Citation: New York University, 2023 CACP 22
Commissioner's Decision #1655
Décision du commissaire nº 1655
Date: 2023-08-01

TOPIC:	B00	Claims—Ambiguity or Indefiniteness (incomplete)
	C00	Disclosure—Adequacy or Deficiency of Description
	O00	Obviousness
SUJET :	B00	Revendications—Caractère ambigu ou indéfini (incomplet)
	C00	Divulgation—Caractère adéquat ou inadéquat de la description
	G00	Évidence

Application No. 2765099
Demande nº 2 765 099

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,765,099 having been rejected under subsection 199(1) of the *Patent Rules*, has consequently been reviewed in accordance with paragraph 86(7)(c) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected Canadian patent application number 2,765,099, which is entitled “Phosphorylated tau peptide for use in the treatment of tauopathy”. New York University is the sole Applicant. A review of the rejected application has been conducted by a Panel of the Patent Appeal Board pursuant to paragraph 86(7)(c) of the *Patent Rules*.

[2] As explained in more detail below, our recommendation is that the Commissioner of Patents refuse the application.

BACKGROUND

The Application

[3] The application was filed under the Patent Cooperation Treaty and has an effective filing date in Canada of June 10, 2010. It was laid open to public inspection on December 16, 2010.

[4] The rejected application relates to methods and compositions for treating Alzheimer’s disease or other tauopathies by administering immunogenic peptides derived from pathological tau proteins or antibodies recognizing an epitope of said peptides. In particular, peptides containing phosphorylation sites that are prominent in Alzheimer’s disease are expected to generate antibodies that will target pathological hyperphosphorylated tau proteins that are found in patients with Alzheimer’s disease and related tauopathies.

[5] The application has 28 claims on file that were received at the Patent Office on April 3, 2020.

Prosecution History

[6] On January 27, 2021, a Final Action was written under subsection 86(5) of the *Patent Rules*. The Final Action indicates that the specification, insofar as it

relates to the antibodies of claims 1 to 12 and 17 to 28 on file at the time of the Final Action, is insufficient and does not comply with subsection 27(3) of the *Patent Act* and that these claims are further indefinite and do not comply with subsection 27(4) of the *Patent Act*. In addition, the Final Action indicates that the description contains statements that incorporate by reference other documents and does not comply with subsection 57(1) of the *Patent Rules*.

[7] The Response to the Final Action dated May 21, 2021 does not contest the insufficiency or indefiniteness defects and instead submits a set of proposed claims in which all references to tau antibodies from the claims on file are removed. In addition, the Response to the Final Action proposes amendments to the description to remove all statements of incorporation by reference.

[8] On February 14, 2022, the application was forwarded to the Patent Appeal Board for review under paragraph 86(7)(c) of the *Patent Rules* along with a Summary of Reasons explaining that the rejection is maintained.

[9] In a letter dated February 17, 2022, the Patent Appeal Board includes a copy of the Summary of Reasons to the Applicant and requests that they confirm their continued interest in having the application reviewed.

[10] In a letter dated April 6, 2022, the Applicant confirmed their interest in having the review proceed.

[11] The present Panel was formed to review the rejected application under paragraph 86(7)(c) of the *Patent Rules*. On May 18, 2023, the Panel sent a Preliminary Review letter detailing our preliminary analysis and opinion that the specification, insofar as it relates to claims 1 to 12 on file, is insufficient contrary to subsection 27(3) of the *Patent Act* but that claims 17 to 28 do comply with subsection 27(3) of the *Patent Act* and that claims 1 to 12 and 17 to 28 comply with subsection 27(4) of the *Patent Act*. In that letter, the Panel further expresses the preliminary opinion that the description does not comply with subsection 57(1) of the *Patent Rules* as it contains multiple statements that incorporate by reference other documents and that the proposed amendments to the description would overcome this defect. The Preliminary Review letter also expresses the

preliminary opinion that the proposed claims submitted with the Response to the Final Action would overcome the defect of insufficient disclosure raised against the claims on file but they would introduce a new defect in relation to indefiniteness. In addition, the Preliminary Review letter explains why, in our preliminary view, the claims on file, as well as the proposed claims are obvious contrary to section 28.3 of the *Patent Act* and notifies the Applicant of this defect under subsection 86(9) of the *Patent Rules*. Finally, the Preliminary Review letter provides the Applicant with an opportunity to make oral and/or written submissions.

[12] The Response to the Preliminary Review letter dated June 15, 2023 includes a set of newly proposed claims and provides written submissions in support of their patentability. On June 28, 2023, the Applicant submitted amendments to the newly proposed claims and on June 29, 2023 an oral hearing was held. In a letter dated July 31, 2023, the Applicant provided a copy of a decision from the Federal Court of Canada that was referred to during their oral submissions: Bayer AG v Novopharm Ltd, 2006 FC 379.

Issues

[13] In view of the above, the following issues are considered in this review:

- whether the specification, insofar as it relates to the claims 1 to 12 and 17 to 28 on file, is insufficient contrary to subsection 27(3) of the *Patent Act*.
- whether claims 1 to 12 and 17 to 28 on file are indefinite contrary to subsection 27(4) of the *Patent Act;*
- whether the description incorporates by reference other documents contrary to subsection 57(1) of the *Patent Rules*; and
- whether the claims on file are obvious contrary to section 28.3 of the *Patent Act*.

[14] In addition to the claims on file, the proposed claims submitted on June 28, 2023 have also been considered.

PURPOSIVE CONSTRUCTION

Legal Background

[15] According to Free World Trust v Électro Santé Inc, 2000 SCC 66 [Free World Trust] and Whirlpool Corp v Camco Inc, 2000 SCC 67 [Whirlpool], a purposive construction of the claims is performed from the point of view of the person skilled in the art in light of the relevant common general knowledge and considers the specification and drawings. In addition to interpreting the meaning of the terms of a claim, purposive construction distinguishes the essential elements of the claim from the non-essential elements. Whether or not an element is essential depends on the intent expressed in or inferred from the claim, and on whether it would have been obvious to the person skilled in the art that a variant has a material effect upon the way the invention works.

[16] In carrying out the identification of essential and non-essential elements, all elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language.

Analysis

The person skilled in the art and the relevant common general knowledge

[17] The Preliminary Review letter, on pages 4 to 5, states the following with regard to the identity of the person skilled in the art and their expected common general knowledge:

> [Bolding indicates inserted text] On pages 2 to 3, the Final Action identifies the person skilled in the art and the relevant common general knowledge:
>
> > The person skilled in the art to whom the application is directed can be characterized as a team of individuals practicing the field of protein chemistry, immunology and the field of neurobiology and

neurology. Said team would include a neurologist, a neuroscientist, a molecular biologist, a protein chemist and an immunologist.

The person skilled in the art would possess technical experience in the field of protein chemistry, genetic engineering, molecular biology and the production of monoclonal antibodies.

The person skilled in the art (POSITA) would possess the following common general knowledge (CGK) on December 16, 2010, the publication date of the present application:

1) Neurofibrillary tangles with their pathological tau protein conformers are associated with Alzheimer's Disease (AD) and other related pathologies

2) Target proteins for therapy of such diseases include pathological amyloid-beta and/or tau

3) Immunotherapy has emerged as a possible treatment for such diseases. The concept was antibodies generated from peptides derived from proteins such as amyloid-beta or tau would clear amyloid or tau aggregates that may affect neuronal viability

4) No known therapy exists for AD or other related pathologies.

The Response to the Final Action did not contest or comment on either of these characterizations.

After reviewing the specification and the references cited therein, we consider that the characterization of the person skilled in the art presented in the Final Action is reasonable, and therefore we adopt it for the purposes of this preliminary review.

We also agree that it was common general knowledge that neurofibrillary tangles and/or their pathological tau protein conformers are an important target for the treatment of Alzheimer's disease. As explained in the Background of the Invention on page 1 of the description, "[t]he objective of

immunotherapy for tau pathology is that anti-tau antibodies can clear tau aggregates that may affect neuronal viability."

In particular, the use of active immunization to generate antibodies that selectively or specifically recognize the pathological hyperphosphorylated tau protein was also part of the common general knowledge (as evidenced by the review article by Sigurdsson, E.M., "Immunotherapy targeting pathological tau protein in Alzheimer's disease and related tauopathies", Journal of Alzheimer's Disease, 15, pages 157 to 168, 2009 **[Sigurdsson review article]**). With respect to the knowledge of tau peptides that would elicit such antibodies, it was well known that the monoclonal antibody PHF-1 recognizes an epitope containing both phosphorylated Ser_{396} and Ser_{404}— two phosphorylation sites that are prominent in Alzheimer's disease: Otvos, Jr., L., et al., "Monoclonal antibody PHF-1 recognizes tau protein phosphorylated at serine residues 396 and 404", Journal of Neuroscience Research, 39, pages 669 to 673, 1994.

[18] The Applicant made no submissions on these characterizations of the person skilled in the art and the relevant common general knowledge in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above characterizations for this final review.

The claims on file

[19] There are 28 claims on file. Claims 1, 2, 4, 5, 7, 8, 13 to 17, 21 and 23 to 25 are the independent claims and read as follows:

1. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to treat Alzheimer's Disease or other tauopathy in a subject in need thereof;

for treating Alzheimer's disease or said other tauopathy in said subject.

2. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to treat Alzheimer's Disease or other tauopathy in a subject in need thereof;

for the preparation of a medicament for treating Alzheimer's disease or said other tauopathy in said subject.

4. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to promote clearance of tau aggregates from the brain of a subject in need thereof;

for promoting clearance of tau aggregates from the brain of said subject.

5. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to promote clearance of tau aggregates from the brain of a subject in need thereof;

for the preparation of a medicament for promoting clearance of tau aggregates from the brain of said subject.

7. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to slow the progression of a behavioral phenotype that is cause by the presence of pathological tau in a subject in need thereof;

for slowing progression of said behavioral phenotype in said subject.

8. A use of:

(A) an immunogenic tau peptide whose amino acid sequence consists of the amino acid sequence TDHGAEIVYKS*PVVSGDTS*PRHL (SEQ ID NO:13), wherein S* denotes phosphoserine;

or

(B) one or more antibodies, or active binding portion(s) thereof, that specifically recognize(s) an epitope of said immunogenic tau peptide (A), wherein said one or more antibodies is/are:

(1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide;

under conditions effective to slow the progression of a behavioral phenotype that is cause by the presence of pathological tau in a subject in need thereof;

for the preparation of a medicament for slowing progression of said behavioral phenotype in said subject.

13. An isolated tau peptide whose amino acid sequence consists of the amino acid sequence of SEQ ID NO: 13.

14. A tau peptide whose amino acid sequence consists of the amino acid sequence of SEQ ID NO: 13, linked to an immunogenic carrier.

15. A pharmaceutical composition comprising:

    the isolated tau peptide according to any one of claims 13 or 14, and a pharmaceutical carrier.

16. A pharmaceutical composition comprising:

    the isolated tau peptide according to any one of claims 13 or 14, and a pharmaceutical carrier, and one or more additional immunogenic tau peptides having an amino acid sequence selected from the group consisting of SEQ ID Nos: 81-100.

17. An antibody, or active binding portion(s) thereof, that specifically recognizes an epitope of the isolated tau peptide according to any one of claims 13 or 14, wherein said one ore more antibodies is/are:

    (1) elicited by an epitope present on said immunogenic tau peptide, or

(2) recombinantly produced and comprise(s) the amino acid sequence of active binding portion(s) of an antibody elicited by an epitope present on said immunogenic tau peptide.

21. A combination immunotherapeutic comprising:

the antibody, or active binding portion thereof, according to claim 17, and one or more additional antibodies or active binding portions thereof recognizing one or more different amyloidogenic proteins or peptides.

23. A method of diagnosing Alzheimer's disease or other tauopathy in a subject, said method comprising:

detecting, in the subject, the presence of a pathological tau protein conformer using a diagnostic reagent, wherein the diagnostic reagent comprises an antibody of claim 17, or active binding portion(s) thereof, and

diagnosing Alzheimer's disease or other tauopathy in the subject based on said detecting;

wherein said method comprises:

contacting, in vitro, a biological sample obtained from the subject with the diagnostic reagent under conditions effective for the diagnostic reagent to bind to the pathological tau protein conformer in the sample; and

detecting binding of the diagnostic reagent to the pathological tau protein conformer in the sample.

24. A diagnostic kit comprising:

    the antibody, or active binding portion(s) thereof of claim 17, and

    a reagent that comprises a detectable label and that has binding specificity for said antibody or active binding portion(s) thereof.

25. A diagnostic kit comprising:

    the antibody, or active binding portion(s) thereof of claim 17, labeled with a detectable label, and

    a solid phase support suitable for binding said antibody or said active binding portion(s) thereof, or to which said antibody or said active binding portion(s) is bound.

[20] The dependent claims 3, 6, 9 to 12, 18 to 20, 22 and 26 to 28 define further limitations regarding the type of tauopathy being treated (claim 3), the type of tau aggregates being cleared (claim 6), the specificity of the antibodies (claim 9), the presence of an immunogenic carrier linked (claim 10), the source of the antibodies (claims 11 and 19), the type of antibodies (claims 12, 18 and 20), the type of amyloidogenic proteins or peptides (claim 22) and the type of detectable label (claims 26 to 28).

[21] The Applicant made no submissions on these characterizations of the claims on file in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above characterization of the dependent claims.

Essential elements

[22] As stated above, all of the elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language. Further, a claim element is essential when it would have been obvious to the person skilled in the art that its omission or substitution would

have a material effect on the way the invention works: Free World Trust at para 55.

[23] The Preliminary Review letter, on pages 9 to 10, states the following with regard to the elements in the claims that the person skilled in the art would consider to be essential:

> With respect to claim language, our preliminary view is that the person skilled in the art reading claims 1 to 28 in the context of the specification as a whole and in view of their common general knowledge would understand that there is no use of language in any of the claims indicating that any of the elements are optional, preferred or were otherwise intended as being non-essential. Therefore, our preliminary view is that the person skilled in the art would consider all of the elements in the claims to be essential.

[24] The Applicant made no submissions on the identification of the essential elements of the claims on file in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above identification of the claim elements that are essential in this recommendation.

SUFFICIENCY OF DISCLOSURE

Legal Background

[25] Subsection 27(3) of the *Patent Ac*t requires, among other things, a specification of a patent to correctly and fully describe an invention, and to enable its practice:

> 27(3) The specification of an invention must:
>
> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
>
> (b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or

> science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;
>
> […].

[26] A determination of whether the specification complies with paragraphs 27(3)(a) and 27(3)(b) of the *Patent Act* requires that three questions be answered: What is the invention? How does it work? Having only the specification, can the person of skill in the art produce the invention using only the instructions contained in the disclosure? see: Teva Canada Ltd v Novartis AG, 2013 FC 141 citing Teva Canada Ltd v Pfizer Canada Inc, 2012 SCC 60 [Teva] and Consolboard v MacMillan Bloedel (Sask) Ltd, [1981] 1 SCR 504 at 520 [Consolboard].

[27] With respect to this third question, “it is necessary that no additional inventive ingenuity be required in order to make the patent work” (Aventis Pharma Inc v Apotex Inc, 2005 FC 1283 at para 172). A patent will not be invalid for insufficient disclosure where routine experimentation is required of the skilled person, but the Supreme Court of Canada has held that a disclosure is insufficient if the specification “necessitates the working out of a problem” (Idenix Pharmaceuticals, Inc v Gilead Pharmasset LLC, 2017 FCA 161 at para 19, citing Pioneer Hi-Bred v Canada [1989] 1 SCR 1623 at 1641).

[28] In Consolboard, at page 517, the Supreme Court of Canada referred to the textbook Canadian Law and Practice Relating to Letters Patent for Inventions (1969, 4th edition) from which it quoted H.G. Fox as saying “the inventor must, in return for the grant of a patent, give to the public an adequate description of the invention with sufficiently complete and accurate details as will enable a workman, skilled in the art to which the invention relates, to construct or use that invention when the period of the monopoly has expired”.

[29] Further, “it is not enough for the disclosure to teach how to make the preferred embodiment. The disclosure must teach the skilled person to put into practice all embodiments of the invention, and without exercising inventive ingenuity or undue experimentation”: Seedlings Life Science Ventures, LLC v Pfizer Canada ULC, 2021 FCA 154, at para 68.

Analysis

[30] The Preliminary Review letter, on pages 11 to 16, explains that in our preliminary view the specification fails to provide a sufficient disclosure of the antibodies of claims 1 to 12 but that the specification does provide a sufficient disclosure of the antibodies of claims 17 to 28:

> Correct and full description
>
> The Final Action indicates on pages 3 to 9 that the specification fails to correctly and fully describe any tau antibodies that meet all the essential elements defined in independent claims 1, 2, 4, 5, 7 and 8. Although the specification teaches the characterization of various antibodies elicited by a tau peptide whose amino acid sequence consists of SEQ ID NO:13, this characterization was limited to *in vitro* binding studies with phospho-specific and non-phosphorylated tau peptide as well as reactivity of some of said antibodies to brain homogenates of wild type and JNPL3 P301L mice (neurofibrillary tangle mouse model). No antibodies effective to treat Alzheimer's disease or a different tauopathy in a subject in need thereof, effective to promote clearance of tau aggregates from the brain of a subject in need thereof, or effective to slow the progression of a behavioral phenotype that is caused by the presence of pathological tau in a subject in need thereof are described.
>
> The Final Action explains that this view is consistent with Office practice as found in the Manual of Patent Office Practice (CIPO) at 23.07.02a, revised November 2017, which indicates that simply referencing the immunogenic peptide to which an antibody binds may not be sufficient in cases where the applicant is claiming a particular monoclonal antibody reciting particular functional characteristics that go beyond the simple interaction with the target antigen binding, e.g., where the monoclonal antibody is asserted to have agonist, antagonist or neutralizing activity, specificity for a particular epitope, or a remarkably high affinity constant or where the target antigen is complex.

In such cases, more detailed support is required. Depending on the facts of the particular case, this detailed support may come, for example, in the form of a disclosure of a representative embodiment of the antibody, a biological deposit, or an explicit description of the amino acid sequences of the binding regions of the monoclonal antibody, the epitope and/or the binding pocket of the target antigen essential to its function.

The Final Action explains that in the present case the essential elements of the antibodies defined in independent claims 1, 2, 4, 5, 7 and 8 warrant such special consideration. However, the working Examples in the Description do not describe with sufficient particularity any antibodies possessing the functional characteristics defined in the claims. As such, the specification does not provide a sufficient disclosure of the claimed antibodies.

The Final Action also points to the guidance in Teva to explain that a proper and sufficient disclosure must enable the public “to make the same successful use of the invention as the inventor could at the time of his application”. In that case, there was no basis for the person skilled in the art to determine which of the two exemplified compounds contained the useful compound i.e. sildenafil and the disclosure deemed insufficient. In the present application the claimed invention is not properly disclosed as no actual tau antibody possessing the functional characteristics defined in the claims is described with any particularity in terms of e.g. structure or Biological Deposit.

The Response to the Final Action does not contest the above views and instead proposes amendments that include removing all references to tau antibodies from the claims on file “[i]n response to the Examiner’s explanation”.

Having reviewed the description and the drawings, we generally agree with the analysis in the Final Action. The application discloses relevant exemplary embodiments wherein monoclonal antibodies elicited by a tau

peptide whose amino acid sequence consists of SEQ ID NO:13 were produced and tested for their ability to bind the immunizing peptide, as well as singly phosphorylated and non-phosphorylated versions of the same peptide. Several of these antibodies were tested against brain homogenates of wild type and JNPL3 P301L mice (neurofibrillary tangle mouse model) and showed stronger reactivity with the JNPL3 P301L mice brain homogenate than the wild type homogenate. However, as noted in the Final Action, no antibodies which are defined by particular functional characteristics that go beyond the simple interaction with the target antigen binding are described.

In the present case, it is our preliminary view that the specification fails to describe monoclonal antibodies capable of treating Alzheimer's disease or a different tauopathy, capable of promoting clearance of tau aggregates from the brain, or capable of slowing the progression of a behavioral phenotype that is caused by the presence of pathological tau. Therefore, it is our preliminary view that the specification fails to provide a correct and full description of any antibodies which exhibit these particular functional characteristics. It follows that the specification fails to provide a correct and full description of the antibodies of claims 1 to 12 and does not comply with paragraph 27(3)(a) of the *Patent Act* in respect of this subject-matter.

However, it is also our preliminary view that the person skilled in the art would consider that the *in vitro* binding studies used to characterize the monoclonal antibodies elicited by a tau peptide whose amino acid sequence consists of SEQ ID NO:13 provide a correct and full description for antibodies which specifically recognize an epitope of the immunizing tau peptide antigen. In that regard, we note that several of the antibody claims that were identified as defective in the Final Action do not require any particular functional characteristics. Therefore, it is our preliminary view that the specification provides a correct and full description of the antibodies of claims 17 to 28 and complies with paragraph 27(3)(a) of the *Patent Act* in respect of this subject-matter.

Enablement

The Final Action indicates on pages 8 to 10 that the specification does not enable the person skilled in the art to practice the invention as defined in the claims without undue experimentation. Although monoclonal antibody technologies for generating clonal antibodies from sera were part of the common general knowledge and the Description discloses assays to screen for candidate antibodies that meet the claimed uses, a person skilled in the art would still require undue experimentation to identify and produce an antibody of the invention.

Given that the description does not disclose the preparation of an antibody possessing the functional characteristics defined in the claims, the person skilled in the art "would need to start from the beginning":

> With said knowledge, said person would need to start from the beginning: immunizing an animal using the specific tau peptide defined by SEQ ID NO:13, followed by isolating antibodies, clonally selecting specific antibody species, screening many clonal antibody candidates for desired properties and then testing candidate antibodies in animals. The inadequacy of using linear peptides as a binding assay has its pitfalls as discussed above. Other assays disclosed in the Description are more arduous. This process to identify effective antibodies that meet the intended uses requires undue experimentation and therefore do not satisfy the requirements of subsection 27(3)(b) of the *Patent Act*.

The Final Action also points out that even if the monoclonal antibodies generated from the claimed peptide and characterized for peptide binding specificity were later shown to possess the functional characteristics defined in the claims, the specification fails to provide any Biological Deposit information or sequence data to enable the person skilled in the art to use these antibodies.

Finally, the Final Action explains that undue experimentation would be required to identify antibodies that would allow the person skilled in the art to practice the claimed invention.

The Response to the Final Action does not contest the above views and instead proposes amendments that include removing all references to tau antibodies from the claims on file “[i]n response to the Examiner’s explanation”.

Having reviewed the description, we generally agree with the analysis in the Final Action. The description discloses in Example 5 histological analysis of tau pathology that could be used to identify antibodies that bind to tau aggregates and in Examples 6 to 8, tests are disclosed that can be used to determine whether tau immunotherapy results in antibodies which possess the functional characteristics defined in the claims. However, as noted in the Final Action, although the description does disclose monoclonal antibodies that bind to the immunizing peptide, no additional functional characteristics of these antibodies were determined.

With regard to the monoclonal antibodies disclosed, there is no Biological Deposit information or sequence data to enable the person skilled in the art to use these antibodies and so the person skilled in the art “would need to start from the beginning”. Indeed, the level of experimentation and testing, as detailed in the Final Action, that would be required to produce and identify an antibody that possesses any of the functional characteristics defined in the claims goes beyond routine experimentation.

In view of the foregoing, it is our preliminary view that that the specification fails to enable the person skilled in the art to practice the invention without exercising undue experimentation to identify an antibody that possesses any of the functional characteristics defined in the claims. Therefore, it is our preliminary view that the specification fails enable the production of the antibodies of claims 1 to 12 and does not comply with paragraph 27(3)(b) of the *Patent Act* in respect of this subject-matter.

> However, it is our preliminary view that the person skilled in the art would consider that the *in vitro* binding studies used to characterize the monoclonal antibodies elicited by a tau peptide whose amino acid sequence consists of SEQ ID NO:13 provide an enabling disclosure for antibodies which specifically recognize an epitope of the immunizing tau peptide antigen. In that regard, we note that several of the antibody claims that were identified as defective in the Final Action do not rely on any particular functional characteristics. Therefore, it is our preliminary view that the specification provides an enabling disclosure of the antibodies of claims 17 to 28 and complies with paragraph 27(3)(b) of the *Patent Act* in respect of this subject-matter.

[31] The Response to the Preliminary Review letter acknowledges our preliminary views that the specification correctly and fully describes and enables the production of the antibodies of claims 17 to 28 on file. Further, the Response to the Preliminary Review letter, at pages 4 to 5, refers to paragraphs [0136] and [0137] of the description as fully disclosing and enabling the functional recitations of the antibodies of newly proposed claims 1 to 16. Although these submissions were made in respect of the newly proposed claims, at the hearing the Applicant clarified that these submissions also apply to claims 1 to 12 on file. In particular, the Response to the Preliminary Review letter submits that the application teaches a method of therapy that employs phospho-tau specific antibodies and teaches that the recited tau peptide can elicit antibodies that possess the recited therapeutic specificity:

> [Emphasis in original] Applicant respectfully submits that the specification fully discloses and enables the functional recitations of the antibodies of claims 1 to 16 of the newly proposed claims. In this regard, Applicant submits that paragraph [0136] of the present application teaches that conventional cell fusion hybridomas were obtained from mice that had been immunized with the SEQ ID NO: 13 peptide. The paragraph teaches that “numerous” strongly positive clones were identified.

> Significantly, para [0137] of the present application teaches that five out of six isolated antibodies obtained from such immunization with the recited peptide exhibited specificity for the desired phospho-Ser404 tau epitope. Thus, the data shows that the use of the recited peptide was at least 83% effective in eliciting antibodies that possessed the recited therapeutic specificity.
>
> […]
>
> Applicant submits that the invention teaches a method of therapy that employs phospho-tau specific antibodies and teaches a specific peptide that is *overwhelmingly* capable of eliciting such antibodies.

[32] We do not agree that the data shows that the recited peptide was at least 83% effective in eliciting antibodies that possessed the recited therapeutic specificity. As explained in para [0024], a very strong titer was generated against the SEQ ID NO:13 tau peptide with plasma antibodies preferably recognizing both the phospho-Ser_{404} epitope and the non-phospho epitope. Further, from the two immunized mice selected for cell fusion, more than 50 positive clones were detected. Of those, eight phospho-specific and six non-phospho clones were selected for subcloning and of the eight phospho-specific clones, three were selected for further subcloning which resulted in six monoclonal antibodies, four of which retained their specificity for the phospho-Ser_{404} epitope. Therefore, contrary to the 83% effective rate of eliciting antibodies with the desired specificity asserted in the Response to the Preliminary Review, it took three rounds of subcloning designed to select for stable clones which retained their specificity for the phospho-Ser_{404} epitope to identify the six monoclonal antibodies, four of which retained the desired specificity (Example 9, Figure 14A).

[33] Although three of these four phospho-Ser_{404} monoclonal antibodies exhibited a stronger reactivity with the P301L (neurofibrillary tangle mouse model) mice brain homogenate than the wild type homogenate, in our view, the person skilled in the art would not consider this to mean that these antibodies possess the recited therapeutic specificity. Notably, this experiment only detects denatured target

antigens (Figure 15A). This means that the monoclonal antibodies were not being tested for their ability to discriminate between native tau and native pathological tau but rather linear versions of tau and pathological tau, respectively, that have lost their tertiary and secondary structure.

[34] In addition, the SEQ ID NO:13 tau peptide also strongly elicited non-phospho-specific monoclonal antibodies which also exhibited stronger reactivity with the P301L tangle mice brain homogenate than the wild type homogenate (Figure 15B). The description indicates that this is because most of tau is non-phosphorylated, however, if this were the case then strong reactivity with the wild type homogenate should also have been observed.

[35] Thus, the data shows that the SEQ ID NO:13 tau peptide elicits monoclonal antibodies that recognize the phospho-Ser_{404} epitope as well as monoclonal antibodies that recognize the non-phospho epitope. Moreover, both the phospho-Ser_{404} and the non-phospho monoclonal antibodies exhibited stronger reactivity with the P301L tangle mice brain homogenate than the wild type homogenate. Therefore, the data provides an indication that exhibiting stronger reactivity with the P301L tangle mice brain homogenate than the wild type homogenate is also associated with monoclonal antibodies that are not expected to possess the desired therapeutic specificity.

[36] Even if the monoclonal antibodies that recognize the phospho-Ser_{404} epitope had been shown to exhibit stronger reactivity with native pathological tau than native wild type tau, there is no evidence that simply binding to native pathological tau would have the desired functional consequences e.g. treating Alzheimer's disease or a different tauopathy, promoting clearance of tau aggregates from the brain, or slowing the progression of a behavioral phenotype that is caused by the presence of pathological tau. Likewise, there is no evidence that these monoclonal antibodies possess any of these functional characteristics.

[37] Although the description discloses tests that can be used to identify whether these monoclonal antibodies possess the desired therapeutic specificity, there is no Biological Deposit information or sequence data to enable the person skilled

in the art to test these antibodies. Given that producing a monoclonal antibody that possesses the desired therapeutic activity is not predictable and must be determined empirically, it is our view that the level of experimentation and testing that would be required goes beyond routine experimentation. It is therefore our view that the person skilled in the art would need to exercise undue experimentation to produce and identify a monoclonal antibody that possesses any of the functional characteristics defined in claims 1 to 12 on file.

[38] In view of the foregoing, we maintain that the specification fails to correctly and fully describe and enable monoclonal antibodies capable of treating Alzheimer's disease or a different tauopathy, capable of promoting clearance of tau aggregates from the brain, or capable of slowing the progression of a behavioral phenotype that is caused by the presence of pathological tau.

[39] Therefore, we conclude that the specification fails to correctly and fully describe and enable the antibodies of claims 1 to 12 and does not comply with subsection 27(3) of the *Patent Act* in respect of this subject-matter. We also conclude that that the specification correctly and fully describes and enables the antibodies of claims 17 to 28 and complies with subsection 27(3) of the *Patent Act* in respect of this subject-matter.

INDEFINITENESS

Legal Background

[40] Subsection 27(4) of the *Patent Act* requires claims to distinctly and explicitly define the subject-matter of the invention:

> The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.

[41] In Minerals Separation North American Corp v Noranda Mines Ltd, [1947] Ex CR 306 at 352, 12 CPR 99, the Court emphasized the obligation of an Applicant to

make clear in the claims the scope of the monopoly sought, as well as the requirement that the terms used in the claims be clear and precise:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

Analysis

[42] The Preliminary Review letter, on pages 17 to 18, explains that in our preliminary view claims 1 to 12 and 17 to 28 are not indefinite:

> The Final Action, on pages 10 to 11, indicates that claims 1 to 12 and 17 to 28 are indefinite because the antibody recited in the claims is not clearly defined:
>
> The antibody recited in these claims is not defined clearly because it is merely defined by a desired result or a product by process (one or more antibodies that specifically recognize(s) an epitope of the claimed tau peptide that is elicited by an epitope on said peptide) and not by a technical feature that distinguishes said antibody in a clear and unambiguous manner.
>
> The Final Action explains that claim language which defines the antibody by a desired result, or in essence, by the process in which it is made does not clearly indicate all antibodies that fall within said scope in a clear and unambiguous manner. It also does not allow a person skilled in the art to determine if a known antibody falls within said scope.
>
> The Response to the Final Action does not contest the above views and instead proposes amendments that include removing all references to tau

> antibodies from the claims on file "[i]n response to the Examiner's explanation".
>
> Having reviewed claims 1 to 12 and 17 to 28 we do not agree that these claims refer to antibodies that are not clearly defined.
>
> The test for claim clarity analogizes claim terminology to fences that define a claim's boundaries. It also considers whether the "public will be able to know not only where it must not trespass but also where it may safely go." It is our preliminary view that the person skilled in the art would be able to readily determine the scope of the monopoly defined by the antibodies in claims 1 to 12 and 17 to 28. The antibodies in these claims are defined as specifically recognizing an epitope of an immunogenic tau peptide whose amino acid sequence consists of SEQ ID NO:13. Therefore, it is our preliminary view that the person skilled in the art would consider that the structure of the tau peptide provides a distinct and explicit definition for antibodies that are defined as being elicited by an epitope present on said tau peptide.
>
> Although claims 1 to 12 use language to describe specific functional characteristics of these antibodies, in our preliminary view the use of such language does not render the scope unclear to the person skilled in the art. The fact that no antibodies have been described that possess any of the particular functional properties recited in these claims relates to the sufficiency of the disclosure.
>
> Accordingly, it is our preliminary view that the antibodies as characterized in claims 1 to 12 and 17 to 28 are distinctly and explicitly defined and comply with subsection 27(4) of the *Patent Act*.

[43] The Response to the Preliminary Review letter, on pages 5 to 6, acknowledges our preliminary views that claims 1 to 12 and 17 to 28 on file are distinctly and explicitly defined.

[44] Therefore, we maintain the foregoing reasoning and conclude that claims 1 to 12

and 17 to 28 are distinctly and explicitly defined and comply with subsection 27(4) of the *Patent Act*.

INCORPORATION BY REFERENCE

Legal Background

[45] Subsection 57(1) of the *Patent Rules* states:

> The description must not incorporate any document by reference.

Analysis

[46] The Preliminary Review letter, on page 18, explains that in our preliminary view the description contains multiple statements that incorporate by reference other documents:

> The Final Action indicates on page 11 that the description does not comply with subsection 57(1) of the *Patent Rules* as it contains multiple statements that incorporate by reference other documents. Such statements are found at page 21, lines 11 and 24; page 26, line 15; page 30, line 12; page 36, lines 3 and 17; page 44, line 24; page 45, line 4; and page 46, line 29 and should be removed.
>
> The Response to the Final Action proposes amendments to the description to remove the statements of incorporation by reference, as identified in the Final Action, as well as additional statements of incorporation by reference found on page 51, para [0122] and page 56, para [0132].
>
> Having reviewed the description we agree that the description contains the statements of incorporation by reference identified in the Final Action. Therefore, it is our preliminary view that the description does not comply with subsection 57(1) of the *Patent Rules*.

[47] The Response to the Preliminary Review letter, on pages 22 to 23,

acknowledges our preliminary views that the description contains statements of incorporation by reference.

[48] Therefore, we maintain the foregoing reasoning and conclude that the description does not comply with subsection 57(1) of the *Patent Rules*.

OBVIOUSNESS

Legal Background

[49] Section 28.3 of the *Patent Act* requires that the subject-matter of a claim not be obvious to the person skilled in the art:

> The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to
>
> (a) information disclosed before the one-year period immediately preceding the filing date or, if the claim date is before that period, before the claim date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and
>
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[50] In Apotex Inc v Sanofi–Synthelabo Canada Inc, 2008 SCC 61 [Sanofi], the Supreme Court of Canada states that it is useful in an obviousness inquiry to follow the following four-step approach:

> (1)(a) Identify the notional “person skilled in the art”;

(b) Identify the relevant common general knowledge of that person;

(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[51] In the context of the fourth step, the Court in Sanofi accepted that it may be appropriate in some cases to consider an "obvious to try" analysis. For a finding that an alleged invention is "obvious to try", it must be more or less self-evident to try to obtain the alleged invention in advance of routine testing. The mere possibility that something might work is not sufficient.

[52] The Court in Sanofi listed the following non-exhaustive factors to be considered in an "obvious to try" analysis [defined terms added]:

> Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identifiable predictable solutions known to persons skilled in the art? [Self-Evident Factor]
>
> What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine? [Extent and Effort Factor]
>
> Is there a motive provided in the prior art to find the solution the patent addresses? [Motive Factor]

Analysis

The person skilled in the art and the relevant common general knowledge

[53] The person skilled in the art and the relevant common general knowledge have been identified as part of the purposive construction of the claims. Although in this context the information forming the relevant common general knowledge is identified using the publication date, it is our preliminary view that the above identified information was also relevant common general knowledge at the claim date of the present application.

Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it

[54] The Preliminary Review letter, on page 20, identifies the inventive concepts of claims 1 to 28 on file:

> In this assessment, we take into account all of the essential elements of the claims. In our preliminary view, the combination of essential elements of independent claims 1, 2, 4, 5, 7, 8, 13 to 17, 21 and 23 to 25 represents their inventive concepts as well.
>
> Our preliminary view is also that the elements of the dependent claims relating to the type of tauopathy being treated, the type of tau aggregates being cleared, the specificity of the antibodies, the presence of an immunogenic carrier linked, the source of the antibodies, the type of antibodies, the type of amyloidogenic proteins or peptides and the type of detectable label, as set out above, are part of the respective inventive concepts of dependent claims 3, 6, 9 to 12, 18 to 20, 22 and 26 to 28.

[55] The Applicant made no submissions on the identification of the inventive concepts of claims 1 to 28 on file in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above identification of the inventive concepts of claims 1 to 28 on file for this analysis.

Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed

[56] The Preliminary Review letter, on pages 21 to 22, identifies the differences between the inventive concepts of the claims and the cited prior art:

> As mentioned above, we consider that the following two prior art documents are relevant to the assessment of the obviousness of the claims on file:
>
> D1: US 2008/0050383 Sigurdsson et al. 28 February 2008 (28-02-2008)
>
> D2: WO 98/22120 Otvos et al. 28 May 1998 (28-05-1998)
>
> D1 discloses methods of treating or preventing Alzheimer's disease or other tauopathies in a subject by administering an immunogenic tau peptide. Also disclosed are methods of promoting clearance of aggregates from the brain of the subject and of slowing progression of tangle-related behavioral phenotype in a subject. Vaccination of P301L tangle mice with a phosphorylated tau peptide immunogen consisting of tau 379 to 408 [P-$Ser_{396,404}$], referred to as SEQ ID NO:2, led to the generation of antibodies that enter the brain. These antibodies bind to abnormal tau like a monoclonal antibody, PHF-1, against a similar epitope, this type of immunotherapy reduces the extent of aggregated tau in the brain and slows the progression of the behavioral phenotype of these animals. As expected, the therapeutic effect decreases as the functional impairments advance in these animals. D1 also teaches combination immunotherapy targeting amyloid beta or alpha synuclein.
>
> D2 discloses multiphosphorylated peptides derived from the tau protein of the paired helical filaments (PHF) associated with Alzheimer's disease. These multiphosphorylated peptides are useful as immunogens to generate antibodies specific for Alzheimer's disease. D2 explains that it was known that the major recognition site of the known monoclonal antibody PHF-1 is

> phosphorylated Ser_{396}, but recognition is increased when Ser_{404} is also phosphorylated; however, the close-to-minimal or minimal epitopes and exact phosphate requirements of the antibodies have not been characterized. D2 discloses that a phosphorylated tau peptide consisting of tau 390 to 408 [P-$Ser_{396,404}$], referred to as SEQ ID NO:19 was recognized by PHF-1, as well as two additional monoclonal antibodies, PHF-47 and PHF-13 that were generated following immunization of mice with the pathological form of tau, PHF tau. Like PHF-1, PHF-47 and PHF-13 did not recognize an unphosphorylated peptide of tau consisting of 390 to 408.
>
> In our preliminary view the main difference between the inventive concepts of the claims on file and D1 and D2 lies in the specific sequence of the phosphorylated tau peptide immunogen. In the claims on file, the amino acid sequence SEQ ID:13 consists of tau 386 to 408 [P-$Ser_{396,404}$] while the phosphorylated tau peptides of D1 and D2 consist of tau 379 to 408 [P-$Ser_{396,404}$] and tau 390 to 408 [P-$Ser_{396,404}$], respectively.
>
> The additional limitations in the dependent claims relating to the type of tauopathy being treated, the type of tau aggregates being cleared, the specificity of the antibodies, the presence of an immunogenic carrier linked, the source of the antibodies, the type of antibodies, the type of amyloidogenic proteins or peptides and the type of detectable label are disclosed in D1.

[57] The Applicant made no submissions on the identification of the differences in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above differences between the cited prior art and claims 1 to 28 on file for this analysis.

Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[58] In both the Response to the Preliminary Review letter and at the hearing the

Applicant disagreed that the gap between the present application and the cited prior art could be bridged by any other reference or the common general knowledge. Although these submissions were made in respect of the newly proposed claims, we consider that they are also relevant to the claims on file and will be addressed here.

[59] In particular, the Applicant submits that the unimaginative person skilled in the art, reading the cited prior art, would not have arrived at the subject-matter of the newly proposed claims. Further, the Applicant submits that an obvious to try test is warranted in this case and provides comments regarding the cited prior art in the context of this framework.

[60] Although the Preliminary Review letter did not use the obvious to try test at this stage, given that the subject-matter of the claims on file relates to the particular fields of protein chemistry, immunology, neurobiology and neurology, fields which could be considered areas of endeavour "where advances are often won by experimentation" (Sanofi at para 68), we agree that an obvious to try test is appropriate.

Self-Evident Factor

[61] This factor considers whether it would have been more or less self-evident that what is being tried ought to work in advance of routine testing. The mere possibility that something might work is not sufficient but an amount of uncertainty is allowed in the "obvious to try" analysis: Les Laboratoires Servier v Apotex Inc, 2019 FC 616 at para 269.

[62] In this view, what must be considered at this step is whether it would have been more or less self-evident to the person skilled in the art, based on the disclosures of D1 and D2 and the relevant common general knowledge, that a tau peptide having the amino acid sequence of SEQ ID NO: 13 or antibodies that specifically recognize an epitope of said peptide ought to work i.e. ought to be useful in the diagnosis or treatment of Alzheimer's disease or other tauopathy.

[63] In both the Response to the Preliminary Review letter and at the hearing the Applicant submitted that the presumption that structural similarities between the SEQ ID NO: 13 peptide and the peptides of D1 and D2, coupled with the relevance of phosphorylated Ser_{396} and Ser_{404}, would have caused the person skilled in the art to consider that any such phosphorylated tau peptide that is smaller than the peptide of D1 but larger than the peptide of D2 would also elicit desired antibodies is not supported by the art. In particular, the Applicant submits that the use of the SEQ ID NO:13 peptide to elicit antibodies, and the antibodies elicited using such peptide, exhibit significant and unpredicted differences relative to the peptides and antibodies of the prior art, and are inventive over the cited art.

[64] Specifically, the Applicant refers to eleven previously introduced references[1] that are said to demonstrate that it was well known that the flanking amino acids that surround epitopes play a role in stabilizing an immunogenic peptide so that it may adopt a particular three dimensional conformation. Therefore, the person skilled in the art would know that conformations are not predictable based on amino acid sequences, or portions thereof.

[65] In the context of the present application, the Applicant points to three examples said to demonstrate that flanking sequences affect the conformation of the SEQ ID NO:13 peptide in an unexpected and unpredictable manner. Firstly, binding studies using the PHF-1 antibody[2] are said to demonstrate that the flanking sequences of the D2 peptide affect its conformation relative to the conformation of the SEQ ID NO:13 peptide as evidenced by the fact that antibodies elicited by the SEQ ID NO:13 peptide exhibited far greater phosphospecificity than the PHF-1 antibody. Secondly, unlike the PHF-1 antibody which was incapable of binding to a tau 389 to 402 peptide possessing only phosphorylated Ser_{404}, antibodies elicited by the SEQ ID NO:13 peptide were capable of binding to tau peptide

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[1] See Articles 1 to 11 of Schedule F submitted with Applicant's Response to the Preliminary Review letter dated June 15, 2023.

[2] See Article 12 of Schedule F submitted with Applicant's Response to the Preliminary Review letter dated June 15, 2023.

possessing phosphorylated Ser_{404}, but lacking phosphorylated Ser_{396}. As a third example, structural comparisons of the predictive modeling of the SEQ ID NO:13 peptide and the peptides of D1 and D2 show that the predicted structures of the D1 and D2 peptides adopt a N-terminal helical structure, while the SEQ ID NO: 13 peptide adopts a significantly planar structure which is said to be more similar to the structure adopted by the peptide when present in the full-length protein[3].

[66] We agree that the person skilled in the art would understand that flanking residues can influence peptide conformation and affect the presentation of epitopes. However, we disagree that our presumption that structural similarities between the SEQ ID NO: 13 peptide and the peptides of D1 and D2, coupled with the relevance of phosphorylated Ser_{396} and Ser_{404}, would have caused the person skilled in the art to consider that any such phosphorylated tau peptide that is smaller than the peptide of D1 but larger than the peptide of D2 would also elicit desired antibodies is not supported by the art.

[67] Firstly, the Western blot data used to show that antibodies elicited by the SEQ ID NO:13 peptide exhibited far greater phosphospecificity than the PHF-1 antibody does not correlate exactly with immunohistochemical findings. As explained in D1, it is well established that PHF-1 antibody shows greater specificity towards pathological tau on histological sections than in Western blots (see para [0016]). Moreover, D1 discloses that although the staining pattern of tau aggregates/tangles in P301L mice (neurofibrillary tangle mouse model) was not identical between the PHF-1 antibody and polyclonal antibodies from mice immunized with the tau 379 to 408 [P-$Ser_{396,404}$] peptide, the polyclonal antibodies were still shown to specifically recognize pathological tau aggregates in the P301L tangle mice as no immunostaining was observed in wild type mice (see para [0019]). A reasonable interpretation is that the tau 379 to 408 [P-$Ser_{396,404}$] peptide, which contains the PHF-1 epitope, is capable of eliciting antibodies that, like PHF-1, can selectively detect pathological tau aggregates.

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[3] See Article 14 of Schedule F submitted with Applicant's Response to the Preliminary Review letter dated June 15, 2023.

Thus, the different flanking sequence present in the peptide of SEQ ID NO:13 compared to the peptide of D1 does not appear to result in antibodies that behave in an unexpected or unpredictable manner—the peptide of SEQ ID NO:13 is also expected to elicit antibodies capable of binding to full-length pathological tau protein, while being substantially less capable of binding to full-length normal tau protein, which is the goal of the present invention (see page 8 of the Response to the Preliminary Review letter).

[68] Secondly, the fact that the PHF-1 antibody did not recognize a tau 390 to 408 peptide possessing only phosphorylated Ser_{404} does not necessarily mean that the flanking sequences of the D2 peptide affect its conformation relative to the conformation of the SEQ ID NO:13 peptide. Notably, the PHF-1 antibody recognizes both the D2 peptide and the SEQ ID NO: 13 peptide. Thus, the two peptides share the common PHF-1 epitope. Moreover, the different binding affinities of singly phosphorylated versions of these two peptides to the PHF-1 antibody are not a measure of the ability of the doubly phosphorylated peptides to elicit antibodies that bind to a given phospho-specific epitope. In this view, we note that the present description discloses that the SEQ ID NO:13 peptide elicited phospho-Ser_{404} specific antibodies that bound to SEQ ID NO: 13 (which contains phosphorylated Ser_{396} and Ser_{404}) with even higher affinity than the phospho-Ser_{404} singly phosphorylated peptide (Figure 14A). We further note that the ability of these antibodies to recognize the phospho-Ser_{404} singly phosphorylated peptide was not associated with any previously unknown or unexpected effect in the context of selectively binding to pathological tau or in the diagnosis or treatment of Alzheimer’s disease or other tauopathy.

[69] Thirdly, notwithstanding that the predictive modeling suggesting that the D1 and D2 tau peptides adopt a structure that is different than the conformation of the SEQ ID NO:13 peptide was generated post-filing, there is no evidence that the SEQ ID NO:13 peptide actually presents a different antibody epitope than what would be generated by the tau peptides of D1 and D2. Indeed, the fact that the PHF-1 antibody, which specifically and selectively detects pathological tau aggregates, binds to all three of these peptides is evidence that the three peptides share a common epitope and would elicit antibodies to similar or same

epitopes. Moreover, the fact that the PHF-1 antibody was generated following the immunization of mice with the pathological form of tau is evidence that this epitope is also present in the pathological form of tau. Consistent with this view is the fact that the D1 peptide was able to generate antibodies that selectively bind to pathological tau but not normal tau.

[70] Finally, as indicated above, D1 discloses an immunogenic tau peptide consisting of tau 379 to 408 [P-$Ser_{396,404}$], its use for raising antibodies, as well as the use of the peptide and corresponding antibodies for diagnosis and treatment of Alzheimer's disease and other tauopathies. Given the structural similarities between the tau peptides of D1 and D2, the relevance of the epitope encompassing phosphorylated Ser_{396} and Ser_{404} for targeting the pathological aggregation of tau protein that is associated with Alzheimer's disease and the binding of both tau peptides to the PHF-1 antibody, it is our view that the person skilled in the art would expect that the tau peptide of D2 would give rise to similar results as those obtained with the tau peptide of D1 and would be expected to be useful in methods of diagnosing and treating Alzheimer's disease. Analogously, we note that para [00132] of the present application refers to the PHF-1 antibody as a monoclonal analog of polyclonal antibodies elicited by active immunization using the tau 379 to 408 [P-$Ser_{396,404}$] peptide of D1.

[71] In view of the above, it is our view that the person skilled in the art would consider that any such phosphorylated tau peptide that is smaller than the tau peptide of D1 but larger than the tau peptide of D2 would also elicit antibodies to similar or same epitopes and give rise to similar results to those obtained with the tau peptide of D1. There are a finite number of tau peptides encompassed by this range and notably the peptide of SEQ ID NO:13 falls within this scope. In our view, it would have been more or less self-evident to the person skilled in the art that other tau peptides encompassing the common PHF-1 epitope would also be useful in the diagnosis or treatment of Alzheimer's disease or other tauopathy.

[72] Another consideration that was addressed in the Preliminary Review letter was whether post-filing data showing an unexpected benefit for a related tau peptide is a relevant factor. The Preliminary Review letter, on pages 24 to 26, explains

that in our preliminary view a declaration from the inventor, Einar Sigurdsson, containing post-filing data for a related tau peptide is not relevant to our obviousness assessment:

> It is our understanding from the response dated May 3, 2019 that the Applicant relies on a declaration from Einar Sigurdsson, Ph.D. that was submitted in support of the Applicant's European counterpart application signed on September 20, 2017 (Sigurdsson Declaration) as evidence of unexpected non-obvious effects associated with the claimed peptide. We are of the preliminary view that the post-filing data presented in the Sigurdsson Declaration is not relevant to the present assessment as to whether the claimed subject-matter was obvious before the claim date of June 10, 2009 for the following reasons.
>
> First, we consider that the case law does not indicate that the inventiveness of a claimed subject-matter may be ascertained by turning to evidence outside of a patent application disclosure in cases where the alleged benefit or advantage is neither mentioned in the claim, indicated in the remainder of the specification nor reasonably derivable by the person skilled in the art from the information contained in the specification. To the contrary, we consider that the basis for understanding the claimed invention for the purpose of determining its compliance with the patentability requirements of the *Patent Act* must be found within the four corners of the patent application: see Whirlpool at para 49(f).
>
> Second, the Federal Court in Janssen-Ortho Inc v Novopharm Ltd, 2006 FC 1234 offered the following relevant reasoning, at para 113, as to why subsequently recognized advantages would not assist the inquiry as to inventive ingenuity and noted that such advantages may themselves be the subject of a subsequent patent:
>
> > The inventors may have perceived only certain advantages, yet later those inventors or others may determine that other, previously unrecognized advantages lay in the alleged invention. This factor is

> of limited usefulness in considering inventive ingenuity as of the date of the invention. The recognition of later advantages, if unexpected, may themselves be the subject of a patent. To the extent that the United States Courts in cases such as Re Zenitz 33 F. 2d 924 have placed weight upon subsequently discovered advantages that is not the law here. Little, if any, weight should be put on this factor.

The Court applied the above reasoning to the facts of the case at para 114 [emphasis added]:

> Levofloxacin has achieved good acceptance in combating microbes associated with strep pneumonia and in treating infections of the eye. Neither of these uses are specifically suggested in the patent. No weight is given to these subsequent uses.

On appeal, the above rationale has been specifically acknowledged by the Federal Court of Appeal at para 26 of Novopharm Ltd v Janssen-Ortho Inc, 2007 FCA 217:

> I find it difficult to envisage a situation where a subsequently recognized advantage to a claimed invention would be of any assistance in determining whether inventive ingenuity was required to make it. I can imagine a situation where the commercial success of an invention is attributable to a subsequently recognized advantage, but that would not assist the inquiry as to inventive ingenuity. I recognize that it is impossible to imagine every possible situation, but given the current state of the jurisprudence I would be inclined to give this factor no weight except in the most extraordinary case.

Finally, we note that the data provided all concern the testing of a tau peptide having the amino acid sequence of SEQ ID NO: 5, which corresponds to tau 394 to 406 [P-$Ser_{396,404}$], and not the claimed peptide which corresponds to SEQ ID NO: 13.

> For the foregoing reasons, we consider that no weight should be given to the data in the Sigurdsson Declaration. Accordingly, our reasoning as set out above still applies to the claims on file.

[73] The Applicant made no submissions on the relevance of the Sigurdsson declaration in either the Response to the Preliminary Review letter or at the hearing. Accordingly, we adopt the above reasoning and conclude that no weight should be given to the data in the Sigurdsson Declaration.

[74] In light of the above, it is our view that it would have been more or less self-evident to the person skilled in the art, based on the disclosures of D1 and D2 and the relevant common general knowledge, that tau peptides that are smaller than the tau peptide of D1 but larger than the tau peptide of D2, including a tau peptide having the amino acid sequence of SEQ ID NO: 13 or antibodies that specifically recognize an epitope of said peptides ought to work i.e. ought to be useful in the diagnosis or treatment of Alzheimer's disease or other tauopathy.

[75] Although we consider that the above assessments are largely determinative of the obvious to try inquiry in this case, we make the following observations with regard to the other non-exhaustive factors to be considered in an obvious to try analysis.

Extent and Effort Factor

[76] D1 discloses the preparation of an immunogenic tau peptide consisting of tau 379 to 408 [P-$Ser_{396,404}$], its use for raising antibodies, as well as the use of the peptide and corresponding antibodies in the diagnosis and treatment of Alzheimer's disease and other tauopathies. In our view, it would not require any degree of invention from the person skilled in the art to follow the methodology in D1 and make and test the tau peptides that are smaller than the tau peptide of D1 but larger than the tau peptide of D2, including a tau peptide having the amino acid sequence of SEQ ID NO: 13 instead.

[77] In addition, the Federal Court of Appeal has referred to the actual course of

conduct factor as an elaboration of the “Extent and Effort” factor” (Bristol Myers at para 44). We will thus consider the Applicant’s course of conduct as part of the “extent, nature and amount of effort required to achieve the invention”. In that regard, Example 9, found on pages 57 to 58 of the description, discloses the generation of monoclonal antibodies using the tau peptide of SEQ ID NO: 13. Notably, the characterization of the monoclonal antibodies was limited to assessing binding to various phosphorylated tau peptides as well as binding to tau present in brain homogenates of wild type and P301L tangle mice. There is no evidence that the tau peptide of SEQ ID NO: 13 or any of the monoclonal antibodies elicited by said peptide were tested for their ability to diagnose and treat Alzheimer’s disease and other tauopathies but instead are proposed for that purpose on the expectation that they would be effective.

[78] In view of the foregoing, it is our view that the person skilled in the art would have been able to make and test tau peptides that are smaller than the tau peptide of D1 but larger than the tau peptide of D2, including a tau peptide having the amino acid sequence of SEQ ID NO: 13, and antibodies elicited by said peptides, for their ability to diagnose and treat Alzheimer’s disease and other tauopathies using the instructions in D1.

Motive Factor

[79] In both the Response to the Preliminary Review letter and at the hearing the Applicant submitted that the person skilled in the art would not have been motivated by D1 and/or D2 to arrive at the subject-matter of the newly proposed claims. More specifically, the Applicant submitted that the prior art does not suggest that there is a problem or further investigation is needed with the development of antibodies that are capable of specifically binding to full-length pathological tau protein while being substantially less capable of binding to full-length normal tau protein, which is the goal of the present invention. Therefore, there is no motivation in the prior art to search for the solution that the present application provides to solve this problem.

[80] Contrary to the Applicant’s submissions, we note that D1 also identifies a need to

assess the feasibility of immunotherapy targeting pathological tau conformers (para [0004]). Towards this end, P301L tangle mice were vaccinated with a phosphorylated tau peptide immunogen consisting of tau 379 to 408 [P-$Ser_{396,404}$], an immunogen designed to lead to the generation of antibodies that would selectively detect highly phosphorylated tau protein as found in Alzheimer's disease and tangle mouse models (para [0099]). Active immunization with the immunogen led to the generation of antibodies that enter the brain and reduced the extent of aggregated tau in the brain and slowed the progression of the behavioral phenotype in P301L tangle mice. Moreover, polyclonal antibodies from mice immunized with the tau 379 to 408 [P-$Ser_{396,404}$] peptide were shown to specifically recognize pathological tau aggregates in the P301L tangle mice as no immunostaining was observed in wild type mice (para [0019]). This means that the tau 379 to 408 [P-$Ser_{396,404}$] peptide, which contains the PHF-1 epitope, is capable of eliciting antibodies that, like PHF-1, can selectively detect pathological tau aggregates.

[81] Likewise, D2 identifies a need for diagnostic and therapeutic antibodies that can distinguish pathological tau from normal tau, as well as a need to understand how phosphorylation changes the conformation of tau in order to design compounds that are capable of binding to pathological tau (Background of the Invention). Towards this end, monoclonal antibodies were raised against pathological tau and twelve were identified for their ability to specifically detect pathological tau but not recognize normal tau. Several of these antibodies were also demonstrated to bind tau peptide 390 to 408 [P-$Ser_{396,404}$], referred to as SEQ ID NO:19. Notably, the monoclonal antibody PHF-1 was also shown to bind this peptide.

[82] In view of the above considerations, it is our view that D1 and D2 provide the general motivation to test whether other tau phospho-peptides which contain the PHF-1 epitope would elicit antibodies that specifically detect pathological tau, but do not recognize normal tau, making them useful in the diagnosis and treatment of Alzheimer's disease and other tau associated pathologies. In addition, it is also our view that a general motivation to identify immunotherapy targeting pathological tau conformers existed at the claim date in the technical and

scientific fields associated with the prevention, treatment, and diagnosis of Alzheimer's disease and related tauopathies (Sigurdsson review article).

Conclusion on obvious to try

[83] Therefore, in view of the above analyses of the relevant factors pertaining to an obvious to try analysis, we are of the view that it was obvious to try to obtain the subject-matter of independent claims 1, 2, 4, 5, 7, 8, 13 to 17, 21 and 23 to 25.

[84] With respect to the remaining dependent claims, as indicated above, the additional features relating to the type of tauopathy being treated, the type of tau aggregates being cleared, the specificity of the antibodies, the presence of an immunogenic carrier linked, the source of the antibodies, the type of antibodies, the type of amyloidogenic proteins or peptides and the type of detectable label are all known from D1. Therefore, in our view, none of the features from the dependent claims would have required any degree of invention from the person skilled in the art.

[85] In light of the above, our view is that the claims on file would have been obvious to the person skilled in the art, in view of D1 and D2 and the relevant common general knowledge, contrary to section 28.3 of the *Patent Act*.

Conclusion on obviousness

[86] In light of the above considerations, it is our view that claims 1 to 28 on file are directed to subject-matter that would have been obvious to the person skilled in the art, as of the relevant date, having regard to D1 and D2 and the relevant common general knowledge, contrary to section 28.3 of the *Patent Act*.

PROPOSED AMENDMENTS

[87] As indicated above, with the Response to the Preliminary Review letter the Applicant submitted newly proposed claims 1 to 26, as well as an amended description. According to page 5 of the Response to the Preliminary Review

letter, claims 1 to 14 of the newly proposed claims parallel claims 1 to 14 of the previously proposed claims submitted with the Response to the Final Action and newly proposed claims 15 to 26 correspond to claims 17 to 28 of the claims on file. Further, as indicated on pages 22 to 23 of the Response to the Preliminary Review letter, the amended description removes the statements incorporating by reference other documents.

[88] In a letter dated June 28, 2023, the Applicant proposed claim amendments to improve the clarity of newly proposed claims 3 and 15 and requested the newly proposed claims submitted with the Response to the Preliminary Review be replaced accordingly. Given the nature of the amendments, the submissions made in the Response to the Preliminary Review letter apply equally to the replacement set of newly proposed claims provided on June 28, 2023.

[89] Having reviewed the newly proposed claims provided on June 28, 2023, we agree that newly proposed claims 1 to 9 and 11 to 14 correspond to previously proposed claims 1 to 14. Likewise, we agree that newly proposed claims 15 to 26 correspond to claims 17 to 28 on file. However, we do not agree that newly proposed claim 10 corresponds to any of the previously proposed claims. Rather, newly proposed claim 10 most closely corresponds to claim 9 on file when it depends on claim 1 on file. In addition, we note that newly proposed claims 1 to 9 and 11 to 14 also parallel claims 1 to 8, 10 and 13 to 16 on file.

[90] Given that the subject-matter of newly proposed claim 10 is encompassed by the scope of claim 9 on file, our view is that the specification fails to correctly and fully describe and enable the antibodies of newly proposed claim 10 and does not comply with subsection 27(3) of the *Patent Act* in respect of this subject-matter for the same reasons set out for the corresponding claim on file.

[91] With regard to the obviousness defect identified above for corresponding claims 1 to 8, 10 and 13 to 28 on file, as there is no meaningful difference between the claims, our view is that newly proposed claims 1 to 26 would not comply with section 28.3 of the *Patent Act* for the same reasons provided above for the corresponding claims on file.

[92] In our view, the proposed amendments to the description would overcome the incorporation by reference defect.

[93] In view of the foregoing, we conclude that, as the specification fails to correctly and fully describe and enable the antibodies of newly proposed claim 10, contrary to subsection 27(3) of the *Patent Act* and newly proposed claims 1 to 26 would not comply with section 28.3 of the *Patent Act*, the proposed amendments do not qualify as necessary amendments for the purposes of subsection 86(11) of the *Patent Rules*.

CONCLUSIONS

[94] We conclude that the specification, insofar as it relates to claims 1 to 12 on file, is insufficient contrary to subsection 27(3) of the *Patent Act*, claims 1 to 28 on file encompass obvious subject-matter contrary to section 28.3 of the *Patent Act* and that the description incorporates other documents by reference contrary to subsection 57(1) of the *Patent Rules*.

[95] We also conclude that the specification, insofar as it relates to claims 17 to 28 on file, is sufficient and complies with subsection 27(3) of the *Patent Act* and that claims 1 to 12 and 17 to 28 are definite and comply with subsection 27(4) of the *Patent Act*.

[96] The proposed amendments to the description would overcome the incorporation by reference defect, however, newly proposed claim 10 would not overcome the insufficiency of disclosure defect and newly proposed claims 1 to 26 would not overcome the obviousness defect. Therefore, the newly proposed claims are not considered a necessary amendment under subsection 86(11) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[97] In view of the above, the Panel recommends that the application be refused on the grounds that:

- the specification, insofar as it relates to claims 1 to 12 on file, is insufficient contrary to subsection 27(3) of the *Patent Act*;
- claims 1 to 28 on file encompass obvious subject-matter contrary to section 28.3 of the *Patent Act*; and
- the description incorporates other documents by reference contrary to subsection 57(1) of the *Patent Rules*.

Christine Teixeira	Marcel Brisebois	Mary Murphy
Member	Member	Member

DECISION OF THE COMMISSIONER

[98] I concur with the findings of the Board and its recommendation to refuse the application on the grounds that:

- the specification, insofar as it relates to claims 1 to 12 on file, is insufficient contrary to subsection 27(3) of the *Patent Act*;
- claims 1 to 28 on file encompass obvious subject-matter contrary to section 28.3 of the *Patent Act*; and
- the description incorporates other documents by reference contrary to subsection 57(1) of the *Patent Rules*.

[99] Therefore, in accordance with section 40 of the *Patent Act*, I refuse to grant a patent for this application. Under section 41 of the *Patent Act*, the Applicant has six months to appeal my decision to the Federal Court of Canada.

Konstantinos Georgaras

Commissioner of Patents
Dated at Gatineau, Quebec
this 1st day of August, 2023.