Commissioner=s Decision #1319
Décision du Commissaire #1319

TOPIC: B20
SUJET: B20

Application No. : 2,268,812
Demande n^{o}. : 2,268,812

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

The rejection of patent application number 2,268,812 has been reviewed in accordance with subsection 30(6) of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

Agent for the Applicant:

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INTRODUCTION

[1] This decision deals with a review of the rejection of patent application number 2,268,812, filed October 15, 1997.

[2] The Applicant is the University of South Florida and the invention is entitled AMETHOD FOR PRODUCING TRANSGENIC ANIMAL MODELS WITH MODULATED PHENOTYPE AND ANIMALS PRODUCED THEREFROM.@ The inventors are Karen Duff and John Hardy.

PROSECUTION HISTORY

[3] The subject application was rejected in a Final Action dated October 7, 2008 on the grounds that all of the then pending claims were broader than the teachings of the description, contrary to section 84 of the *Patent Rules* and subsection 27(3) of the *Patent Act*. The Applicant replied on April 7, 2009 and submitted claim amendments that converted three dependent claims of narrow scope into independent form. The Applicant submitted that the remaining claims of broader scope were compliant with the Act and Rules. No amendments to these claims were submitted.

[4] The three new independent claims of narrower scope (claims 22-24) were indicated in a Summary of Reasons to be in allowable form. The remaining claims (claims 1-21) were still considered to be too broad and the application was therefore referred to the Patent Appeal Board for review.

[5] A hearing was held on August 17, 2011 at which time the Applicant was represented by Ms. Chantal Saunders of the firm Borden Ladner Gervais LLP, and Mr. Steven Kelber, the Applicant=s United States counsel. Also in attendance were Philip Marshall, the Examiner in charge of the application and his supervisor, Nicholas Ohan.

BACKGROUND

[6] The subject application relates to transgenic animal models that have been genetically engineered to display an accelerated Alzheimer=s Disease (AD) phenotype.

[7] AD is an incurable, terminal illness that is characterized by progressive dementia, memory loss and cognitive dysfunction. Autopsies of patients who have suffered from AD reveal the presence of characteristic plaques in certain regions of the brain. The plaques are made up of extracellular deposits of Aamyloid@ material and intraneuronal tangles. Amyloid material consists mainly of beta-amyloid peptide (Aβ peptide) that is generated through proteolytic cleavage of a larger Aamyloid precursor protein@ (APP). Tangles are made up largely of a cytoskeletal protein termed Atau.@

[8] At the time of filing the subject application, there was considerable interest in discovering the underlying genetic basis for AD. The background of the invention mentions that mutations in the gene encoding APP were known to be associated with AD. Some transgenic mice expressing an APP mutant gene displayed AD-type pathology as well as cognitive impairment, but others showed either no pathology or weak pathology. Even at that, the AD animal disease models carrying a mutant APP gene only displayed an AD phenotype later in their lives B

which means that the animals must be housed and maintained for extended periods of time before they can be used.

[9] A second type of mutant gene was also known to be associated with AD. Mutant presenilin 1 (PS1) and presenilin 2 (PS2) genes were known to result in increased amounts of beta-amyloid peptide. However, the precise mechanism that caused increased production was not known and, while transgenic mice carrying a mutant PS1 gene showed an elevation of beta-amyloid peptide, they showed no pathology.

[10] Against this backdrop the description states that Ait would be useful therefore to have transgenic models which show the full range of pathology of AD at an earlier age@ (page 6, lines 24-25).

THE INVENTION

[11] The invention is summarized on page 7 and basically allows for the production of improved transgenic AD animal models. This is accomplished by generating doubly-mutated transgenic animals which carry a mutant APP gene and a mutant PS gene. More specifically, the description teaches that two types of transgenic animals are first produced: one carrying a mutant APP gene and one carrying a mutant PS gene. Next, animals of each type are crossed to produce offspring which can then be screened for those expressing both mutations and which have enhanced AD pathology.

[12] The inventors observed that the doubly-mutated animals rapidly accumulated Aβ peptide in their brain tissues and developed AD symptoms as early as three months of age. They conclude that there is a synergistic effect when mutant PS and APP genes are combined and expressed in transgenic animals.

THE CLAIMED SUBJECT-MATTER

[13] Claim 1 is representative of the claims considered to be defective:

> A method of preparing a non-human transgenic animal with enhanced amyloid pathology by:
>
> a) introducing a first expressible transgene encoding for a mutant presenilin polypeptide into a first non-human parental animal, and a second expressible transgene encoding a mutant amyloid precursor protein (APP) into a second non-human parental animal, to produce first and second transgenic heterozygous parents, such that the first and second transgenes are integrated into the genome of the first and second parental animals, respectively; and
>
> b) selecting among offspring, of an F_1 generation produced by crossing the first and second transgenic heterozygous parents, for those which express the first transgene and the second transgene and which have enhanced amyloid pathology,

wherein upon expression the mutant presenilin polypeptide has the same phenotypic effect as presenilin M146L, and wherein upon expression the mutant amyloid precursor protein has the same phenotypic effect as APP695 K670N, M671L.

[14] The claim refers to two particular mutants: presenilin AM146L@ and AAPP695 K670N, M671L.@ These mutants are the ones that the inventors have described in the exemplary portion of the description.

[15] Of note is the fact that claim 1 uses language that expands the scope of the claim such that it includes presenilin and APP mutants beyond the two particular mutants described in the exemplary portion of the description. This is accomplished through the use of the expressions Aa mutant presenilin polypeptide . . . wherein upon expression the mutant presenilin polypeptide has the same phenotypic effect as presenilin M146L@ and Aa mutant amyloid precursor protein . . . wherein upon expression the mutant amyloid precursor protein has the same phenotypic effect as APP695 K670N, M671L.@ The rejected claims thus include not only the exemplified mutants, but also more broadly include presenilin and APP mutants that achieve the same phenotypic effects. This is the focus of the debate between the Examiner and the Applicant.

THE GROUNDS FOR REJECTION

[16] The subject-matter of the three new independent claims (claims 22-24) is limited to the exemplified combination of the mutant presenilin 1 protein termed M146L and the APP mutant termed APP695 K670N, M671L. These claims have been indicated to be allowable.

[17] However, the Final Action takes issue with the fact that the remaining claims (claims 1-21) more broadly include presenilin or APP mutants other than the two that have been specifically exemplified:

> Claims 1-24 [now claims 1-21] are broader in scope than the teachings of the description and do not comply with section 84 of the *Patent Rules* and subsection 27(3) of the *Patent Act*. Applicant has only taught a mouse model for amyloid plaque deposits as a result of crossing a mouse that features a human presenilin transgene bearing the mutation M146L with a mouse that has a human amyloid precursor transgene bearing a mutation K760N or M671L. In his letter dated September 20, 2007 applicant amended the claims to define presenilin and amyloid precursor that have the same phenotype as presenilin M146L and amyloid precursor K760N or M671L respectively. However by defining the genes by their desired result said claims encompass mutations that have not been taught by the applicant. Further applicant defines a phenotype that results as a combination of two mutated transgenes, presenilin and amyloid precursor, not just one of the two. Finally the phenotype disclosed by the applicant is defined only by an accumulation of Aβ plaque deposits in the brain of the mice that feature both presenilin and amyloid precursor mutations. Therefore a person skilled in the art who reads the present application has no factual basis to predict gene mutations that will feature the same phenotype other than M146L presenilin combined with amyloid precursor K760N or M671L. Similarly applicant has no factual basis to predict which gene mutations can modulate an Alzheimer's phenotype neither can he predict which two transgenes will modulate an Alzheimer's phenotype other than presenilin M146L and amyloid precursor K760N or M671L. Therefore the examiner maintains the objection.

[18] The scope of the claims is thus considered to be too broad, contrary to section 84 of the *Patent Rules* and subsection 27(3) of the *Patent Act*. This means that the claims are not fully supported across their scope and/or that the specification contains insufficient disclosure.

[19] The Final Action contains certain language B such as, Ano factual basis [exists] to predict which gene mutations can modulate an Alzheimer's phenotype@B which invokes the doctrine of Asound prediction@ of utility. It is alleged that other mutated AD genes, beyond the two particular ones that have been exemplified, will not work. That being the case, the question of lack of utility under section 2 of the Act is also brought into play.

THE ISSUES

[20] The Final Action gives rise to two questions, both of which concern the scope of claims 1-21:

(1) Is the disclosure sufficient to support the breadth of the rejected claims?

(2) Given that the claims are not restricted to the particular mutants used in the example, do they go beyond the limits of a sound prediction?

QUESTION 1: SUPPORT/SUFFICIENCY

Legal Principles

[21] Section 84 of the Rules and subsection 27(3) of the Act are related since both are concerned with the relationship between the extent of disclosure and the scope of the claims.

[22] Section 84 of the *Patent Rules* reads :

> The claims shall be clear and concise and shall be fully supported by the description independently of any document referred to in the description.

[23] Section 84 of the Rules operates in conjunction with subsection 27(3) of the Act, the relevant paragraphs of which read:

> 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; . . .

[24] Sufficiency of disclosure primarily concerns two questions that are relevant for the purpose of subsection 27(3) of the *Patent Act*: What is the invention? How does it work? (*Consolboard v. MacMillam Bloedel*, [1981] 1 S.C.R. 504 at 526, 56 C.P.R. (2d) 145 at 157). The description of the invention must be correct and full and the specification must enable the invention across its entire scope as claimed. The skilled person must not be called upon to display inventive ingenuity or undertake undue, as opposed to routine, experimentation.

Analysis

Is the Invention Correctly and Fully Described?

[25] In terms of providing a correct and full description of the invention, the Final Action alleges that the Aclaims encompass mutations that have not been taught by the applicant@, and instead define transgenes by their Adesired result.@

[26] In response to the Final Action, the Applicant referred to patent documents and information that became available after the filing date of the present application:

> [T]he literature and commercial practice is now replete with examples of the phenotypic mice claimed . . . which exhibit the phenotype of the recited APP x PS1 mutants, but employ mutations other than the specific mutations of the specification

[27] However, what is relevant is what was commonly known and what has been described by the Applicant in the specification at the time of filing, not what others described afterwards. At the hearing and in the written submissions presented to the Board, the Applicant advanced arguments that the Examiner did not have the full benefit of considering at the time the Final Action was written. The Applicant focussed on what the description says about mutant proteins associated with AD:

> There are many known, and there were many known when the Application was filed. See, page 13 of that application, lines 13B30, which identifies no less than sixteen (16) different and authoritative sources from which to identify such mutant transgenes which are expressible and give rise to enhanced Aß 42/43 deposition but not AD phenotype. Claim 1 also requires that parent be crossed with another parent which bears a different expressible mutant transgene B this one in the PS1 gene, which are again identified in sources cited in the Specification (see page 13). The entire point of the Specification=s introduction is in fact that these types of mutations are known B but by themselves, are insufficient to provide animal models by which we can arrive at therapies to treat or prevent AD.

[28] Page 13 of the description generally teaches that various mutant APP and mutant presenilin genes can be inserted into the genomes of transgenic parental lines. If a person of skill in the art were to review the references mentioned on page 13, as the specification directs, that person would appreciate the following facts:

> $ the amino acid sequences of APP and presenilin proteins were available
> $ mutations in each type of protein were known to be associated with AD and to affect the amount, length and fibrollogenicity of Aβ
> $ the Aβ peptides produced from within the APP protein were known
> $ APP mutations that are associated with AD are found either within or near the Aβ coding region
> $ there were at least seven particular APP mutations known to be associated with AD
> $ there were at least thirty one particular presenilin 1 mutations known to be associated with AD
> $ there were two particular presenilin 2 mutations known to be associated with AD
> $ presenilin 1 and 2 have a high degree of structural similarity
> $ presenilin mutations where found at sites common to both presenilin 1 and 2

[29] These facts establish that much was known about the two types of proteins associated with AD and that there existed a number of representative particular mutated AD genes of both the APP type and the presenilin type. Much was also known about the properties and effects of mutant genes associated with AD. The skilled person would therefore appreciate that within the classes of mutant AD genes then available, there existed other candidate mutated AD genes that could be selected and substituted for the particular ones used in the Applicant=s example.

[30] For instance, one logical candidate mutant is described in one of the references mentioned on page 13: see Duff et al., Nature, vol. 383, pp. 710-713, 1996. The presenilin 1 mutant termed AM146V@ described by Duff et al. differs from the exemplified mutant presenilin protein by a single amino acid. Nonetheless, the Duff reference establishes that both mutants produce the same phenotypic effect B that being, the production of increased amounts of an Aβ peptide. The M146V mutant therefore qualifies as one that fits within the language of the claims since it is Aa mutant presenilin polypeptide . . . wherein upon expression the mutant presenilin polypeptide has the same phenotypic effect as presenilin M146L.@

[31] In respect of candidate APP mutants, it is apparent that they too have been described and could be selected. A review of the documents mentioned on page 13 of the description indicates that the exemplified K670N, M671L mutant results in increased accumulation of Aβ peptide. The same literature indicates that other APP mutations produce the same phenotypic effect (see for example Andrä et al., Neurobiol. Ag., vol. 17, pp. 183-190, 1996).

[32] The Final Action asserts that Aby defining the genes by their desired result said claims encompass mutations that have not been taught by the applicant.@ This is a concern rooted in the use of the expressions Awherein upon expression the mutant amyloid precursor protein has the same phenotypic effect as APP695 K670N, M671L@ and Awherein upon expression the mutant presenilin polypeptide has the same phenotypic effect as presenilin M146L.@ These expressions expand the claims such that they embrace not only the M146L and K670N,M671L mutants, but also those that would behave similarly. But not for the appearance of these expressions in the rejected claims, they would have been considered allowable.

[33] These expressions qualify the phenotype of each of the transgenes when expressed. They define neither the desired result of the invention itself nor the phenotype of the transgenic animal models that are produced according to the claimed methods. The desired result of the invention is the production of transgenic animal models that possess the phenotype of accelerated AD pathology. To achieve that result the inventors have hit upon the idea of combining two types of mutant genes known to be associated with AD such that they are both expressed in a transgenic animal.

[34] This situation brings to mind the following passage from *Free World Trust v. Électro Santé Inc.*, 2000 SCC 66, at para 32:

> [T]he ingenuity of the patent lies not in the identification of a desirable result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desirable result. It is not legitimate, for example, to obtain a patent for a particular method that grows hair on bald men and thereafter claim that anything that grows hair on bald men infringes.

[35] The ingenuity here is the identification of a combination of transgenes that work together synergistically to achieve a desirable result. The application is not concerned with mutant transgenes *per se.* The claims neither embrace any kind of method for producing the desired result nor do they embrace any transgene associated with AD. From a review of the supporting and guiding references cited in the specification, it would also be apparent to the skilled person that the desired phenotypic effect of each type of transgene could be achieved using APP and/or presenilin mutants other than those specifically exemplified.

[36] It therefore appears that the claim language used to define the transgenes is appropriate in

view of what has been described in the remainder of the specification.

Is the Invention Enabled Across Its Scope?

[37] In relation to the question of enablement, the Applicant argued in its submissions that the skilled person would not have to exercise inventive ingenuity or conduct non-routine experimentation in order to practice the invention across its breadth as claimed. The portions that touch on this aspect read, in part, as follows:

> There is nothing about such a claim that is beyond the skill of those in the art. Those of skill in the art are taught expressible mutants in the Specification, and others can easily be discerned. There is no difficulty in making parents with these expressible mutations. If there was any question, one of skill would read the application as originally filed, from page 10, line 7 B page 11, line 14 and learn how. They would also consult page 12, line 5 B page 13, line 7 and the twenty-seven (27) different authorities referred to therein.
> . . .
> There is no unknown test or methodology required to determine whether the offspring carry both mutations. See, the application as originally filed, page 16, lines 11B17. And there is no mystery or unknown technique in determining whether each of the mutations carried by the F1 offspring are in fact expressed. Such immunohistochemical methods are well known to those of skill in the art and are discussed at page 17 of the application as originally filed, line 18 B page 18, line 9, again with reference to appropriate authorities.
>
> The Specification teaches that other double cross models of AD can be arrived at following this methodology, and using different expressible mutations B one in PS1 that effects amyloid processing, and one in APP that effects amyloid processing.

[38] Having reviewed the specification we agree that the skilled person would require only routine skill in order to practice the invention in respect of embodiments that have not been exemplified. The skilled person would be guided by the same steps and procedures as those set out in the example but would modify them appropriately when that person wished to employ mutant APP and/or presenilin transgenes other than those exemplified. This would entail selecting from amongst alternative transgenes, substituting them into genetic constructs, generating transgenic parental lines, screening these parental lines for gene expression using the methods described, crossing parental lines, and then screening the resultant offspring. All of these steps have been described in the specification and/or are generally known in the art.

[39] Given the absence of rationale to the contrary, we are left to conclude that the claims are enabled across their scope.

[40] In view of our findings in respect of description of the invention and enablement, we conclude that the rejected claims are fully supported and that the specification is sufficient.

QUESTION 2: SOUND PREDICTION

Legal Principles

[41] Section 2 of the Act requires that an invention be Auseful.@ From this comes the concept of utility.

[42] As of the filing date of the application, there must be either demonstration of the utility of

the invention or a sound prediction of the utility: see *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77 B A*AZT*@. In the present case, the claims encompass transgenes other than the two that have been specifically exemplified, i.e., embodiments that have neither been prepared nor tested. As such there is a lack of demonstrated utility for these embodiments and the Applicant must rely on a sound prediction to establish utility across the scope of the claims.

[43] The second question is thus related to the first in that the scope of the claims is again brought into question. However, it is worth remembering that the requirement for a sound prediction of utility and a requirement that the disclosure be sufficient are separate and distinct: see *Eli Lilly Canada Inc. v. Novopharm Limited*, 2010 FCA 197 at para. 120.

[44] An invention that relies on a sound prediction of utility must satisfy three requirements (*AZT*):

> (1) there must be a factual basis for the prediction;
> (2) the inventor must have at the date of the patent application an articulable and Asound@ line of reasoning from which the desired result can be inferred from the factual basis; and
> (3) there must be proper disclosure.

[45] These requirements must be measured against the predicted utility:

> The present invention provides a method of preparing a transgenic animal model with enhanced, accelerated pathology for Alzheimer's Disease (AD) and the transgenic animal made by the method. [page 7, lines 2-5]
> . . .
> The rapid development of the AD phenotype in these mice will be advantageous in addressing mechanistic issues of amyloid toxicity, and testing the efficacy of agents proposed to interact with select aspects of the AD phenotype. [page 15, lines 17-22]

Analysis

Factual Basis

[46] The Final Action suggests that Aa person skilled in the art who reads the present application has no factual basis to predict gene mutations that will feature the same phenotype other than M146L presenilin combined with amyloid precursor K760N or M671L.@

[47] The factual basis that the specification provides in support of the predicted utility would be understood by the skilled person to include the following:

> $ knowledge of the existence of APP and presenilin genes that were known to be associated with AD
> $ knowledge of the existence of representative numbers of mutations in these genes, knowledge of their structural characteristics, and knowledge of their resultant phenotypic properties
> $ the disclosure of an exemplar consisting of the preparation of transgenic mice mutated with the APP695 K670N, M671L and presenilin M146L genes
> $ the disclosure of a previously unknown synergistic effect between mutant APP and

presenilin transgenes consisting of accelerated, complete, AD pathology
$ the appreciation that the mode of interaction between APP and presenilin proteins, and the precise manner they may co-operatively contribute to AD was not known
$ the awareness that the molecular basis for AD had not been fully elucidated at the time of filing and it remains, even today, a mysterious disease

Articulable and Sound Line of Reasoning

[48] The example disclosed in the specification is key to the inventors= prediction. It includes statistically valid data from genetic, histochemical and behavioural experiments conducted on doubly-mutated transgenic mice as well as control groups consisting of singly-mutated and non-transgenic mice. The skilled person would accept the inventors= claim that the doubly-mutated mice showed a synergistic effect between the two transgenes.

[49] Taking this information in conjunction with the remaining relevant facts, the skilled person would also accept that extrapolating these results to the wider classes of APP and presenilin mutants would be logical and reasonable. It is true that the example describes the use of only one APP mutant used in combination with one presenilin mutant, but the fact that other mutants that fit the claim language were readily available means that the inventors= predictions are not so broad as to be unreasonable.

[50] While much was unknown and unpredictable in the field of AD research at the time the inventors made their discovery, it should be remembered that a sound prediction does not mean a certainty and that it provides no measure of forgiveness should inutility be established within the claimed area at a later time.

Proper Disclosure

[51] There does not appear to be a lack of disclosure of either the factual basis or the inventors= line of reasoning B both would be readily apparent to the skilled person after reading the specification.

[52] Having met all three requirements, we therefore conclude that the inventors= predicted utility is sound over the entire scope of the claims.

CONCLUSIONS AND RECOMMENDATION

[53] We find in favour of the Applicant on both questions and conclude that the rejected claims comply with the section 84 of the Rules, subsection 27(3) of the Act and section 2 of the Act. We recommend that the Commissioner inform the Applicant that the issues identified in the Final Action have been addressed in its favour.

Member Member Member

COMMISSIONER=S DECISION

[54] I accept the recommendation of the Board and find that the issues identified in the Final Action have been overcome.

Sylvain Laporte

Commissioner of Patents

Dated at Gatineau, Quebec
this 3rd day of November, 2011