Commissioner’s Decision # 1273

Décision du Commissaire # 1273

TOPIC: C00, B00

SUJET: C00, B00

Application No.: 2,017,025

Demand no.: 2,017,025

COMMISSIONER'S DECISION SUMMARY

C.D. 1273 Application No. 2,017,025

Lack of Support (C00), Indefiniteness (B00)

The application related to a tumor necrosis factor inhibitory protein isolated from human urine which inhibits the cytotoxic effects of tumor necrosis factor and contained claims to recombinant DNA molecules encoding the protein. The application was rejected by the examiner on the grounds that the description failed to provide a complete amino acid sequence of the protein and that the isolation or production of a DNA molecule encoding the protein would require undue experimental effort. The examiner also rejected certain claims directed to the protein on the grounds that the protein was not defined in a complete and explicit manner. The Board agreed with the applicant on the question of indefiniteness but agreed with the examiner on the question of support reasoning that the description merely directed a person of skill in the art to a pathway which might be followed in order to eventually arrive at the desired DNA products. The Board therefore recommended that the applicant be given the opportunity to delete the claims related to DNA molecules -- a recommendation which was accepted by the Commissioner -- failing which it was the Board's recommendation that the entire application be refused.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,017,025 having been rejected under Subsection 30(4) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

Agent for the Applicant

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This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application number 2,017,025 which was filed on 17 May 1990 and is entitled "TUMOR NECROSIS FACTOR BINDING PROTEIN II, ITS PURIFICATION AND ANTIBODIES THERETO ". The Applicant is Yeda Research and Development Company Limited, assignee of inventors David Wallach, Hartmut Engelmann, Dan Aderka, Daniela Novick and Menachem Rubinstein.

The Examiner in charge issued a Final Action on 26 June 2002 rejecting claims 1 to 6, 13, 16, 17, 19 to 35, 38 to 53 and 56 under Subsection 27(4) of the Patent Act as indefinite and claims 19 to 35, 38 to 50, 54 and 56 under Subsection 138(2) of the Patent Rules for lack of support in the description.

On 20 December 2002, the Applicant replied to the Final Action and argued it should be withdrawn. The Examiner was not convinced by the arguments put forth. At the applicant's request, the Patent Appeal Board conducted an oral hearing on 24 March 2004, at which time the Applicant was represented by Dr. David Conn, Ms. Susan Beaubien and Dr. David Barrans all of the firm of Borden Ladner Gervais LLP, and by Mr. Henry Einav. The Patent Office was represented by Dr. Daniel Bégin, who is the Examiner in charge of the application, Dr. Linda Brewer and Dr. Holly Notman.

The invention relates to a tumor necrosis factor (TNF) binding protein II (hereinafter TBP-II) isolated from human urine. The protein binds to, and inhibits the cytotoxic effects of, TNF.

Claims 1, 19 to 24 and 51 to 54 are representative of the claims which stand rejected and read as follows:

1. A Tumor Necrosis Factor (TNF) Binding Protein II (TBP-II), and salts, functional derivatives, precursors and active fractions thereof and mixtures of the foregoing, having the ability to inhibit the cytotoxic effect of TNF and containing the following amino acid sequence:

Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr.

19. The TBP-II of claim 1, 2, 9, 10, 11, 12, 14, 15, 16, 17 or 18 which is a recombinant protein.

20. The TBP-II of claim 19 which is produced in a prokaryotic host, or in a eukaryotic host.

21. A DNA molecule comprising a nucleotide sequence coding for the TBP-II of claim 1 or 2.

22. A replicable expression vehicle comprising the DNA molecule of claim 21 and capable, in a transformant host cell, of expressing the TBP-II defined in claim 1, 2, 9, 10, 11, 12, 14, 15, 16, 17, 18 or 20.

23. A host cell selected from a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 22.

24. A process for producing recombinant TBP-II comprising the steps of:

(a) culturing a transformed host cell according to claim 23 in a suitable culture medium; and

(b) isolating said TNF Binding Protein TBP-II.

51. An isolated and purified Tumor Necrosis Factor (TNF) Binding Protein (TBPII) having the following characteristics:

I. an N-terminal amino acid sequence: Xaa-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr, where Xaa consists of the following amino acid sequences: Thr, Val-Ala-Phe-Thr-, and Phe-Thr;

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells; and

iii. a molecular weight of about 30 kd in reducing SDS-PAGE analysis.

52. An isolated and purified Tumor Necrosis Factor (TNF) Binding Protein (TBPII) having the following characteristics:

I. an N-terminal amino acid sequence: Xaa-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr, where Xaa consists of the following amino acid sequences: Thr, Val-Ala-Phe-Thr-, and Phe-Thr; and

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells.

53. An isolated protein which specifically binds to TNF, said protein having the amino acid sequence of a glycoprotein which is derivable from urine and includes the amino acid sequence: Xaa-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr, where Xaa is selected from the group consisting of the following amino acid sequences: Thr, Val-Ala-Phe-Thr-, and Phe-Thr.

54. A protein according to claim 53, produced by the process which comprises:

culturing a prokaryotic transformant host cell transformed with a replicable expression vehicle comprising DNA having a nucleotide sequence coding for a protein which specifically binds to TNF, said protein having the amino acid sequence of a protein which is derivable from human urine and includes an amino acid sequence: Xaa-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr, where Xaa is selected from the group of the following amino acid sequences: Thr, Val-Ala-Phe-Thr-, and Phe-Thr.

The Board first considered the Examiner's Subsection 27(4) rejection. The rejected claims fall into two groups - those which are independent (claims 1 and 51 to 53) and those which have been rejected by virtue of the fact that they depend on claim 1 (as listed in the Final Action). The Board has considered only the independent claims as these claims form the basis for the Examiner's rejection.

The Examiner stated in his Final Action that the claimed TBP-II "is not defined in a complete and explicit manner" and that "[m]inimally, when an allegedly novel protein has only been partially characterized, it is required that its **source** (human), **molecular weight** (30 kDa) and **function** be also indicated in order to avoid claiming subject matter not contemplated by the applicant."

The Applicant responded to the Final Action by stating, in part:

> It is surprising that at the same time as the Patent Office, in the Manual of Patent Office Practice, at Chapter 11-08, calls for products to be defined in one of three ways, including structure, the Examiner calls for the compound to be defined (less clearly, it is submitted) by way of source and molecular weight. The Manual of Patent Office Practice, which it is conceded is a guide only, states at 11.08: 'The most explicit and definite form of claims (sic) for a product defines the product by structure'. Applicant has fulfilled this requirement in providing a unique, identifying structure in claim 1. The structure is incomplete but a moment's computation will show that it is sufficient for the purposes of Subsection 27(4). It is usually accepted that there are 20 'natural amino acids'. All else equal, each amino acid has a one in twenty (0.05) chance of being found in a particular position. Simple arithmetic yields a probability of Applicant's 10-amino acid sequence appearing at random given an equal frequency of each amino acid of $(0.05)^{10}$. This is vanishingly small and becomes smaller if the frequency of occurrence of any of the amino acids deviates from 0.05 (for each amino acid that is more common, one or more other amino acids must be less common). The Figure $(0.05)^{10}$ is a <u>maximum</u> probability of the occurrence of this sequence at random. This is all to demonstrate that a person skilled in the art having a polypeptide containing this sequence with the specified utility is as certain as almost anything is likely to be in this world to possess the invention and to know it. The Examiner's position begs the question as to whether or not any other compound other than that claimed can have the features claimed (function and partial amino acid sequence). Contrary to the Examiner's position the only thing more definite is disclosure of more of the same sequence which, in the context of the probabilities disclosed above, is unnecessary overkill in the pursuit of definiteness. Subsection 27(4) requires the subject matter be claimed distinctly and in explicit terms. It is respectfully submitted that the amino acid sequence is both distinct and explicit."

The Applicant argued that the same reasoning applies to independent claims 51-53.

In the Examiner's brief to the Board ("Summary of Reasons", a copy of which was sent to the Applicant prior to the oral hearing), the Examiner summarized the objections made in the Final Action and the Applicant's response thereto. The Examiner has also stated that "[t]he language of claim 1 encompasses functional derivatives and active fractions that may not contain the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Glu-Pro-Gly-Ser-Thr." It's not clear if this is a new argument improperly raised for the first time in the Examiner's summary or merely an example of "subject matter not contemplated by the applicant" as stated in the Final Action. Nevertheless, the Applicant addressed the notion of claim "language" at the oral hearing and the Board has considered the issue.

At the hearing, the Applicant argued first that the Examiner was wrong in his interpretation of the "language" of claim 1 and secondly that a claim to a partially characterized protein need not also

include the protein's source, molecular weight and function. The Applicant's brief to the Board states:

> 15. The wording of claim 1 is clear and unambiguous. On reading of the language of the claim, it is clear that the particular amino acid sequence, namely Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr must be present not only in the TBP-II protein, but in any salt, functional derivative, precursor and active fraction thereof and mixtures of the foregoing. As such, the amino acid sequence is an essential and limiting feature of the claimed subject matter.
> .....
>
> 20. In the present case, the essential elements of the TBP-II protein are two-fold, namely:
> (1) a structural element, being the presence of the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr, and
> (2) the functional element, namely the ability to inhibit the cytotoxic effect of TNF.
>
> 21. Both conditions must be fulfilled before a protein will fall within the ambit of claim 1.

With respect to the issue of "language" in claim 1, the Board agrees with the Applicant and is satisfied that the claim does not include within its scope proteins which do not contain the structural element recited in the claim.

On the second issue, i.e., that the claims must include a reference to source, molecular weight and function, the Applicant argued that these are non-essential features whose inclusion would unduly restrict the scope of the claims.

Subsection 27(4) of the Act provides that "[t]he 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."

An applicant has an obligation to make clear in his claims the ambit of the monopoly sought and the terms used in the claims must be clear and precise. The Exchequer Court in *Minerals Separation North American Corp. V. Noranda Mines, Ltd.*, [1947] Ex. C.R. 306 used the analogy of "fences" and "fields" (at page 352) with reference to patent claims:

> 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.

In claims 1 and 51 to 53, TBP-II is defined at least by function and a partial amino acid sequence, i.e., a partial chemical structure. The Manual of Patent Office Practice, at section 11.08, states that "[t]he most explicit and definite form of claims for a product defines the product by structure." Although the structure recited in the claims is only a partial structure, as the Applicant has pointed out in its response to the Final Action, the probability of other proteins containing this same structure is "vanishingly small". Nonetheless, the claims include the additional feature that the protein must inhibit the cytotoxic effect of TNF. There is nothing unclear or imprecise about this "condition" and when read in combination with the structural element, it is clear to the Board what the Applicant seeks to protect. The Board does not agree with the Examiner that the claims are indefinite because the protein is not further defined by source and molecular weight.

The Board next considered the Examiner's rejection of claims 19 to 35, 38 to 50, 54 and 56 under Subsection 138(2) of the Patent Rules. Subsection 138(2) provides that "[e]very claim must be fully supported by the description."

In the Final Action, the Examiner stated, in part:

> Applicant has not disclosed or prepared any DNA expression vehicle or transformed host capable of producing recombinant TBP-II, and must therefore restrict the claims to the matter he actually disclosed. Applicant is reminded that a DNA molecule is a chemical compound and must be defined like any other chemical compound, i.e., by structure, in terms of its physical and chemical properties or in terms of a process that was used to prepare it, wherein said process uniquely produces the claimed compound. Applicant's lengthy discussion on the appropriate techniques which may be used to produce the claimed final products is in no manner support thereto. Applicant is in fact claiming hoped-for compounds which represent nothing more than ideas. It is deemed that the isolation of a cDNA or a genomic DNA encoding TBP-II, the preparation of an expression vehicle and the transformation of a suitable host in order to be able to produce recombinant TBP-II would require undue experimentation since the amino acid sequence of TBP-II, as provided in the description, contains only partial amino acid sequence information. A DNA encoding TBP-II could not be readily deduced from it and no nucleotide sequence information has been disclosed in any manner.

The Applicant responded to the Final Action as follows:

> ... DNA coding for TBP-II, its expression vector and a transformed host cell could be obtained in a conventional manner as of the filing date (or for that matter as of the convention priority date). With a knowledge of the polypeptide sequence it is a simple matter to look up alternative DNA coding sequences ... There is a simple logical progression from possession of the polypeptide to its partial amino acid sequence analysis (at which point the application was filed) through to a complete amino acid sequence analysis and a DNA coding sequence. In this case, the present specification as filed described the claimed DNA in sufficient detail to establish that Applicant was in possession of the genus of DNA, each species of which encode TBP-II.... As Applicant stated in the application as filed that they considered such DNA sequence to be part of their invention, and as Applicant taught how to deduce such DNA sequence from the genetic code, and as the full amino acid sequence (from which the genus of encoding DNA sequences may be deduced) was inherently a part of the present specification, it is as if the nucleotide sequence were fully set forth.

The response to the Final Action included a declaration of Professor William Brammar regarding the making and use of nucleotide probes based on the polypeptide sequence disclosed, to screen cDNA or genomic libraries for DNA encoding TBP-II. The Applicant also argued that the Examiner's rejection for lack of support should be withdrawn in that the subject matter of the rejected claims meets the test of "sound prediction" as set out by the Supreme Court in *Apotex et al. v Wellcome Foundation Limited et al.* [2002] 4. S.C.R. 153 (hereinafter "Apotex").

The rejected claims fall into two groups - those directed to recombinant products and processes (claims 19 to 24, 49, 50 and 54) and those which have been rejected because they depend directly or indirectly on these claims (claims 25 to 35, 38 to 48 and 56). The Board has considered only the first group of claims.

Claims 19, 20, 49, 50 and 54 are claims to TBP-II defined as "recombinant" or produced by a recombinant process. Claims 21 to 24 are directed to recombinant products (DNA molecule, expression vehicle and host cell) and a recombinant process.

Claims 21 to 24 are defined in terms of a nucleotide sequence encoding TBP-II. The chemical structure (formula) and physical and chemical properties of this sequence are not disclosed in the application. Rather, the Applicant has described processes, known in the art, that could be carried out to obtain the nucleotide sequence and what is predicted is that one of skill in the art will be successful in this endeavour. The declaration of Professor William Brammar has been submitted in support of this prediction.

Essentially, the application describes how mRNA could be extracted from TBP-II-producing cells and converted to cDNA using reverse transcriptase. The cDNA could then be made double-stranded and inserted into a vector for transforming a suitable host cell. An oligonucleotide probe encoding the amino acid sequence of the TBP-II fragment disclosed in the application could then be made and used to screen for clones containing cDNA encoding TBP-II. If a TBP-II-encoding cDNA is found, it could then be inserted into an expression vector for transforming a host cell which in turn could be cultured under conditions where TBP-II would be produced in the cell. However, there is no evidence in the application, nor was any presented at the hearing, that at the filing date of the application, a cDNA encoding TBP-II had been isolated and characterized or that such a cDNA had been inserted into an expression vector or that transformed host cells capable of expressing TBP-II had been made. Rather, the Applicant is predicting that these products could be made.

At the hearing, the Applicant argued that the claims to products defined in terms of a nucleotide sequence encoding TBP-II, which were rejected for lack of support, meet the test of "sound prediction" as set out by the Supreme Court in "Apotex" where the "doctrine of sound prediction" was defined in terms of three components: 1) a factual basis for the prediction; 2) an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; 3) proper disclosure.

In "Apotex", the patentee was predicting that AZT would be useful in the treatment and prophylaxis of HIV/AIDS in humans and the 3-part test set out by the Court was a test for predicting "utility". The patentee was not predicting, as in the instant application, that a chemical

compound (oligonucleotide sequence) which had not been disclosed could be obtained by following a prescribed pathway. Similarly, in an earlier decision of the Supreme Court in *Monsanto Co. v. Commissioner of Patents* [1979] 2 S.C.R. 1108, the "utility" of a group of compounds as rubber vulcanization inhibitors was "soundly predicted". Although only several members of the group had been prepared and tested, all of the compounds were fully disclosed in terms of a chemical structure.

The Commissioner of Patents, in the application which issued as Canadian patent no. 1,338,323 (see *Re Institut Pasteur Patent Application* 76 C.P.R. (3d) 206) (hereinafter "Pasteur"), refused to grant a patent with claims to monoclonal antibodies since none had been disclosed and there was nothing upon which to base a sound prediction. The "Pasteur" application referred one of skill in the art to techniques which could be used to obtain monoclonal antibodies without actually disclosing any. In the instant application, the Board is satisfied that the Applicant, or one of skill in the art, would have been able to use the amino acid sequence encoding a fragment of TBP-II as a tool to eventually obtain a nucleotide sequence encoding TBP-II and thereafter the products defined by claims 21 to 23, to be used in the process of claim 24. However, the application does not disclose the nucleotide sequence which forms the basis of the claims. Rather, the application describes only a pathway or process to be followed to obtain such a sequence and essentially invites others to follow the pathway to isolate the sequence. In this respect, the application is similar to the "Pasteur" application. The Board is not satisfied that there has been "proper disclosure" in respect of a TBP-II-encoding nucleotide sequence and hence there is no support for the products and processes defined by claims 21 to 24. The *quid pro quo* of the patent system is that one must disclose one's invention in exchange for the rights conferred by a patent.

The Board next considered claims 19, 20, 49, 50 and 54, directed to TBP-II. These claims depend, directly or indirectly on claims 1 and 53 and further define TBP-II either as "recombinant" or produced by a "recombinant" process. In essence, in claims 19, 20, 49, 50 and 54, TBP-II is defined in terms of how it is prepared. In order for TBP-II to be "recombinant" as in claim 19, produced in a prokaryotic or eukaryotic cell as in claims 20, 49 and 50, or produced by the process recited in claim 54, a nucleotide sequence encoding the protein is necessary. Since the Board has already decided that there is no support in the application for such a sequence it follows that there is no support for the subject matter of claims 19, 20, 49, 50 and 54.

In summary, the Board concludes 1) that claims 1 to 6, 13, 16, 17, 19 to 35, 38 to 53 and 56 comply with Subsection 27(4) of the Patent Act and should not have been rejected by the Examiner and 2) that claims 19 to 24, 49, 50 and 54 do not comply with Subsection 138(2) of the Patent Rules and that the Examiner correctly rejected these claims. The Board recommends that the Commissioner:

1) inform the Applicant that the Examiner's rejection of claims 1 to 6, 13, 16, 17, 19 to 35, 38 to 53 and 56 under Subsection 27(4) of the Patent Act is reversed;

2) inform the Applicant, in accordance with paragraph 31(c) of the Patent Rules, that the following amendments of the application are necessary for compliance with the Patent Act and Patent Rules: a) deletion of claims 19 to 24, 49, 50 and 54; b) amendment of claims 25, 28, 45 and 46 so that these claims do not depend on claim 20, c) the renumbering of claims 25 to 48 as claims 19 to 42, respectively, with amendment of claim dependencies where necessary; the renumbering of claims 51 to 53 as claims 43 to 45, respectively; and the renumbering of claims 55 and 56 as claims 46 and 47, respectively, with appropriate amendment of the dependency of claim 56.

3) invite the Applicant to make the above amendments within three (3) months of the date of the Commissioner's decision; and

4) advise the Applicant that, if the above amendments are not made within the specified time, the Commissioner intends to refuse the application.

M. Gillen	M. Wilson	J. Cavar
Chairman	Member	Member

I concur with the findings and recommendations of the Patent Appeal Board. Accordingly, I invite the Applicant to make the above amendments within three (3) months from the date of this decision, failing which I intend to refuse the application.

David Tobin
Commissioner of Patents

Dated at Gatineau, Quebec,
this 17th day of January , 2007