Commissioner’s Decision #1395

Décision du Commissaire #1395

TOPIC: G00: Utility

SUJET: G00: Utilité

Application No.: 2,654,413

Demande n°.: 2,654,413

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,654,413 having been rejected under subsection 30(3) of the *Patent Rules*, has been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner is to allow the application.

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INTRODUCTION

[1] Application 2,654,413, entitled "Use of VEGF and homologues thereof to treat neuron disorders", is owned by the Vlaams Interuniversitair Instituut Voor Biotechnologie VZW, and the D. Collen Research Foundation VZW. It stands rejected after the issuance of a Final Action because the claimed subject matter was considered to lack utility, contrary to section 2 of the *Patent Act*. The Applicant's response to the Final Action asserts that there is a proper basis for utility, but the Examiner remains of the view that the application is non-compliant. Consequently, the application has been referred to the Patent Appeal Board (the Board) for review.

BACKGROUND

[2] The present invention relates to members of a family of known biochemical growth factors, called "vascular endothelial growth factors" (VEGFs), that are useful for enhancing the survival of motor neurons and for treating neurodegenerative disorders that affect motor neurons, such as Amyotrophic Lateral Sclerosis ("ALS", also known as "Lou Gehrig's Disease").

[3] Prior to the filing of the present application, VEGFs were known to be involved in the development of new blood vessels. However, no link had been made between VEGFs and motor neuron disorders. The invention thus relates to a new use for a known molecule.

[4] There are several members of the VEGF family, including VEGF-A and VEGF-B. Although all members share the ability to promote the development of new blood vessels (angiogenesis), and all exert their effects by binding to molecules on the surface of cells known as "receptors", VEGFs can differ in their particular structures and receptor binding behaviour. A given VEGF acts as a notional "key" that precisely fits only certain receptor "locks", of which there may be several. In the present case, only a few VEGFs are implicated: two forms of VEGF-A, known as $VEGF_{165}$ and $VEGF_{121}$; and VEGF-B. The VEGF receptors known as "VEGF-R1", "VEGF-R2" and "neuropilin-1" are the receptors

to which these particular VEGFs may or may not bind. Upon VEGF binding, VEGF-R1 or VEGF-R2 receptors may set off a series of intracellular biochemical reactions, ultimately yielding a physiological response.

CASE HISTORY

[5] The subject application is a divisional application and effectively carries the same filing and publication dates as its parent patent: April 12, 2001, and October 18, 2001, respectively.

[6] The parent patent claims the use of one particular VEGF, $VEGF_{165}$, for enhancing motor neuron survival and for treating motor neuron disorders. The subject application claims similar uses, but identifies the use of another member of the VEGF family: VEGF-B.

[7] The subject application was rejected in a Final Action on December 3, 2013 for non-compliance with section 2 of the *Patent Act* because the Examiner was not satisfied that the Applicant has made a "sound prediction" that VEGF-B is useful for the purposes asserted. Subsection 27(3) of the Act and section 84 of the *Patent Rules* were also cited as relevant statutory provisions.

[8] In a response to the Final Action dated June 3, 2014, the Applicant amended the claims and argued that there is a proper basis for soundly predicting that VEGF-B is useful for enhancing motor neuron survival and treating ALS. The Examiner remained of the view that the application was non-compliant and therefore prepared a Summary of Reasons (SOR) and forwarded the application to the Board for review. The present panel of three Board members was established to conduct the review.

[9] On April 8, 2015 the Board received additional written submissions from the Applicant as well as an affidavit from a person with knowledge of VEGFs.

[10] This recommendation is based on a review of the application and the record as it presently stands.

THE ISSUE

[11] In view of the grounds for rejection we must address the following question: Are claims 1-4 based on a sound prediction of utility and therefore compliant with section 2 of the *Patent Act*?

[12] In addition to section 2 of the Act, subsection 27(3) of the Act and section 84 of the Rules were identified in the Final Action as relevant provisions. These additional provisions require, respectively, that the specification sufficiently disclose the invention, and that the claims be fully supported. The underlying reasoning for all of the defects is the same. For the purposes of this review, the issue to be resolved will therefore be dealt with solely as one concerning sound prediction of utility under section 2 of the Act. Consequently, if found to be compliant with section 2 of the Act, the application will also be considered compliant with subsection 27(3) of the Act and section 84 of the Rules.

LEGAL PROVISIONS AND PRINCIPLES

Claim construction

[13] In accordance with *Free World Trust v Électro Santé Inc*, 2000 SCC 66 [*Free World Trust*] essential elements are identified through a purposive construction of the claims done by considering the whole of the disclosure, including the specification and drawings (see also *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras. 49(f) and (g) and 52) [*Whirlpool*]. In accordance with the *Manual of Patent Office Practice* §13.05 [revised June 2015], the first step of purposive claim construction is to identify the person skilled in the art and their relevant common general knowledge ("CGK"). The next step is to identify the problem addressed by the inventors and the solution disclosed in the application. Essential elements can then be identified as those elements of the claims that are required to achieve the disclosed solution.

Common general knowledge

[14] The skilled person is "thought to be reasonably diligent in keeping up with advances in the field to which the patent relates": *Whirlpool* at para. 74.

[15] A piece of particular knowledge becomes common general knowledge "when it becomes part of their common stock of knowledge relating to the art": *British Acoustic Films Ltd et al v Nettlefold Productions*, (1936) 53 RPC. 221, at 250 cited with approval in *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd*, [1972] RPC 457, [1971] FSR 417 (UKCA.), in turn cited with approval in *Eli Lilly and Company v Apotex Inc*, 2009 FC 991 at para 97.

Utility

[16] Section 2 of the Act requires that an invention be useful. As of the filing date of the application, there must be either a demonstration or a sound prediction of the utility of the subject-matter of the claim: *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 ("*AZT*").

[17] In a case, such as the present one, where an applicant claims a new use for a known molecule and relies on a sound prediction to establish utility, a tripartite test must be satisfied (*AZT*, para 70):

(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 "sound" line of reasoning from which the desired result can be inferred from the factual basis; and
(3) there must be proper disclosure.

[18] A factual basis can rely on information disclosed in the specification as well as information forming part of the common general knowledge of the skilled person, the latter of which need not be explicitly disclosed in the specification: *Bell Helicopter Textron Canada Limitée v Eurocopter*, 2013 FCA 219 at paras 153-155 [*Bell Helicopter*].

[19] Predictions are measured taking into account any explicit "promises" made in the specification; however, "if there is no explicit promise of a specific result, then a mere scintilla of utility will do" (see *Sanofi-Aventis v Apotex Inc*, 2013 FCA 186 at para 50). Where a promise is clearly and unequivocally expressed by the inventor in the claims, then that expression can be viewed as the promise of the patent (see *Fournier Pharma Inc v Canada (Health)*, 2012 FC 741 at para 126).

CLAIM CONSTRUCTION

The person skilled in the art

[20] Based on the Background of the invention, the person skilled in the art is taken to be a composite of a neurologist and an experimental neuroscientist.

The common general knowledge

[21] The nature of the skilled person in this case, and the Background to the invention (page 1, lines 22-30; page 3, lines 7-10) indicates that the common general knowledge includes a general understanding of the pathogenesis of neurodegenerative disorders, that VEGFs are responsible for the development of new blood vessels (angiogenesis), that VEGFs are implicated in neuropathological conditions (such as stroke, spinal cord ischemia and diabetic neuropathy), and that VEGFs were known to have neurotrophic activity on peripheral neurons. This indicates that the common general knowledge includes knowledge of VEGFs and their receptors.

[22] It is important to further clarify the skilled person's common general knowledge of VEGFs and their receptors for four reasons: (i) because it is required as a matter of claim construction; (ii) because it has not been fully set out in the description; (iii) because it can form part of the factual basis from which utility may be inferred through a sound line of reasoning (*Bell Helicopter*, *supra*); and, (iv) because the Applicant raised it as a point for our consideration.

[23] Three documents are relevant to our assessment of the common general knowledge of VEGFs and their receptors:

(1) a scientific article by *Makinen*[1] published before the filing date of the application and submitted by the Applicant to the Board on April 8, 2015 in support of the argument that it was commonly known in the art that VEGF-B bound to a receptor known as neuropilin-1;

1 : Makinen, T. et al.,"*Differential binding of vascular endothelial growth factor B splice and proteolytic isoforms of neuropilin-1*", J. Biol. Chem., 274: 21217-21222, 1999

(2) an affidavit from Dr. Diether Lambrechts (the *Lambrechts* affidavit) submitted by the Applicant to the Board on April 8, 2015 in which the affiant makes statements supporting the Applicant's arguments concerning the *Makinen* article; and,

(3) a scientific review article by *Robinson & Stringer*[2] independently identified by the panel as a document that corroborates the disclosures of the *Makinen* article and the *Lambrechts* affidavit, and which is relevant to the common general knowledge.

[24] In order to supplement the factual basis set out in the description regarding VEGF-B, the Applicant submitted the *Makinen* article to establish that it was commonly known that VEGF-B bound to the neuropilin-1 receptor. In our view, the common general knowledge is not adequately represented in the singular scientific article by *Makinen*. We also consider the scientific review article by *Robinson & Stringer* to be relevant common general knowledge because it speaks to the Applicant's submissions, was published before the filing date of the application, and is thorough in its disclosures.

[25] Independent of what the Applicant has submitted, we note that the *Robinson & Stringer* review article discloses the receptor binding profile of VEGF-B, including that it binds to neuropilin-1 (page 856, left-hand column). The *Lambrechts* affidavit (paras. 8 and 11) is consistent with what has been described by *Robinson & Springer*, which itself cites the *Makinen* article. We are therefore satisfied that the skilled person would have been aware that VEGF-B binds to neuropilin-1 because all three documents are aligned on that point.

[26] The *Robinson & Springer* review article indicates that the following salient points also formed part of the common general knowledge as of the filing date of the application:

- there are several forms of VEGF, including VEGF-A and VEGF-B;
- VEGF-A itself has several variants of differing size, including $VEGF_{165}$ and $VEGF_{121}$;

2 : Robinson, C.J. and Stringer, S.E., "*The splice variants of vascular endothelial growth factor (VEGF) and their receptors*", J. Cell Sci., 114:853-865, March 20, 2001

- there are several receptors located on the surface of cells through which a given VEGF can mediate its angiogenesis effect, including VEGF-R1, VEGF-R2 and neuropilin-1;
- each VEGF has a specific receptor binding profile, and specific pairings of receptors can co-operatively mediate a given VEGF's angiogenesis activity;
- $VEGF_{165}$ binds to VEGF-R1, VEGF-R2 and neuropilin-1;
- binding of $VEGF_{165}$ to neuropilin-1 alone would not be expected to be able to mediate angiogenesis activity because neuropilin-1, unlike VEGF-R1 and VEGF-R2, lacks the biochemical activity required to set off the series of intracellular reactions that ultimately lead to angiogenesis;
- neuropilin-1 and VEGF-R2 can work as a pair to mediate the angiogenesis activity of $VEGF_{165}$;
- $VEGF_{121}$ binds to VEGF-R1 and VEGF-R2, but does not bind to neuropilin-1; and
- VEGF-B binds to VEGF-R1 and neuropilin-1, but does not bind to VEGF-R2.

[27] The foregoing points of common general knowledge can therefore also be relied upon to supplement the factual basis set out in the description insofar as VEGFs and their receptors are concerned.

The claims and their construction

[28] There are four claims on file. Claims 1 and 2 are representative of the claimed invention:

1. Use of a VEGF-B protein for enhancing survival of motor neurons.
2. Use of a VEGF-B protein for enhancing the survival of motor neurons in the central nervous system in a human subject having amyotrophic lateral sclerosis (ALS).

[29] The skilled person understands that neurodegenerative disorders which affect motor neurons are a serious problem. The solution proposed by the Applicant is broadly described as relating to "the involvement of vascular endothelial growth factor (VEGF)

and homologues in the aetiology of motor neuron disorders" (page 1, lines 5-6). The description can thus literally be taken as proposing the use of any VEGF for enhancing the survival of motor neurons (page 10, line 23). However, the description also suggests that not all VEGFs may actually enhance motor neuron survival because one homologue, $VEGF_{121}$, was tested and observed to have no appreciable effect. This indicates to the skilled person that, based on a purposive construction, the use of each VEGF homologue can represent a different solution.

[30] The claims at issue are "use" claims. In claim 1, the skilled person would understand that the use is for "enhancing survival of motor neurons", at least to some degree, wherever the neurons are found, and for whatever disorder might jeopardize their survival. In claim 2, the motor neurons are found in the central nervous system of a human having ALS. In both claims the agent responsible for enhancing motor neuron survival is VEGF-B.

SOUND PREDICTION

The predicted utility

[31] The predicted utility of the invention is echoed in the claims. As stated above, the utility in the case of claim 1 is for "enhancing motor neuron survival." We note that there is no explicit promise of maximal motor neuron survival in either the description or the claim. As such, the skilled person would understand that the predicted utility is enhancement of motor neuron survival, at least to some degree. In the case of claim 2, the utility is extrapolated to humans suffering from ALS.

[32] A review of the prosecution indicates that no distinction has been made between the utility of the invention as claimed in claim 1 versus that of claim 2. The point of contention lies in the nature of the agent responsible for the utility, VEGF-B, and whether the Applicant has soundly predicted its utility to enhance motor neuron survival.

Factual basis

[33] The factual basis includes the results of experiments conducted by the inventors that involve receptor binding studies which suggest that not all VEGFs may actually be neuroprotective. The results demonstrate that $VEGF_{165}$ protects motor neurons from cell

death (figure 2a; page 27, lines 2-3) whereas $VEGF_{121}$ had no appreciable effect. VEGF-B was not tested.

[34] The factual basis also includes the common general knowledge established above in respect of VEGFs and their receptors.

[35] Knowledge of a VEGF's receptor binding behaviour, and the results of the inventors' experiments, is important because it can illuminate the mechanism through which it may, or may not, exert its effects. Such information collectively forms the factual basis for a sound line of reasoning from which the utility of a VEGF may be inferred.

Sound line of reasoning

[36] There was disagreement between the Examiner and the Applicant on what the skilled person would infer from the factual basis and whether there is a sound line of reasoning leading to the predicted utility. In particular, the receptor binding behaviours of VEGFs and their ability, or inability, to exert a neuroprotective effect was the topic of discussion during prosecution.

[37] According to the reasoning expressed in the Final Action, if the utility of VEGF-B is soundly predicted it must exert its effects in the same manner as $VEGF_{165}$ which was tested and demonstrated to be neuroprotective. Since the wording of the description (see page 1, lines 14-17; page 15, lines 22-23) and the experimental results indicate that $VEGF_{165}$ exerts it neuroprotective effect by binding the VEGF-R2 and neuropilin-1 receptors, VEGF-B must also bind these same receptors if it is to have utility. Since VEGF-B does not bind VEGF-R2, the Final Action concludes that the prediction is not sound.

[38] In contrast, the Applicant argues that binding of a VEGF to both VEGF-R2 and neuropilin-1 is not required for there to be a neuroprotective effect. The Applicant asserts that "the results from the present application do highlight that an ability of a VEGF protein to bind neuropilin-1 is a reasonable and sound predictor of the ability to bring about a neuroprotective effect" (page 3, Applicant's response to the Final Action). This is based on the observation that $VEGF_{121}$ does not bind neuropilin-1 and does not provide an appreciable neuroprotective effect. It is also based on receptor binding experiments on

$VEGF_{165}$ that indicate its neuroprotective effect is highest when it binds to both VEGF-R2 and neuropilin-1. A partial effect is seen when it binds to either VEGF-R2 or neuropilin-1 (figure 2c; page 27, lines 5-7).

[39] The Applicant goes so far as to suggest that the factual basis in the description is "consistent with $VEGF_{165}$ being able to exert a neuroprotective effect, at least partially, through neuropilin-1 or VEGFR-2" (page 2, Applicant's response to the Final Action; emphasis in original). According to the *Lambrechts* affidavit provided by the Applicant, the factual basis "actually suggests that binding VEGF-R2 may not even be necessary for a neuroprotective effect" (para. 20).

[40] In our view, the observation that VEGF-B does not bind VEGF-R2 is neither evidence of inutility nor something that necessarily means that it cannot plausibly exert a neuroprotective effect. The skilled person would understand that a VEGF need not exert its neuroprotective effect in precisely the same manner as $VEGF_{165}$ and would see that there exists a sound line of reasoning. The skilled person would not accept, however, that the Applicant's arguments are in complete accord with the line of reasoning.

[41] Neuropilin-1 binding is implicated in a VEGF's ability to enhance motor neuron survival. The skilled person would see a VEGF's ability to do so as a valid predictor of utility. Since the skilled person knows, based on their common general knowledge, that VEGF-B binds neuropilin-1, the Applicant's line of reasoning makes sense to a considerable extent in that respect.

[42] However, the skilled person would not accept the Applicant's suggestion that neuropilin-1 alone is able to mediate a neuroprotective effect because it is difficult to reconcile with the common general knowledge. The common general knowledge admits that binding of a $VEGF_{165}$ to neuropilin-1 alone would not be expected to be able to mediate activity, at least as far as angiogenesis is concerned. Neuropilin-1 lacks the biochemical activity required to do so. As such, the involvement of another, biochemically active, receptor in the mediation of a neuroprotective effect would be expected by the skilled person. Any inconsistency with the common general knowledge in that regard is resolved by considering that VEGF-B, like $VEGF_{165}$, is able to bind to another partner receptor, VEGF-

R1, which has biochemical activity and through which it could plausibly exert a new effect.

[43] We therefore conclude that there is a sound line of reasoning from which VEGF-B's utility can be inferred.

Proper disclosure

[44] The requirement for proper disclosure under the *AZT* test has been met in this case by virtue of disclosure of the underlying experimental data supporting the factual basis, through the common general knowledge which need not be explicitly disclosed, and through the disclosure of a sound line of reasoning from which VEGF-B's predicted utility can be inferred.

CONCLUSION

[45] Claims 1-4 are based on a sound prediction of utility and therefore compliant with section 2 of the *Patent Act*. Consequently, the application is also compliant with subsection 27(3) of the Act and section 84 of the Rules.

RECOMMENDATION

[46] For the reasons set out above, we are of the view that the rejection is not justified on the basis of the defects indicated in the Final Action notice and have reasonable grounds to believe that the application complies with the *Patent Act* and the *Patent Rules*. We recommend that you notify the applicant in accordance with subsection 30(6.2) of the *Patent Rules*.

Ed MacLaurin	Mark Couture	Ian de Belle
Member	Member	Member

DECISION OF THE COMMISSIONER

[47] I concur with the findings and the recommendation of the Board. In accordance with subsection 30(6.2) of the *Patent Rules*, I hereby notify the Applicant that the rejection of the application is withdrawn, the application has been found allowable and I will direct my officials to issue a Notice of Allowance in due course.

Johanne Bélisle,
Commissioner of Patents
Dated at Gatineau, Quebec,
this 15th day of April, 2016