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Case Number: T 0713/08 - 3.3.04

Application Number: 03779769.3

Publication Number: 1589988

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Title of invention:
Modulation of activity of neurotrophins

Applicant:
H. Lundbeck A/S

Headword:
Neurotrophins/H. LUNDBECK A/S

Relevant legal provisions:
EPC Art. 123(2)
RPBA Art. 12(1), 13(4)

Keyword:
"Main and first auxiliary request - added matter (yes)"
"Second auxiliary request - admissibility (no)"

Decisions cited:
T 0329/99

Catchword:
-

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Case Number: T 0713/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 24 October 2012

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 2 November 2007 refusing European patent application No. 03779769.3 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
R. Morawetz

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application 03779769.3 with the title "*Modulation of activity of neurotrophins*" which was filed as international application PCT/DK2003/000919 on 19 December 2003 and published as WO 2004/056385.

II. The application was filed with *inter alia* the following claims:

"1. A method for modulating the activity of at least one neurotrophin and/or a pro-neurotrophin in a cell or an organism, such as an animal, comprising administering to said animal a sufficient amount of an agent capable of
(i) binding to a receptor of the Vpsl0p-domain receptor family and/or
(ii) interfering with binding between a receptor of the Vpsl0p-domain receptor family and a neurotrophin and/or proneurotrophin and/or
(iii) modulating the expression of a receptor of the Vpsl0p-domain receptor family.

6. The method according to any of claims 1-3, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5.

8. The method according to any of the preceding claims, wherein the animal is a mammal.

9. The method according to claim 8, wherein the mammal is a human being.

10. The method according to any of the preceding claims, wherein the receptor is selected from SorLA, Sortilin, SorCS1, SorCS-2, or SorCS-3.

11. The method according to claim 10, wherein the receptor is Sortilin.

12. The method according to any of the preceding claims, wherein the agent is selected from proteins, peptides, polypeptides, antibodies, antisense RNA, antisense-DNA or organic molecules, SiRNA.

13. The method according to any of the preceding claims, wherein the agent is capable of inhibiting binding of said neurotrophin or said pro-neurotrophin to the receptor.

14. The method according to any of the preceding claims, wherein the agent is capable of binding to an extracellular part of the receptor.

26. A method for treating a disease or disorder in an individual, comprising administering to said individual a sufficient amount of an agent as defined in any of the claims 1-25.

27. The method according to claim 26, wherein the disease or disorder is selected from one or more of the following diseases or disorders: inflammatory pain, diseases or disorders of pancreas, kidney disorders, lung disorders, cardiovascular disorders, various types

of tumours, psychiatric disorders or neuronal disorders.

44. An agent capable of modulating the activity of at least one neurotrophin and/or pro-neurotrophin when said neurotrophin and/or pro-neurotrophin binds to a receptor of the Vpsl0p-domain receptor family.

54. A soluble receptor of the Vps10p-domain receptor family or a fragment or a variant thereof.

55. Use of a soluble receptor as defined in claim 54 for the preparation of a medicament."

III. The examining division decided that *inter alia* claim 1, of the main request (claims 1 to 29), of the first auxiliary request (claims 1 to 27) and of the second auxiliary request (claims 1 to 27) before them failed to comply with the requirements of Article 123(2) EPC. In three sections entitled "o*biter dictum*" the examining division further provided arguments that the claimed subject-matter of the three requests did not meet the requirements of Article 83 and 84 EPC, was not novel (Article 54 EPC) and did not involve an inventive step (Article 56 EPC).

Independent claim 1 of the main request before the examining division read:

"1. Use of an agent capable of inhibiting the binding of a proneurotrophin to a Vpsl0p-domain receptor by binding to an extracellular part of the receptor, an intracellular part of the receptor, or a segment of the transmembrane part of the receptor in the manufacture

of a medicament for treating and/or preventing neurological diseases and disorders in an animal."

Claims 2 to 24 were dependent directly or indirectly on claim 1. Claims 25, 28 and 29 were further independent claims. Claims 26 and 27 were dependent on claim 25.

IV. With the statement of the grounds for appeal the appellant filed a new main request (claims 1 to 26) and two new auxiliary requests (claims 1 to 26 and claims 1 to 3). Claim 1 of the main request read:

"1. Use of an agent capable of inhibiting binding of a pro-neurotrophin to a receptor of the Vpsl0p-domain receptor family for the preparation of a medicament for treating a neurological disease or disorder in an individual."

V. The board summoned the appellant to oral proceedings to take place on 24 October 2012 and informed the appellant in a communication pursuant to Article 15(1) of the RPBA of its preliminary opinion that claim 1 of the main request (see Section IV) and of the first auxiliary request contravened the requirements of Article 123(2) EPC as the technical effects of the binding of either neurotrophin or pro-neurotrophin were so distinct that the skilled person could not derive a direct and unambiguous selection or dismissal of any of the various diseases and disorders referred to on page 32, lines 7 to 12 and claim 27 of the patent application as originally filed in relation to either neutrophin or pro-neutrophin.

VI. In its response to the board's communication dated 21 September 2012 and in preparation of oral proceedings, the appellant filed a new main request and three auxiliary requests.

Claim 1 of the new **main request** read as follows:

"1. An agent, wherein the agent is an antibody directed against an extracellular part of a receptor, namely sortilin, capable of inhibiting binding of a pro-neurotrophin to said receptor of the Vpsl0p-domain receptor family, for use in treating a neurological disease or disorder in an individual, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5."

Claim 1 of the **first auxiliary request**, which combines the subject-matter of claim 1 and 2 of the main request read:

"1. An agent, wherein the agent is an antibody directed against an extracellular part of a receptor, namely sortilin, capable of inhibiting binding of a pro-neurotrophin to said receptor of the Vpsl0p-domain receptor family, for use in treating a neurological disease or disorder in an individual, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or proNT-4/5, and wherein the neurological disease or disorder is selected from Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea, stroke, ALS, peripheral neuropathies, necrosis or loss of neurons, nerve damage due to trauma, kidney dysfunction, injury, and the toxic effects of chemotherapeutica used to treat cancer and AIDS,

aberrant sprouting in epilepsy, schizophrenia, pancreas or lung injury and/or dysfunction, injury and/or dysfunction of the central and/or peripheral nervous systems."

Claim 1 of the **second auxiliary request** read:

"1. Use of an agent, wherein the agent is an antibody directed against an extracellular part of a receptor, namely sortilin, for inhibiting binding of a pro-neurotrophin to said receptor of the Vpsl0p-domain receptor family, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5."

VII. Oral proceedings before the board were held on 24 October 2012. During the oral proceedings the appellant withdrew the third auxiliary request.

VIII. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or the first or second auxiliary request all filed on 21 September 2012.

IX. The appellant's arguments can be summarised as follows:

Main request - Article 123(2) EPC

– Claim 1 of the main request was formulated in the "EPC 2000 medical use format" and was a combination of claims 1 to 5 of the main request submitted with the statement of the grounds of appeal (see Section IV, above), whereby the agent was re-defined as being an antibody directed

against an extracellular part of the receptor, namely sortilin, and the pro-neurotrophin was structurally defined.

– Claim 1 of the main request found support under Article 123(2) EPC in claims 1, 6, 9, 11 to 14, 26, 27, 44 and 55 as originally filed as well as in the passages on page 27, lines 11 to 13 and page 32, lines 11 to 12 of the description in the application as originally filed.

– The skilled person knew that ProNGF (a pro-neurotrophin) and NGF (a neurotrophin) elicited opposing cellular responses, i.e. nerve cell death and nerve cell survival, respectively. Clinically promoting apoptosis of neurons lead to diseases associated with neuron degeneration or damage and the use of NGF or the inhibition of proNGF was suggested for the treatment of neurodegenerative diseases.

– The skilled person knew that the p75 receptor bound proNGF, but that p75 alone could not account for the binding of the dimeric proNGF ligand to the $p75^{NTR}$ expressing cells because the binding affinity of the p75 receptor for proNGF was much lower than could be expected to explain the low amount of proNGF necessary to obtain an apoptotic effect.

– The examples of the application (see e.g. Figure 3, showing that proNGF bound with a higher affinity to sortilin than to TrkA and p75) showed that sortilin (a receptor of the Vpsl0p-domain family),

was the main receptors for proNGF. It was therefore confirmed that pro-neurotrophins, like neurotrophins, signal through two different receptors to exert their effect.

– The knowledge that pro-neurotrophins exerted a pro-apoptotic effect and the finding that receptors in the Vpsl0p-domain family were the main receptor for pro-neurotropins inevitably lead the skilled person to conclude that inhibition of binding of proNGF to sortilin lead to an inhibition of the pro-neurotrophic effects.

– When reading the patent application, in particular page 27, taken together with page 32, the person skilled in the art - faced with only one necessity of selection, i.e. either the binding of neurotrophin or the binding of pro-neurotrophin to the receptor sortilin - should be inhibited from treating the diseases explicitly listed in the description.

– The description of the application aimed at providing pharmaceutical compositions which were capable of the treatment of a disease and it taught that the neurotrophin activities (not the pro-neurotrophin activities) such as neuronal survival, neuronal differentiation, involvement in anti-depressive action and involvement in accelerating nerve process growth (see page 25, lines 23 to 32) were the desired ones. This was further supported by the disclosures in a number of background art documents on file (see e.g. WO00/44396, page 1, lines 13 to 17; WO98/46254,

page 1, 3rd paragraph; US 6,011004, column 1. lines 41 to 46 and US 6,333,310, column 1, lines 14 to 23 and column 2, lines 20 to 32). Thus, a person skilled in the art reading the description with a mind willing to understand would have known that it did not make sense to inhibit the neurotrophin activity as this would be contra-productive to the treatment of diseases, where neuronal activity was desired.

First auxiliary request - Article 123(2) EPC

– The same amendments had been carried in claim 1 as in claim 1 of the main request with the addition that the diseases had been defined in accordance with the language of claim 17 of the main request which had been submitted with the statement of the grounds of appeal (see Section IV, above). Claim 1 was thus a combination of claims 1 and 2 of the main request.

Second auxiliary request

Amendments

– Claim 1 was a newly drafted claim in the "use"-format and its subject-matter reflected the heart of the invention disclosed in the patent application which had for the first time shown that the specifically claimed antibody, binding to the extracellular part of sortilin, was able to inhibit the binding of sortilin to pro-neurotrophins.

Admissibility into the proceedings

– The claim request was filed at a late stage of the proceedings in view of the fact that the representative had changed and it constituted a fair attempt to protect the invention within the thrust of the claims as previously on file.

Reasons for the Decision

1. The appeal is admissible.

Main request - Article 123(2) EPC

2. The main ground for the refusal of the patent application was the finding that the subject-matter of claim 1 of the main request before the examining division did not comply with the requirements of Article 123(2) EPC.

3. Before the examining division the applicant had indicated as a basis for claim 1 of the main request then on file (see section III, above) *inter alia* the passages on page 27, lines 26 to 31 (in particular: "*the agent may be capable of inhibiting the binding of said neurotrophin or said pro-neurotrophin to a Vpsl0p-domain receptor by binding to an extracellular part of the receptor, an intracellular part of the receptor, or a segment of the transmembrane part of the receptor*"), taken in combination with the passages on page 32, lines 10 to 12: "*Accordingly, agents of the present invention may be utilized in methods for the treatment of a variety of neurological diseases and disorders.*"

4. The examining division decided however that these two passages taken together failed to provide a direct and unambiguous link between the diseases to be treated and the agent to be used. The agents to be used were disclosed in the application **either** to inhibit the binding of a neurotrophin **or** a pro-neurotrophin (which have opposing effects) to the receptor and as a consequence decrease their activity, or to bind to the receptor and increase their activity. Also claim 13 as originally filed, the passage on page 27, lines 1 to 14 and the passage on page 31, line 26 onwards ("*capable of interfering with binding between a receptor of the Vpsl0p-domain receptor family and a neurotrophin and/or pro-neurotrophin*") left the choice between a neurotrophin and/or pro-neurotrophin inhibitor open. A direct and unambiguous link between the specific inhibition of the binding of a pro-neurotrophin to a Vpsl0p-domain receptor and the specific treatment of neurological diseases and disorders was also not derivable from claim 27 as originally filed as this claim mentioned neural disorders among other diseases. Claim 1 thus related to a new combination of features, which as such was neither disclosed nor directly and unambiguously derivable from the originally filed application.

5. Claim 1 of the main request before the board has been amended as compared to claim 1 of the main request before the examining division essentially by defining the agent which is capable of inhibiting the binding of a pro-neurotrophin (now e.g. proNGF) to a defined Vpsl0p-domain receptor (now sortilin) to be an antibody directed against an extracellular part of sortilin. The

antibody is now claimed "*for use in treating a neurological disease or disorder in an individual*".

6. The board therefore notes that besides the more detailed description of the pro-neurotrophin (now e.g. proNGF) concerned and the Vpsl0p-domain receptor (now sortilin), and the change of the claim format from a second to a first medical use, the amended claim still relates to a specific combination of the inhibition of the binding of a pro-neurotrophin to a Vpsl0p-domain receptor by binding of an agent to the extracellular part of the receptor in the treatment of a neurological disease or disorder. The reasoning of the examining division would therefore still be applicable to this claim.

7. In accordance with established case law of the Boards of Appeal, the relevant question to be decided in assessing whether an amendment adds subject-matter extending beyond the content of the application as filed is whether the proposed amendment is directly and unambiguously derivable from the patent application as filed.

8. In a primary line of argumentation the appellant has referred to a combination of various claims as originally filed which when taken in combination supported claim 1. However, the board notes that when combining the various embodiments of the claims as recited in section II, above, it transpires that the specific subject-matter of claim 1 can only be derived therefrom when making a variety of specific selections from the lists of embodiments which are the subject of these claims. By way of example the board refers to

claim 12 as filed in which antibodies are listed among other candidate inhibitory binding compounds; to claim 13 as filed, in which a choice has to be made between pro-neurotrophin and neurotrophin and to claim 27 as filed where neuronal diseases are merely one of the numerous diseases listed to be treated.

9. Accordingly, the claims as originally filed cannot provide a basis for claim 1 to comply with the requirements of Article 123(2) EPC.

10. In a second line of argumentation the appellant has referred to the description of the patent application as a whole to support the insight of the skilled person that the claimed subject-matter was disclosed in a clear and unambiguous manner.

11. The following disclosures in the patent application as originally filed are of relevance for the assessment of this argument.

11.1 The paragraph bridging pages 1 and 2 discloses that according to then current knowledge neurotrophins bind to two discrete receptor types which can be distinguished pharmacologically, i.e. the Trk and $p75^{NTR}$ neurotrophin receptors, and (see page 2, line 30 to page 3, line 4) that they are of clinical interest as they play an important role in neuronal cell survival and differentiation. Trk receptors transmit signals promoting neuronal survival, whereas $p75^{NTR}$ can induce neuronal apoptosis as well as neuronal survival depending on any co-expression of TrkA, i.e. activation of the TrkA receptors can negate the proapoptotic effect of $p75^{NTR}$. By reference to Lee *at al*. 2001

(Science, Vol. 294, pages 1945-1948) the application further states that it is probable that propeptides of neurotrophins play important biological roles: pro-neurotrophin and its proteolytically processed and mature counterpart product differentially activate pro- and anti-apoptotic cellular responses through preferential activation of $p75^{NTR}$ and Trk receptors, respectively, whereby pro-neurotrophin has an enhanced affinity for $p75^{NTR}$ receptors and a reduced affinity for Trk receptors relative to the mature forms of the neurotrophin. It had been demonstrated that pro-NGF induced $p75^{NTR}$-dependent apoptosis in cultured neurons with minimal activation of TrkA-mediated differentiation or survival (page 3, lines 5 to 13).

11.2 Concerning the understanding of the role of the Vps10p-domain receptor family members, such as sortilin, the application discloses a possible involvement in Golgi-endosome sorting (page 4, line 25 to page 3, line 2).

11.3 In general terms the application states at page 5, lines 23 to 32, that the invention relates to "*a method for modulating the activity of at least one neurotrophin and/or pro-neurotrophin in an animal comprising administering to said animal a sufficient amount of an agent capable of (i) binding to a receptor of the Vps10p-domain receptor family and or (ii) interfering with binding between a receptor of the Vps10p-domain receptor family and a neurotrophin and/or pro-neurotrophin (...)*".

11.4 In the Figures and their corresponding legends (page 6, line 9 to page 8, line 17) various experiments are disclosed whereby the *in vitro* binding of *inter alia*

the neurotrophin NGF, its proneurotrophin proNGF or the propeptide as such to p75, TrkA and sortilin is measured (see Figures 2 to 4 and page 6, lines 12 to page 7, line 12) demonstrating a preferential binding of proNGF to sortilin and a low binding affinity of NGF for sortilin.

11.5 In a section called "*Detailed description*" on page 24 the application re-iterates that the "*inventors have identified that neurotrophins bind to receptors of the Vps10p-domain receptor family. Accordingly, the present invention relates to modulation of the activity of at least one neurotrophin*." (page 24, lines 6 to 8). It then continues on page 24, lines 10 to 28:

"*Without being bound by theory it is believed that Vps10p-domain receptor family is involved in one or more of the following mechanisms in relation to neurotrophins:*
- Retrograde transport, including uptake of proneurotrophin, neurotrophin and p75
- Transport within biosynthetic pathways, including sorting of proneurotrophin and transport from the Golgi network
- Release of neurotrophins
- Signalling, including modulation of cellular transport and signalling by formation of ternary complexes with p75 and neurotrophin or pro-neurotrophin

Thus, one aspect of the present invention is a method for modulating the activity of at least one neurotrophin and/or a pro-neurotrophin in a single cell or an organism, including an animal, comprising administering to said animal a sufficient amount of an

agent capable of binding to a receptor of the Vps10p-domain receptor family or capable of interfering with binding between a receptor of the Vps10p-domain receptor family and a neurotrophin and/or proneurotrophin."

11.6 In the following sections of the description the terms "*Receptors of the Vps10p-domain receptor family*" (page 24, line 30 to page 25, line 4) and "*Neurotrophins*" and "*Pro-neurotrophins*" (page 25 line 6 to 19) are defined. In the subsequent section "*Modulation of neutrophin activity*" on page 25, line 21 to page 26, line 7, the application defines that the "*terms "neurotrophin-mediated" activity, "activity of a neurotrophin" or "neurotrophin activity" refer to a biological activity that is normally promoted, either directly or indirectly, in the presence of a neurotrophin or a proneurotrophin*." It is then stated that "*Neurotrophin activities include, but are not restricted to, neuronal survival, neuronal differentiation including process formation and neurite outgrowth, biochemical changes such as enzyme induction, involvement in depression and antidepressant action, involvement in accelerating nerve process growth, and involvement in decreasing general cell motility. It has been hypothesized that the lack of neurotrophic factors is responsible for the degeneration of selective neuronal populations as it occurs in Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis*." The application then continues that "[t]*he activities of pro-neurotrophins include, but are not restricted to, differentially activating both pro- and anti-apoptotic cellular responses, through preferential activation of p75 or TrkA receptors respectively*."

11.7 In a following section entitled "*Agents capable of modulating activity*" starting on page 26, line 15, various "preferred embodiments" of the invention are disclosed such as *inter alia* (page 26, lines 17 to 23):

"*In one preferred embodiment of the present invention, an agent is administered to the animal, said agent being capable of modulating the binding between a receptor of the Vps10p-domain receptor family and a neurotrophin and/or proneurotrophin.*

In another, equally preferred embodiment, the agent is capable of binding to a receptor of the Vps10p-domain receptor family or a neurotrophin and/or pro-neurotrophin thereby interfering with the activity of a neurotrophin, either directly or indirectly."

Further on page 26, in line 33, it is then specified that the agent may be a antibody or a polypeptide.

On page 27, lines 1 to 9, it is continued that "(...) *the agent administered to the animal is capable of modulating the activity of a sortilin receptor in relation to a neurotrophin, said activity may be, but is not restricted to, one or more of the following:*
i) cellular sorting of the receptor
ii) receptor binding directly or indirectly by ligand bridging to other receptors, such as the p75 and Trk receptors
iii) sortilin receptor signalling".

In the following paragraphs (page 27, line 11 to page 28, line 6) it is then stipulated that the agent

may be *"capable of inhibiting binding of a neurotrophin or pro-neurotrophin to a receptor of the Vps10p-domain receptor family"* either by binding to the neurotrophin and/or proneurotrophin or by binding to an extracellular part of a receptor of the Vps10p-domain receptor family, whereby an example is an antibody directed against an extracellular part of the receptor which sterically blocks the binding of the neurotrophin and/or proneurotrophin to the receptor.

11.8 "*Methods for treating a disease or disorder*" are dealt with on page 31, line 26 to page 34, line 20 and are stated to comprise "*administering to said individual, in a pharmaceutically acceptable carrier, a sufficient amount of an agent capable of interfering with binding between a receptor of the Vps10p-domain receptor family and a neurotrophin and/or proneurotrophin*" (page 31, lines 30 to 32). In the following paragraph it is stated that the "[a]*gents of the present invention are believed to be useful in promoting the development, maintenance, or regeneration of neurons in vitro and in vivo, including central (brain and spinal chord), peripheral (sympathetic, parasympathetic, sensory, and enteric neurons), and motor neurons. Accordingly, agents of the present invention may be utilized in methods for the treatment of a variety of neurological diseases and disorders.*" The description subsequently refers to a variety of diseases in which "the agents of the invention" can be used and then concludes on page 34, lines 18 to 20, that "[a]*ccordingly, a method of treating a neural disorder in a mammal comprising administering to the mammal a therapeutically effective amount of one or more agents of the present invention is provided*."

12. The board concludes that, as far as the function of the binding partners are concerned and as can be taken from points 11.1 and 11.2, above, it was known in the art that pro-neurotrophin and neurotrophin differentially activate pro- and anti-apoptotic cellular responses, respectively. It was furthermore known that relative to neutrophin, pro-neurotrophin had a higher affinity for $p75^{NTR}$ and a reduced affinity for Trk receptors. In addition it was thought that Vps10p-domain receptor family members were possibly involved in Golgi-endosome sorting. The application now demonstrates, see point 11.4, above, that sortilin binds preferentially to proNGF over NGF. The inventors conclude (see point 11.5, above) that accordingly the invention relates to the modulation of the activity of at least one neurotrophin and postulate the involvement of Vps10p-domain receptor family members in a number of activities, which are more refined in relation to neurotrophin in the sections mentioned in point 11.7, above. The passages referred to in points 11.5 to 11.7, above, do not, however, disclose that the binding of any specific (pro-) neurotrophin to Vps10p-domain receptor family members has a direct bearing on a specific medical use let alone a treatment for a disease or disorder. The board considers furthermore that this lack of a disclosure of this link is not remedied by the mere disclosure of a number of possible activities of neurotrophin as referred to in point 11.6, above, because there is no clear and direct link with the binding of the neurotrophin to a Vps10p-domain receptor family member disclosed. Indeed, the passage referred to in point 11.6, above, merely refers to the

binding with p75 and Trk receptors and not with sortilin.

13. In view of the above considerations, the board considers that the skilled person would read the crucial passages in the description of the patent application (see point 11.8, above) rather as a general listing of possible diseases in which agents of the invention could well be applied based on the generally known functions of neurotrophins, rather than a specific disclosure of the use of antibodies, directed against the extracellular part of sortilin for the inhibition of the binding of specifically pro-neurotrophins to a member of the Vps10p-domain receptor family in the treatment of neurological diseases or disorders. Accordingly, the application does not disclose a clear and unambiguous link between the use of any particular antibody and any particular disease group.

14. The appellant has extensively argued that in view of the disclosure of the patent application the skilled person reading the specification would inevitably be lead to conclude that the inhibition of the binding of proNGF to sortilin resulted in an inhibition of the effects of pro-neurotrophin. In this respect the board notes however that, for the assessment of the compliance of a claim with the requirements of Article 123(2) EPC, it is not of relevance which technical teaching is rendered obvious to a skilled person by a disclosure, but rather the subject-matter which the skilled person in fact can derive from this disclosure in a clear and unambiguous manner, be it implicitly or explicitly (see e.g. decision T 329/99 of

5 April 2001, see point 4 of the reasons for the decision).

15. The board concludes therefore that in the light of the above analysis no teaching can be derived from the patent application as filed which in a clear and unambiguous manner links the inhibition of the binding of specifically pro-neurotrophin selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5 to a receptor of the Vps10p-domain receptor family (sortilin) to the treatment of neurological diseases or disorders.

16. Accordingly, claim 1 does not comply with the requirements of Article 123(2) EPC.

First auxiliary request - Article 123(2) EPC

17. The above considerations apply *mutatis mutandis* to claim 1 of the first auxiliary request. The appellant agreed to this finding. Accordingly, this point needs no more reasoning. Claim 1 therefore does not comply with the requirements of Article 123(2) EPC.

Second auxiliary request - admissibility into the proceedings

18. The second auxiliary request (see section VI, above) was filed by the appellant in response to the board's communication in preparation for the oral proceedings. In this communication the board had indicated its preliminary opinion that the claim requests as filed with the statement of the grounds for appeal did not remedy the deficiencies under Article 123(2) EPC invoked by the examining division in its decision.

19. The subject-matter of claim 1 of this request is, unlike claim 1 of the main and auxiliary requests, substantially different from the former requests in that it concerns the use of antibodies directed against the extracellular part of sortilin for inhibiting the binding of pro-neurotrophins to sortilin. The claim is now devoid of any direct reference to a specific disease to be treated or activity to be impaired by the inhibition of the binding.

20. The board considers that such an attempt by the appellant to overcome the objections under Article 123(2) EPC could have been made during the first instance stage of these proceedings, or upon filing the appeal at the latest. If only for these reasons it would be within the discretion of the board to hold the second auxiliary request inadmissible pursuant to Article 12(4) RPBA.

21. Furthermore, the board doubts the straightforward allowability of the claims of this second auxiliary request as their subject-matter appears to raise questions to be dealt with *inter alia* under Article 53(c) EPC as well as under Article 57 EPC. Accordingly, and also in view of Article 13 RPBA, the board decides not to admit the second auxiliary request into the proceedings.

22. In view of the above findings, the board decides that the appeal cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar | The Chairman

P. Cremona | C. Rennie-Smith