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(71) Applicants *(for all designated States except US)*: **NORTHWESTERN UNIVERSITY** [US/US]; 633 Clark Street, Evanston, IL 60208 (US). **INTELLECT NEUROSCIENCES INC.**; 45 West 36th Street, 3rd Floor, New York, NY 10018 (US).

(72) Inventors; and
(71) Applicants : **BINDER, Lester, I.** [US/US]; 777 N Michigan Ave #2100, Chicago, IL 60611 (US). **CHAIN, Daniel, G.** [GB/—]; 205 East 16th Street, Apt 3B, New York, NY 10003 (US). **FU, Yifan** [US/—]; 565 Willowcreek Ct, Clarendon Hills, IL 60514 (US). **PATTERSON, Kristina** [US/—]; 750 N. Dearborn Street, Apt 2104, Chicago, IL 60654 (US).

(74) Agents: **IOSELEVICH, Oleg** et al.; Davidson, Davidson & Kappel, LLC, 485 Seventh Avenue, 14th Floor, New York, NY 10018 (US).

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(54) Title: ANTIBODIES SELECTIVE FOR PATHOLOGICAL TAU DIMERS AND OLIGOMERS AND THEIR USES IN TREATMENT, DIAGNOSIS, MONITORING OF TAUOPATHIES

(57) Abstract: Antibodies selective for pathological tau dimers and/or prefibrillar pathological tau oligomers, immunogenic peptides and epitopes of these antibodies, hydridomas producing these antibodies, uses of these antibodies, immunogenic peptides and epitopes in preparation of pharmaceutical compositions for the treatment of tauopathies, and uses of these antibodies, immunogenic peptides, epitopes and pharmaceutical compositions in the treatment of tauopathies are described. Also described are uses of these antibodies, immunogenic peptides, epitopes in diagnosis and monitoring of tauopathies.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395; C12P 21/08 (2012.01)
USPC - 424/141.1, 424/172.1; 530/388.1, 530/387.9
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; C12P 21/08; A61K 39/00; G01N 33/00 (2012.01)
USPC - 424/141.1, 424/172.1; 530/388.1, 530/387.9; 424/184.1; 436/86

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/395; C12P 21/08; A61K 39/00; G01N 33/00 (2012.01) - see keyword below
USPC - 424/141.1, 424/172.1; 530/388.1, 530/387.9; 424/184.1; 436/86 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: Tau, antibody, anti-Tau, bind, specific, aggregated, aggregate, oligomeric, Tau Oligomers, TOMA, TOC-1, tauC3, oligomer, Tau40, hTau, hTau40, dimer, cysteine, cross-link, complex, prefibrillar, fibrillar, benzophenone-4-maleimide, Histidine, probe, Alzheimer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/026031 A1 (Kayed) 03 March 2011 (03.03.2011), para [0003], [0006], [0007], [0008], [0009], [0010], [0026], [0027], [0028], [0029],[0030], [0036], [0040], Fig 3A, and Fig 5A	1-8, 13/(1-8)
A	DAVIDOWITZ et al. Targeting tau oligomers for therapeutic development for Alzheimer's disease and tauopathies. Curr Topics Biotech. 2008, Vol 4, p. 47-64. pg 48, col 2, and Table 1; and pg 49, Figure 1; pg 51, col 2, last para; pg 52, col 2, lower para; and pg 54, col 1, para 1	1-8, 13/(1-8)
A	MO et al. Low Micromolar Zinc Accelerates the Fibrillization of Human Tau via Bridging of Cys-291 and Cys-322. J Biol Chem. 2009, Vol. 284(50), p. 34648-57. Abstract	1-8, 13/(1-8)
A	SAHARA et al. Assembly of two distinct dimers and higher-order oligomers from full-length tau. Eur J Neurosci. 2007, Vol. 25(10), p. 3020-9. pg 3021, col 1, para 1	1-8, 13/(1-8)
A	ALZFORUM_News, Chicago: Tau and a-Synuclein Oligomers Follow A.Beta Footsteps, 5 November 2009, [online]. [Retrieved on 2012.08.23]. Retrieved from the Internet: <URL: http://www.alzforum.org/new/detail.asp?id=2276> PDF file: pg 1-5. Entire documentation, especially, pg 3, para 1	1-8, 13/(1-8)
A	US 2008/0220449 A1 (VASAN et al.) 11 September 2008 (11.09.2008), para [0016], [0018], [0030], and [0072]	1-8, 13/(1-8)
A	US 2005/0054572 A1 (Marshall) 10 March 2005 (10.03.2005), para [0083]	1-8, 13/(1-8)

☒ 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
08 November 2012 (08.11.2012)	10 DEC 2012

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	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PATTERSON et al. Characterization of Prefibrillar Tau Oligomers in Vitro and in Alzheimer Disease. J Biol Chem. 2011 Jul 1;286(26):23063-76. Epub 2011 May 6. Entire documentation, especially Abstract; pg 23064, col 1, para 1-3, and col 2, para 1; pg 23066, Fig 1; pg 23067, col 1, lower para, and col 2, middle para; pg 23068, col 1, para 1, col 2, para 1-2; pg 23070, col 2, last para; and pg 23071, col 1; pg 23072, col 1, lower para	1-8, 13/(1-8)

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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.: 14-46, 48-50, 55-58, 62-69, 76, 78-79, 82-94, 100-105, 107-108, 112-116
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:
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 1-13, 47, 109-111 drawn to an antibody that selectively recognizes a cross-linked Tau. The first named invention (claims 1-8, 13/(1-8)) is limited to an antibody which shows reactivity with aggregated tau, prefibrillar Tau aggregates, an oligomer of Tau, wherein the aggregated tau or oligomer Tau comprises at least two tau proteins crosslinked to each other, either directly or through a linker, at one or more cysteine residues (Specification: [0041] The term "oligomer(s)" as used in the present application refers to tau aggregates ... which are intermediates between monomers of Tau and NFTs. The term "oligomer(s)" does not include monomers of tau (e.g., hTau40), dimers of tau and NFTs'). Applicant is invited to elect an antibody that selectively recognizes a conformation induced by a cross-linked Tau dimer, wherein the cross-linked Tau dimer comprises at least two tau proteins cross-linked in vitro to each other, and an antibody which binds to an epitope found in a tau oligomer or a tau dimer prepared by cross-linking at least two tau proteins to each other in-vitro; and an antibody which selectively recognizes a tau dimer conformation which is the conformation selectively recognized by TOC1 antibody (claims 9-12, 13/(9-12), 47, 109-111), to be searched by paying an additional fee.
continued in extra sheet*

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.:
1-8, 13/(1-8), limited to an antibody which shows reactivity with aggregated tau, see above

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.

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Continuation of:
Box No III (unity of invention is lacking)

Group II, claims 51-54, 59-61, 80-81, drawn to an isolated oligomer of Tau having an apparent molecular mass of 180 kDa, wherein the oligomer comprises at least two tau proteins cross-linked to each other, either directly or through a linker at one or more cysteine residues, or a method of inducing an immunogenic response in a mammal, the method comprising administering an immunogenic dose of an oligomer of hTau40 to said mammal, wherein the oligomer comprises at least two tau proteins cross-linked to each other, either directly or through a linker at one or more cysteine residues.

Group III, claims 70-75, 77 drawn to a method of preventing or treating a tauopathy in a mammal, comprising administering to a mammal in need of therapy for a tauopathy antibodies having selectivity to abnormal forms of tau, or method of preventing or slowing down formation of tau aggregates in the brain of a mammal, comprising administering to a mammal antibodies having selectivity to dimers of Tau or prefibrillar oligomers of tau, said antibodies showing no reactivity with monomeric Tau, wherein abnormal form of Tau, the dimers of Tau or prefibrillar oligomers of Tau comprise two or at least two tau proteins cross-linked to each other, either directly or through a linker, at one or more cysteine residues.

Group IV, claims 95-99, drawn to a method of cross-linking of hTau40 comprising reacting hTau40 with benzophenone-4-maleimide.

Group V, claim 106, drawn to a diagnostic marker for diagnosing Alzheimer's disease comprising a quantitative ratio of TOC1 antibody to Histidine probe.

The inventions listed as Groups I+-V 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:

Groups I+- IV do not include the inventive concept of a diagnostic marker for diagnosing Alzheimer's disease comprising a quantitative ratio of TOC1 antibody to Histidine probe, as required by Group V.

Groups I+-III, and V do not include the inventive concept of reacting hTau40 with benzophenone-4-maleimide, as required by Groups IV.

Groups I+-II and IV-V do not include the inventive concept of administering to a mammal antibodies, as required by Group III.

Group I, and III-V do not include the inventive concept of an isolated oligomer of Tau or administering an immunogenic dose of an oligomer of hTau40, as required by Group II.

Furthermore, among Group I+, claims 1-8 and 13/(1-8) do not include inventive concept of a tau dimer conformation which is the conformation selectively recognized by TOC1 antibody, and an antibody which binds to an epitope found in a tau oligomer or a tau dimer prepared by cross-linking at least two tau proteins to each other in-vitro, as required by claims 9-12, 13/(9-12), 47 or 109-111.

The inventions of Groups I+ and III share the technical feature of an antibody selectively recognizes aggregated tau, prefibrillar Tau aggregates, an oligomer of Tau, or a cross-linked Tau, wherein the aggregated tau or oligomer Tau comprises at least two tau proteins crosslinked to each other; and Groups I+ through III further share the technical feature of an oligomer of Tau comprises at least two tau proteins cross-linked to each other, either directly or through a linker at one or more cysteine residues. However, this shared technical feature does not represent a contribution over prior art as being anticipated by WO 2011/026031 A1 to Kayed as follows:

Kayed discloses an antibody which shows reactivity with aggregated tau, prefibrillar Tau aggregates, or an oligomer of Tau, and substantially no reactivity with unaggregated Tau (para [0028] - 'T2286 (Novel tau oligomer specific antibody) detects only tau oligomers but not monomeric tau or tau fibrils'; para [0029] - 'tau oligomers detected by T-2286 are elevated in AD brain (red) ... T -2286 dosn't recognize monomeric tau'; para [0008] - the antibody is a monoclonal antibody or antibody fragment that specifically binds Tau oligomers and does not bind soluble Tau or Tau fibrils... "Tau oligomer" refers to a protein aggregate having about 3 to 24 Tau polypeptides ? "soluble Tau" refers to a monomer or dimer of Tau proteins. ... "Tau fibrils" refers to insoluble Tau aggregate differing in conformation (e.g., having distinct epitopes as compared to Tau oligomer)', wherein ' binds Tau oligomers and does not bind... Tau fibril' indicates the 'Tau oligomers' are ' prefibrillar Tau aggregates', and the antibody 'selectively recognizes prefibrillar Tau aggregates'; para [0003] - 'Pathological aggregation of the microtubule-associated protein Tau and accumulation of neurofibrillary tangles (NFT)'; Specification: [0041] The term "oligomer(s)" as used in the present application refers to tau aggregates ... which are intermediates between monomers of Tau and NFTs. The term "oligomer(s)" does not include monomers of tau (e.g., hTau40), dimers of tau and NFTs');
—wherein the aggregated tau comprises at least two or three tau proteins (para [0008] - 'the antibody is a monoclonal antibody or antibody fragment that specifically binds Tau oligomers and does not bind soluble Tau or Tau fibrils... "Tau oligomer" refers to a protein aggregate having about 3 to 24 Tau polypeptides').

Although Kayed does not expressively discloses wherein at least two or three tau protein scross-linked to each other, either directly or through a linker at one or more cysteine residues, this limitation is inherent by the inherent property of oligomer of Tau, as cysteine residues are essential for the Tau oligomer formation and the consequent fibrillization of Tau (please see an article entitled 'Targeting tau oligomers for therapeutic development for Alzheimer?s disease and tauopathies' by Davidowitz; Curr Topics Biotech. 2008, Vol 4, p. 47-64: pg 51,col 2, last para - 'disulfide bond formation in tau oligomerization the aggregation of tau 4R/2N ...The absence of both cysteines slowed the rate of dimer formation and prevented the formation of SDS-stable higher order oligomers'; pg 52, col 2, lower para - 'C291A or C322A, but conversion of both cysteines strongly inhibited the accumulation of dimer'; Please also see an article entitled 'Low Micromolar Zinc Accelerates the Fibrillization of Human Tau via Bridging of Cys-291 and Cys-322' by Mo et al.; J Biol Chem. 2009, Vol. 284(50), p. 34648-57: Abstract - 'one Zn2 binds to one Tau molecule...low micromolar zinc accelerates the fibrillization of human Tau protein via bridging Cys-291 and Cys-322'). Without a shared special technical feature, the inventions lack unity with one another.

**********Continued in the next extra sheet**********

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Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

The inventions of Groups II and IV further share the technical feature of an oligomer/cross-linked hTau40. However, this shared technical feature does not represent a contribution over prior art. Specifically, Kayed further discloses preparing Tau oligomers using human Tau 2N4R, which is hTau40 (para [0027] - 'Tau oligomers prepared by seeding with preformed oligomers in PBS,...oligomers/tau. (A), Western blot of tau oligomers prepared by cross-seeding ... recombinant human tau (2N4R tau 1-441)', wherein 'human tau (2N4R tau 1-441)' is 'hTau40'; Please see an article entitled 'Assembly of two distinct dimers and higher-order oligomers from full-length tau' by Sahara et al.; Eur J Neurosci. 2007, Vol. 25(10), p. 3020-9: pg 3021, col 1, para 1 - 'human tau cDNAs based on htau40... which encodes a 441-amino acid polypeptide (4R2N tau)'; Specification: [00102] - 'the longest tau isoform, htau40, contains two N-terminal inserts and four microtubule binding (2N4R) domains'), wherein oligomer of Tau hTau40 is inherently cross-linked, as discussed above. Without a shared special technical feature, the inventions lack unity with one another.

The inventions of claims 9-12, 13/(9-12) of Groups I+ and IV further share the technical feature of preparing Tau dimer in vitro by cross-linking. However, this shared technical feature does not represent a contribution over prior art. Specifically, a poster entitled 'Chicago: *Tau and a-Synuclein Oligomers Follow A.beta Footsteps' by Alzforum_News (5 November 2009, [online]. [Retrieved on 2012.08.23].* Retrieved from the Internet: <URL: http://www.alzforum.org/new/detail.asp?id=2276> PDF file: pg 1-5) discloses a method for preparing Tau dimer in vitro by cross-linking (PDF file: pg 3, para 1 - 'tau oligomers. ... used chemical cross-linking to stabilize tau oligomers in vitro. ... used a benzophenone cross-linker that binds cysteine with one end, but any carbon-hydrogen bond with the other'). Without a shared special technical feature, the inventions lack unity with one another.

Finally, the inventions of claim 47 of Group I+ and Group III further share the technical feature of an antibody having selectivity to dimers of Tau, and the inventions of claim 47 of Group I+ and Group V further share the technical feature of an antibody which selectively recognizes a tau dimer conformation which is the conformation selectively recognized by TOC1 antibody. However, this shared technical feature does not represent a contribution over prior art. Specifically, Kayed further discloses an antibody that recognizes tau oligomer having dimer molecular weight (Fig 5A, T2286 - the bands around 80 kd to around 150 kd are dimer position; para [0009] - 'Tau dimers are approximately 80Kd to 1500 Kd', wherein '1500 Kd' should be '150 Kd'; please see Davidowitz: pg 54, col 1, para 1 - 'the human tau construct... at apparent molecular weight (MW) of 55 kDa (tau55) ... the presence of tau in two additional bands at 140 (tau140) and 170 kDa (tau170) indicating the presence of oligomers composed of 2 or more tau proteins').

Kayed further discloses a method for generating antibody by preparing Tau oligomers of hTau40 (para [0027] - 'Tau oligomers prepared ..... recombinant human tau (2N4R tau 1-441)', wherein 'human tau (2N4R tau 1-441)' is 'hTau40', as discussed above), and a method for screening antibodies that specifically binds to Tau oligomers (prefibrillar Tau aggregates) but not monomer or fibrillar Tau aggregates (para [0010] - 'identifying a Tau oligomer specific antibody comprising: (a) independently contacting antibodies that bind Tau oligomers with Tau oligomers, soluble Tau, or Tau fibrils; and (b) identifying antibodies that specifically bind Tau oligomers and do not bind soluble Tau or Tau fibrils at levels that are detectable above background'; [0008]), wherein the antibody specifically binds to Tau oligomers and can detect pathological Tau aggregates from a patient suffering an Alzheimer's disease (para [0030]- ' T2886 detects tau *oligomers in the PBS fraction of AD brains (A) T2886 only recognizes higher molecular weight species and not monomer*'; para [0028] - 'T2286 (Novel tau oligomer specific antibody) detects only tau oligomers but not monomeric tau or tau fibrils'; Fig 5A), and do not bind to a-synuclein (para [0028] - 'T2286 (Novel tau oligomer specific antibody) detects only tau oligomers but not monomeric tau or tau fibrils; moreover, it does not detect oligomers from other proteins..... (7) a-synuclein oligomers'; Fig 3A- lane 7). Furthermore, Alzforum_News discloses a method for preparing Tau dimer in vitro by cross-linking using a benzophenone cross-linker (PDF file: pg 3, para 1 - 'tau oligomers. ... used chemical cross-linking to stabilize tau oligomers in vitro. ... used a benzophenone cross-linker that binds cysteine with one end, but any carbon-hydrogen bond with the other'), which is the method used in the application for dimer preparation (Specification: para [0018] - "to isolated antibodies ... two or at least two tau monomers cross-linked to each other... through a linker (e.g., benzophenone-4-maleimide'). One of ordinary skill in the art at the time the invention was made would have been motivated to combine the method of Kayed and the disclosure of Alzforum_News for antibody generation and screening to obtain antibodies that bind to different epitopes of Tau oligomers including an antibody that selectively recognizes a tau dimer conformation which is the conformation selectively recognized by TOC1 antibody.

Furthermore, please note, the binding feature of TOC1 comprising preferentially binding to Tau oligomers but not to monomeric tau, tau fibrils or a-synuclein (Specification: para [0061] - 'TOC1 preferentially labeling Tau oligomers (i.e., apparent 180-kDa Tau oligomers)'; para [0060] - 'TOC1 preferentially... labels uncross-linked Tau oligomeric and filamentous aggregates prepared with AA as *opposed to unaggregated Tau ... TOC1 did not react with either a-synuclein'), indicating the ' tau dimer conformation which is the* conformation selectively recognized by TOC1 antibody' is a conformation that is shared by oligomers, and further wherein the binding feature of TOC1 is shared by the antibodies taught by Kayed (Fig 5A; para [0028]-[0030]; [0008]). In addition, TOC1 preferentially binds to uncross-linked Tau (Specification: para [0060] - 'TOC1 preferentially... labels uncross-linked Tau oligomeric and filamentous aggregates prepared with AA'), indicating the epitope that TOC1 binds is not only present on the Tau dimer resulting from vitro cross-linking with linkers. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-V therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note re item 4: Claims 14-46, 48-50, 55-58, 62-69, 76, 78-79, 82-94, 100-105, 107-108, 112-116 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note:

1) Claim 12 comprising self-referring. For the purposes of this ISR, ' The antibody of anyone of claims 12' in claim 12, is assumed to be 'The antibody of claim 11'.
2) Claims 25 and 76 are self-referring. For the purposes of this ISR, claims 25 and 76 are assumed to be dependent upon claim 24 or claim 75, respectively.
3) ' Histadine probe' in claim 106 is read as 'Histidine probe' according the specification (para [0062] - 'deletion mutants of hTau40 expressed as the ratio of TOC1: total Tau. Total Tau was measured with ... a His probe antibody').