



- (51) International Patent Classification:
A61K 39/395 (2006.01) G01N 33/53 (2006.01)
C07K 16/18 (2006.01)
- (21) International Application Number:
PCT/US2013/063945
- (22) International Filing Date:
8 October 2013 (08.10.2013)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/711,204 8 October 2012 (08.10.2012) US
61/719,281 26 October 2012 (26.10.2012) US
61/840,432 27 June 2013 (27.06.2013) US
61/872,366 30 August 2013 (30.08.2013) US

(74) Agents: **CELLI, Rosemarie L.** et al.; Alston & Bird LLP, 100 South Tyron Street, Bank of America Plaza, Suite 4000, Charlotte, North Carolina 28280-4000 (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, IR, 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, 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, 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).

(71) Applicant: **NEOTOPE BIOSCIENCES LIMITED** [IE/IE]; 25-28 North Wall Quay, Dublin, 1 (IE).

(72) Inventors; and

(71) Applicants (for US only): **BARBOUR, Robin** [US/US]; 250 Normandy Lane, Walnut Creek, California 94598 (US). **GAMES THIEL, Kate Dora** [US/US]; 503 Alameda de las Pulgas, Belmont, California 94002 (US). **NIJJAR, Tarlochan, S.** [US/US]; 712 Ironbark Court, Orinda, California 94563 (US).

Published:

— with international search report (Art. 21(3))

[Continued on next page]

(54) Title: ANTIBODIES RECOGNIZING ALPHA-SYNUCLEIN

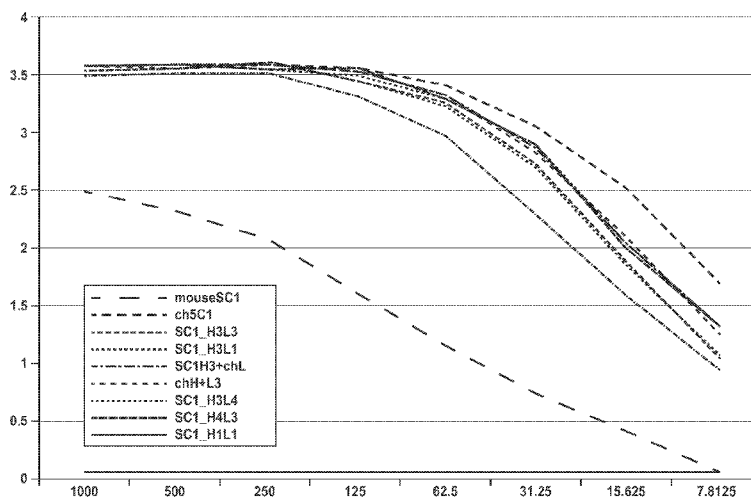


FIG. 5

(57) Abstract: The invention provides monoclonal antibody 5C1 and related antibodies. The 5C1 antibody binds to an epitope with residues 118-126 of α -synuclein. The antibodies of the invention are useful, for example, for treating and/or diagnosing disorders associated with α -synuclein, particularly accumulation of α -synuclein deposits. Such disorders include Lewy body diseases, such as Parkinson's disease, Diffuse Lewy Body Disease (DLBD), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson disease, pure autonomic failure and multiple system atrophy (MSA).

WO 2014/058924 A3

— *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:
5 June 2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/63945

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; C07K 16/18; G01N 33/53 (2014.01)

USPC - 424/143.1; 435/69.6, 252.3

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 39/395, 39/00; C07K 16/18, 16/00; G01N 33/53, 33/50, 33/00 (2014.01)

USPC: 424/143.1, 141.1, 42.1, 130.1, 133.1; 435/69.6, 69.1, 252.3, 243, 7.93

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; Pubmed/Pubmed Central/NCBI Blast; UniProt; antibody, immunoglobulin, 'antigen binding protein,' 'alpha-synuclein,' 'alpha-synuclein,' '5C1,' humanized, chimeric, epitope, 'binding site,' antigen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	WO 2005/047860 A2 (CHILCOTE, T et al.) May 26, 2005; paragraphs [0007], [0018], [0039]-[0057], [0079]; Claims 46, 47	1, 5, 8/1, 8/5 ----- 6, 7, 8/6, 8/7, 18-26, 33, 34, 41, 42
A	MIHARA, M et al. CTLA4Ig Inhibits T Cell-Dependent B-Cell Maturation In Murine Systemic Lupus Erythematosus. J. Clin. Invest. July 2000, Vol. 106, No. 1; pages 91-101; page 97, second column, first paragraph; Genbank supplement, page 1; DOI: 10.1172/JCI9244.	6, 7, 8/6, 8/7, 41-44
A	HACKETT, J et al. Recombinant Mouse-Human Chimeric Antibodies As Calibrators In Immunoassays That Measure Antibodies To Toxoplasma gondii. J Clin Microbiol. May 1998, Vol. 36, No. 5; pages 1277-1284; page 1277, second column, fourth paragraph; page 1280, second column, third paragraph; Genbank supplement, pages 1-2; PMID: 9574691.	6, 7, 8/6, 8/7, 18-26, 33, 34, 41-44
A	YANG, H et al. Structural Basis Of Immunosuppression By The Therapeutic Antibody Daclizumab. Cell Res. Dec 2010, Vol. 20, No. 12; pages 1361-1371; page 1362, first column, second paragraph to second column, fourth paragraph; Genbank supplement, pages 1-3; DOI: 10.1038/cr.2010.130.	18-26, 33, 34
A	US 2009/0202432 A1 (SCHENK, DB et al.) August 13, 2009; paragraphs [0018], [0019], [0181]	18-26, 33, 34
A	US 2012/0204275 A1 (SCHENK, DB et al.) August 9, 2012; paragraphs [0022]-[0024]	43, 44

 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

27 March 2014 (27.03.2014)

Date of mailing of the international search report

22 APR 2014

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. 571-273-3201

Authorized officer:

Shane Thomas

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/63945

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.: 9-17, 27-32, 35-40, 45-56
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.:

Group I: Claims 1, 5-7, 8 (in-part), 18-26, 33, 34, 41-44

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.

***-Continued from Box 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.

Group I: Claims 1, 5, 6, 7, 8 (in-part), 18-26, 33, 34 and 41-44 are directed toward an isolated monoclonal antibody comprising three light chain CDRs as defined by Kabat and three heavy chain CDRs as defined by Kabat of monoclonal antibody 5C1, wherein the antibody specifically binds to human alpha synuclein; and a method of producing a humanized, chimeric or veneered form of 5C1.

Group II: Claims 2-4 and 8 (in-part) are directed toward an isolated monoclonal antibody that binds to human alpha synuclein, wherein alanine scanning mutagenesis of residues 118-126 of full-length human alpha synuclein indicates residues 120, 121, and 122 each contributes to the monoclonal antibody binding more than each of residues 123 and 124, and residues 123 and 124 each contributes to binding more than each of residues 118, 119, 125 and 126.

The inventions listed as Groups I-II 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 Group I include an antibody comprising three light chain CDRs as defined by Kabat and three heavy chain CDRs as defined by Kabat of monoclonal antibody 5C1, and methods of producing such an antibody, which are not present in Group II, the special technical features of Group II including wherein alanine scanning mutagenesis of alpha synuclein residues 118-126 of full-length human alpha synuclein indicates residues 120, 121, and 122 each contributes to the monoclonal antibody binding more than each of residues 123 and 124.

Groups I-II share the technical features including an isolated monoclonal antibody, wherein residues 120, 121 and 122 of human alpha synuclein contribute to the binding of the antibody (i.e. the epitope on human alpha synuclein comprises residues 120, 121 and 122, the same epitope as antibody 5C1, of the instant PCT application; paragraph [0103]).

However, these shared technical features are previously disclosed by the article entitled 'Fine Epitope Mapping Of Monoclonal Antibodies Specific To Human Alpha-Synuclein' by Choi, et al. (hereinafter 'Choi'). Choi discloses an isolated monoclonal antibody, Syn-1, which binds to an epitope comprising residues 121 and 122 of human alpha synuclein (an isolated monoclonal antibody, Syn-1, which binds to an epitope comprising residues 121 and 122 of human alpha synuclein; abstract).

Since none of the special technical features of the Groups I-II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Choi reference, unity of invention is lacking.