a subject by administering an agent that decreases intracellular coenzyme A levels); abstract; paragraph [00125]; as further indicated by the Huang reference that TOFA inhibits acetyl-CoA and decreases alternative macrophage activation in a subject; page 7, first paragraph); a pharmaceutical composition comprising an agent that decreases intracellular coenzyme A levels for administration to a subject to decrease alternative macrophage activation (a pharmaceutical composition comprising an agent that decreases intracellular coenzyme A levels for administration to a subject to decrease alternative macrophage activation; abstract; paragraphs [0009], [00125]; as further indicated by the Huang reference that TOFA inhibits acetyl-CoA and decreases alternative macrophage activation in a subject; page 7, first paragraph); use of an agent that decreases intracellular coenzyme A levels for administering to a subject to decrease alternative macrophage activation (use of TOFA (an agent that decreases intracellular coenzyme A levels) for administering to a subject to decrease alternative macrophage activation; abstract; paragraphs [0009], [00125]; as further indicated by the Huang reference that TOFA inhibits acetyl-CoA and decreases alternative macrophage activation in a subject; page 7, first paragraph); a method for suppressing or treating non-alcoholic steatohepatitis, nonalcoholic fatty liver disease, pulmonary fibrosis, cardiac hypertrophy, fibrosis and fibrotic diseases and disorders (method of treating fibrosis; abstract), and suppresses tumorigenesis or cancer growth comprising administering to a subject an agent that decreases alternative macrophage activation (administering to a subject TOFA (an agent) that decreases alternative macrophage activation; abstract; paragraphs [0009], [00125]; as further indicated by the Huang reference that TOFA inhibits acetyl-CoA and decreases alternative macrophage activation in a subject; page 7, first paragraph); a method for suppressing or treating non-alcoholic steatohepatitis, nonalcoholic fatty liver disease, pulmonary fibrosis, cardiac hypertrophy, fibrosis and fibrotic diseases and disorders (method of treating fibrosis; abstract), and suppresses tumorigenesis or cancer growth comprising administering to a subject an agent that decreases intracellular levels of coenzyme A (comprising administering to a subject TOFA (an agent) that decreases intracellular levels of coenzyme A; abstract; paragraphs [0009], [00125]).

Since none of the special technical features of the Groups I+, II+ and III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Huang and Tobira references, unity of invention is lacking.