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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/005107 A3

(51) International Patent Classification:
A61K 38/54 (2006.01) *A61K 9/127* (2006.01)

(21) International Application Number:
PCT/US2013/048736

(22) International Filing Date:
28 June 2013 (28.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/665,818 28 June 2012 (28.06.2012) US
61/780,126 13 March 2013 (13.03.2013) US

(71) Applicant: **ANSUN BIOPHARMA, INC.** [US/US]; 10665 Sorrento Valley Road, San Diego, California 92121 (US).

(72) Inventors: **LI, Tiejun**; 10665 Sorrento Valley Road, San Diego, California 92121 (US). **THOME, Brian**; 10665 Sorrento Valley Road, San Diego, California 92121 (US).

(74) Agent: **MEIKLEJOHN, Anita, L.**; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, MN 55440-1022 (US).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, 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, 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))*

(88) Date of publication of the international search report:
1 May 2014

WO 2014/005107 A3

(54) Title: MICROPARTICLE FORMULATIONS FOR DELIVERY TO THE UPPER AND CENTRAL RESPIRATORY TRACT AND METHODS OF MANUFACTURE

(57) Abstract: Microparticle formulations are produced by contacting an aqueous solution of a protein or other active agent with an organic solvent, a counterion and a scavenging agent, and chilling the solution. The microparticles are useful for preparing stable, uniform pharmaceuticals of predetermined defined dimensions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/48736

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/54, 9/127 (2014.01)
USPC - 424/94.3, 94.1, 450, 400
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)
IPC(8): A61K 38/54, 38/17, 9/14, 9/127, 47/02; C12N 9/36; C07K 1/30 (2014.01)
USPC: 424/94.3, 94.1, 450, 400, 502, 43; 514/169; 435/206, 252.3; 530/418

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; ProQuest; KEYWORDS: 'DAS181 or sialidase fusion protein,' 'feedstock composition or raw material*,' 'lactose,' 'inhaler,' 'capsule*,' 'counterion,' 'Organic solvent* OR aliphatic hydrocarbon* OR aromatic hydrocarbon'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0116062 A1 (MALAKHOV, MD et al.) May 10, 2012; paragraphs [0004]-[0010], [0016], [0017], [0020], [0024], [0026], [0029], [0033], [0040], [0042], [0045], [0046], [0053], [0062], [0063], [0068], [0078], [0087], [0088], [0092], [0094], [0105], [0011]-[0116], [0124], [0140], [0152], [0194], [0494], [0520], [0524], [0520]	1, 11-14, 15/1, 15/11-15/14, 16/15/1, 16/15/11-16/15/14, 17-20, 25 ----- 2-10, 15/2-15/10, 16/15/2-16/15/10, 21-24, 29, 52-72, 73/52, 73/59, 73/66, 74/73/52, 74/73/59, 74/73/66, 75/74/73/52, 75/74/73/59, 75/74/73/66, 76/75/74/73/52, 76/75/74/73/59, 76/75/74/73/66
Y	US 2011/0171132 A1 (FANG, F et al.) 14 July 2011; paragraphs [0196], [0352], [0195], [0351], [0168], [0167]	21-24, 52-72, 73/52, 73/59, 73/66, 74/73/52, 74/73/59, 74/73/66, 75/74/73/52, 75/74/73/59, 75/74/73/66, 76/75/74/73/52, 76/75/74/73/59, 76/75/74/73/66

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
15 February 2015 (15.02.2015	0 4 MAR 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/48736

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0112751 A1 (FANG, F et al.) May 26, 2005; paragraphs [0046], [0058]; SEQ ID NO: 19	2-10, 15/2-15/10, 16/15/2-16/15/10, 29, 52-58, 62-69, 73/52, 74/73/52, 75/74/73/52, 76/75/74/73/52
Y	US 2002/0037316 A1 (WEERS, JG et al.) March 28, 2002; paragraphs [0031], [0043], Table X, page 17	53, 57, 58, 60, 61, 70-72

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/48736

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/48736

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.: 26-28, 30-43
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.:

Groups I+: Claims 1-25, 29, 52-76, SEQ ID NOs: 1, 2

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.:

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/US13/48736

-***-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 1-25, 29, 52-76 (in-part) and SEQ ID NO: 1 (DAS181 amino acid sequence) are directed toward a method of making a composition comprising microparticles comprising DAS181, the method comprising: a) providing a feedstock composition comprising DAS181, a counterion and an organic solvent; and b) cooling the composition to below 25 degrees C, whereby a composition comprising microparticles comprising DAS181 is formed; a composition comprising microparticles wherein the microparticles comprise about 60-70% wt/wt DAS181, 1-2% wt/wt histidine, 8-10% wt/wt histidine hydrochloride, 7-10% wt/wt trehalose, 4-8% wt/wt magnesium sulfate, 1-3% citrate, and 6-10% water; a composition comprising microparticles, wherein the microparticles, when anhydrous, comprise about 65-75% wt/wt DAS181 (SEQ ID NO: 1), 1-3% wt/wt histidine, 8-11% wt/wt histidine hydrochloride, 8-11% wt/wt trehalose, 5-8% wt/wt magnesium sulfate, and 1-3% citrate; a composition comprising microparticles wherein the microparticles comprise about 60-80% wt/wt DAS181, 4.5-6.5% wt/wt histidine, 3.5-5.5% wt/wt histidine hydrochloride, 7-11% wt/wt trehalose, 1-4% citrate, and 6-10% water; a composition comprising microparticles that, when anhydrous, comprise about 70-80% wt/wt DAS181, 5-7% wt/wt histidine, 4-6% wt/wt histidine hydrochloride, 9-11% wt/wt trehalose, and 1.5-3.5% citrate.

The method of making a composition comprising microparticles comprising DAS181, compositions comprising DAS181, histidine, histidine hydrochloride, trehalose, magnesium sulfate and citrate and compositions comprising DAS181, histidine, histidine hydrochloride, trehalose, and citrate will be searched to the extent that they encompass SEQ ID NO: 1 (DAS181 amino acid sequence). It is believed that claims 1, 2, 4, 7, 11-25, 48-61, 66-68, 70-76 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (DAS181 amino acid sequence). Applicants must 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: SEQ ID NO: 2 (DAS181 amino acid sequence).

Groups I+ share the technical features including a method of making a composition comprising microparticles comprising DAS181, the method comprising: a) providing a feedstock composition comprising DAS181, a counterion and an organic solvent; and b) cooling the composition to below 25 degrees C, whereby a composition comprising microparticles comprising DAS181 is formed; a composition comprising microparticles wherein the microparticles comprise about 60-70% wt/wt DAS181, 1-2% wt/wt histidine, 8-10% wt/wt histidine hydrochloride, 7-10% wt/wt trehalose, 4-8% wt/wt magnesium sulfate, 1-3% citrate, and 6-10% water; a composition comprising microparticles, wherein the microparticles, when anhydrous, comprise about 65-75% wt/wt DAS181, 1-3% wt/wt histidine, 8-11% wt/wt histidine hydrochloride, 8-11% wt/wt trehalose, 5-8% wt/wt magnesium sulfate, and 1-3% citrate; a composition comprising microparticles wherein the microparticles comprise about 60-80% wt/wt DAS181, 4.5-6.5% wt/wt histidine, 3.5-5.5% wt/wt histidine hydrochloride, 7-11% wt/wt trehalose, 1-4% citrate, and 6-10% water; a composition comprising microparticles that, when anhydrous, comprise about 70-80% wt/wt DAS181, 5-7% wt/wt histidine, 4-6% wt/wt histidine hydrochloride, 9-11% wt/wt trehalose, and 1.5-3.5% citrate.

However, these shared technical features are previously disclosed by US 2012/0116062 A1 to Malakhov, et al. (hereinafter 'Malakhov') in view of US 2011/0171132 A1 to Fang, et al. (hereinafter 'Fang'). Malakhov discloses a method of making (method of making; paragraph [0008]) a composition (composition; paragraph [0008]) comprising microparticles (microparticles; paragraph [0007]) comprising DAS181 (DAS181; paragraphs [0087], [0116]), the method comprising: a) providing a feedstock composition (a solution comprising a polypeptide (a feedstock composition; paragraph [0011]) comprising DAS181 (DAS181; paragraphs [0087], [0116]), a counterion (a counterion; paragraph [0011]) and an organic solvent (and an organic solvent; paragraph [0012]); and b) cooling the composition to below 25 degrees C (cooling the composition to below 25 degrees C; paragraph [0013]), whereby a composition comprising microparticles is formed (whereby a composition comprising microparticles is formed; paragraph [0013]) comprising DAS181 (comprising DAS181; paragraphs [0087], [0116]); and wherein the microparticles may comprise from about 70% to about 85%, or up to 99% wt/wt of the polypeptide (paragraphs [0033], [0115]), as well as the use of histidine (paragraph [0123]), histidine hydrochloride (histidine HCl salt (histidine hydrochloride); paragraphs [0123], [0124]), trehalose (paragraph [0558]; Table 12), magnesium sulfate (paragraphs [0017], [0028], [0037]) and citrate (paragraphs [0115], [0016], [0121]) in the production of microparticles comprising DAS181 (paragraphs [0481], [0484], [0485]).

Malakhov does not disclose wherein the microparticles comprise about 60-70% wt/wt DAS181, 1-2% wt/wt histidine, 8-10% wt/wt histidine hydrochloride, 7-10% wt/wt trehalose, 4-8% wt/wt magnesium sulfate, 1-3% citrate, and 6-10% water; wherein the microparticles, when anhydrous, comprise about 65-75% wt/wt DAS181, 1-3% wt/wt histidine, 8-11% wt/wt histidine hydrochloride, 8-11% wt/wt trehalose, 5-8% wt/wt magnesium sulfate, and 1-3% citrate; wherein the microparticles comprise about 60-80% wt/wt DAS181, 4.5-6.5% wt/wt histidine, 3.5-5.5% wt/wt histidine hydrochloride, 7-11% wt/wt trehalose, 1-4% citrate, and 6-10% water; or about 70-80% wt/wt DAS181, 5-7% wt/wt histidine, 4-6% wt/wt histidine hydrochloride, 9-11% wt/wt trehalose, and 1.5-3.5% citrate.

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

-***-Continued from Previous Supplemental Box:

Fang discloses microparticles (microparticles; paragraph [0351]) comprising DAS181, histidine, magnesium sulfate or a citrate salt, trehalose, and water (paragraph [0195]), wherein the DAS181 may be from about 0.01% to about 100% wt/wt, in combination with histidine or histidine-HCl in an amount between about 0.01% to about 90% wt/wt, magnesium sulfate or citrate salt between about 0.01% and 90% wt/wt, trehalose between about 0.01% and 90% wt/wt, and water between about 0.00% and 90% wt/wt (paragraph [0196]) with preferred amounts in the ranges of about 70% DAS181, between 7% and about 20% histidine and histidine-HCl, between about 7% and 20% magnesium sulfate or citrate, between about 7% and 20% trehalose and between about 7% and 20% water (paragraph [0196]); wherein the microparticles comprise about 60-75% wt/wt DAS181 (about 64.5-64.7% wt/wt DAS181 (about 60-75% wt/wt DAS181); paragraph [0352]), 3-6% wt/wt histidine (4.3-4.6% wt/wt histidine (3-6% wt/wt histidine); paragraph [0352]), 4-8% wt/wt histidine hydrochloride (5.8-6.3% wt/wt histidine hydrochloride (4-8% wt/wt histidine hydrochloride); paragraph [0352]), 7-11% wt/wt trehalose (9.1-9.7% wt/wt trehalose (7-11%wt/wt trehalose); paragraph [0352]), 4-8% wt/wt magnesium sulfate (4.7-5.8% magnesium sulfate (4-8% wt/wt magnesium sulfate); paragraph [0352]), and 8-12% water (10% water (8-12% water); paragraph [0352]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the formulations of the particles previously disclosed by Malakhov, including those comprising about 60-70%, about 65-75%, about 60-80% or about 70-80% wt/wt DAS181; about 1-2%, about 1-3%, about 4.5-6.5% or about 5-7% histidine; about 8-10%, about 8-11%, about 3.5-5.5%, or about 4-6% wt/wt histidine hydrochloride; about 7-10%, about 8-11%, about 7-11% or about 9-11% wt/wt trehalose; about 4-8%, or about 5-8% wt/wt magnesium sulfate; about 1-3%, about 1-4%, or about 1.5-3.5% wt/wt citrate; and 6-10% or 0.0% wt/wt water, through routine experimentation and testing, based upon the amounts of these components previously disclosed by Fang, for providing a desired dose of DAS181 utilizing a composition having stable sialidase activity (Malakhov; Table 12).

Since none of the special technical features of the Groups I+ 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 Malakhov and Fang references, unity of invention is lacking.

Based on Applicant's election, claims 44-46 and 48-51 are excluded from this Search Report as drawn to non-elected subject matter.