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REGISTERED MAIL

April 15, 2016

SMART & BIGGAR
P.O. Box 11115 Royal Centre
2300 – 1055 West Georgia Street
Vancouver, British Colombia
V6E 3P3

Dear Sir/Madam:

Applicant No:	2,654,413
Applicant:	**VLAAMS INTERUNIVERSITAIR INSTITIIT VOOR BIOTECHNOLOGIE VZW, AND THE D. COLLEN RESEARCH FONDATION VZW**
Title:	"USE OF VEGF AND HOMOLOGUES THEREOF TO TREAT NEURON DISORDERS"
Your File No:	**81906-24(D)**

Please find enclosed a Commissioner's Decision concerning the above mentioned patent application.

Yours sincerely,

Jek-Hui Sim
Acting Chair, Patent Appeal Board

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.

Agent for the Applicant:

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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

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.

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;

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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

- 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)

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

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