Intellectual Property Office

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PATENTS ACT 1977

APPLICANT	EOS Neuroscience, Inc. and Wake Forest University Health Sciences, Inc.
ISSUE	Whether patent application GB1219768.7 complies with Sections 1(1)(b) and 4A of the Patents Act.
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision concerns patent application GB1219768.7 entitled *"Methods and compositions for decreasing chronic pain"* in the names of EOS Neuroscience, Inc. and Wake Forest University Health Sciences, Inc. (hereafter the applicant). More specifically, it concerns whether the invention claimed in this application is inventive as defined in Section 1(1)(b) and Section 3 of the Patents Act 1977 (hereafter the Act); and whether it relates to a non-patentable method of treatment or diagnosis as defined in Section 4A of the Act.

Background

2 This application was filed under the provisions of the Patent Cooperation Treaty (PCT) on 05 April 2011, claiming an earliest priority date of 05 April 2010, and was initially published as WO 2011/127088 on 13 October 2011. On entering the national phase in UK, it was subsequently re-published as GB 2492719 on 09 January 2013.

3 Between May 2015 and October 2017, there was an extensive correspondence, including proposed amendments, between the applicant and the examiner dealing with this case. While an initial objection under novelty was successfully addressed by the applicant, the examiner has maintained throughout that the invention (as variously claimed) lacks inventiveness over the cited prior art. Latterly, the examiner has also argued that the application relates to a non-patentable method of treatment or diagnosis, specifically, a method of surgery.

4 In the Agent's letter dated 20 October 2017, the applicant requested a decision from a senior officer based on the papers currently on file. In addition to the set of claims already on file (referred to as Main Request claims dated 11 October 2017), the applicant also included a first auxiliary amended claim set and a second auxiliary amended claim set. The applicant asked that the senior officer consider each of these three claim sets in turn as part of their decision. The applicant argued that each of these claim sets were inventive over the cited documents and did not relate to a non-patentable method of surgery.

5 As set out in the pre-hearing report of 26 October 2017, the examiner considered that the main request claim set and both auxiliary request claim sets lack an inventive step and that the main request claim set and the first auxiliary request claim set each relate to a non-patentable method of surgery.

6 The matter came before me for a decision based on the papers on file. Senior examiner Dr Simon Grand acted as assistant to the Hearing Officer on this case.

The Application

7 This application falls in the field of optogenetics and nociception. Optogenetics combines techniques from optics and genetics to control and monitor the activities of cells, such as neurons (nerve cells), in living tissue. Opsins are a group of light-sensitive proteins, which use a chromophore to convert photons of light into electrochemical signals. Microbial opsins, also referred to as Type I opsins, form ion channels or proton/ion pumps and are activated directly by light. They are used in optogenetics to switch on or off neuronal activity. Such opsins include channelrhodopsin (ChR2), halorhodopsin (NpHR), and archaerhodopsin (Arch). Expression of such proteins is controlled using a light source of appropriate wavelength.

8 Neurons use the electrical currents created by depolarization to generate communication signals (e.g., nerve impulses) in the body. Such cells use rapid depolarization to transmit signals throughout the body and for various purposes, such as motor control (e.g., muscle contractions), sensory responses (e.g., touch, hearing, and other senses) and computational functions (e.g., brain functions). By facilitating or inhibiting the flow of positive or negative ions through the cell membranes, such cells can be briefly depolarized, depolarized and maintained in that state, or hyperpolarized. Control of this depolarization process can be beneficial for a number of different purposes, including treatment of disease and related pain experience where control of visual, muscular or sensory function is important. Light-sensitive protein channels, pumps, and receptors permit millisecond-precision optical control of cells. Although light-sensitive proteins in combination with appropriate wavelengths of light can be used to control the flow of ions through cell membranes, the targeting and delivery of such proteins to cells requires additional steps related to the specific diseases, disorders, or pain circuits of interest.

9 Nociception[1] is the sensory nervous system's response to certain harmful or potentially harmful stimuli. In nociception, intense chemical (e.g., chili powder in the eyes), mechanical (e.g., cutting, crushing), or thermal (heat and cold) stimulation of sensory nerve cells, called nociceptors, produces a signal that travels along a chain of nerve fibres, or neurons, via the spinal cord to the brain. Nociception triggers a variety of physiological and behavioral responses and usually results in a subjective experience of pain in sentient beings, such as humans. Pain is the *experience* and nociception is the *process* or mechanism that produces that experience.

10 The patent application at issue relates to compositions and methods for the selective silencing of neurons in pain pathways using a combination of inhibitory light-sensitive protein gene transfer and wavelength specific illumination. It discloses a recombinant nucleic acid comprising a nucleic acid fragment encoding a light-sensitive protein and a regulatory nucleic acid fragment that is capable of directing selective expression of the light sensitive protein in cells of the dorsal root ganglion (DRG). The DRG is found at the base of individual branching spinal nerves, very close to the spinal cord itself, where it forms a little bulge at the base of each spinal nerve. The application discloses that neuropathic pain in a subject can be treated by controlling the neural activity in a DRG cell expressing the claimed recombinant nucleic acid using an optical source to modulate the expression of the light-sensitive protein.

11 The claims as originally filed included independent claims to the recombinant nucleic acid, a composition comprising the recombinant nucleic acid, a recombinant virus comprising the recombinant nucleic acid, a host cell derived from a cell transfected with the recombinant virus, a method of optically controlling neural activity, a method of relieving neuropathic pain and the corresponding second medical use claims.

The Claims

12 As noted above, the applicant's letter dated 20 October 2017 referred to three claim sets; a main request, a first auxiliary request and a second auxiliary. Each claim set comprises one independent claim relating to the use of a recombinant nucleic acid substance with certain features for the treatment of neuropathic pain in a subject.

13 Claim 1 of the main request is defined as:

> *A recombinant nucleic acid for use in a method of relieving neuropathic pain, wherein the recombinant nucleic acid comprises:*
>
> *a nucleic acid fragment encoding a light-sensitive protein; and*
>
> *a regulatory nucleic acid fragment that is capable of directing selective expression of said light-sensitive protein in a cell of the central nervous system (CNS);*
>
> *and wherein the method comprises:*

[1] from Latin *nocere* 'to harm or hurt'. The term "*nociception*" was coined to distinguish the physiological process (nervous activity) from pain (a subjective experience)

expressing in a cell of the dorsal root ganglia in a subject the recombinant nucleic acid; and

controlling the neural activity of said cell with a light beam to modulate the activity of said light-sensitive protein, thereby relieve the neuropathic pain in said subject.

14 Claim 1 of the first auxiliary request is defined as:

A recombinant nucleic acid for use in a method of relieving neuropathic pain, wherein the recombinant nucleic acid comprises:

a nucleic acid fragment encoding a light-sensitive protein; and

a regulatory nucleic acid fragment that is capable of directing selective expression of said light-sensitive protein in a cell of the ***dorsal root ganglia (DRG)****; and*

wherein said recombinant nucleic acid is expressed in the cell of the DRG of a subject*, and*

the expressed light-sensitive protein is modulated by a light beam to control neural activity of said cell*, thereby relieving the neuropathic pain in said subject.*

15 Claim 1 of the second auxiliary request is defined as:

A recombinant nucleic acid for use in a method of relieving neuropathic pain, wherein the recombinant nucleic acid comprises:

a nucleic acid fragment encoding a light-sensitive protein; and

a regulatory nucleic acid fragment that is capable of directing selective expression of said light-sensitive protein in a cell of the central nervous system (CNS);

and wherein the method comprises:

expressing in a cell of the dorsal root ganglia in a subject the recombinant nucleic acid; and

controlling the neural activity of said cell with a light beam ***delivered transdermally to modulate the activity of said light-sensitive protein****, thereby relieve the neuropathic pain in said subject.*

I have indicated (in bold) the differences between the main, first auxiliary and second auxiliary claim sets.

16 Based on the letter filed by the applicant, I consider that the main amended claim set is the latest claim set currently on file. The first auxiliary and second auxiliary claim sets have been provided as possible alternatives to consider should I find that the main amended claim set is not acceptable. In my decision below, I will consider the

main amended claim set and only refer to the first auxiliary and second auxiliary claim sets to consider if they provide a useful way forward in terms of possible amendments.

Issues to be decided

17 I will consider first whether the invention as claimed relates to a non-patentable method of treatment by surgery. If I find that it does, then I need proceed no further. However, if I find that it does not, I will go on to consider whether the invention, as claimed, lacks an inventive step.

18 In dealing with inventive step, I will consider the main amended claim set and move on to consider the first and second auxiliary claim set, in that order, only if I consider it appropriate to do so.

19 If I decide that one of the current amended claim sets meets the requirements of the Act, then the application will need to be remitted to the examiner for completion of the examination process. As noted in the official report dated 26 October 2017, the question of whether the amended claim set and the description are in conformity will have to be addressed prior to grant.

Method of Treatment by Surgery – Section 4A

The Relevant Law

20 The section of the Act dealing with methods of treatment or diagnosis by surgery is section 4A. This states:

> *4A.-(1) A patent shall not be granted for the invention of-*
>
> *(a) a method of treatment of the human or animal body by surgery or therapy, or*
> *(b) a method of diagnosis practised on the human or animal body.*
>
> *(2) Subsection (1) above* ***does not apply to an invention consisting of a substance or composition for use in any such method****.*
>
> *(3) In the case of an invention consisting of a substance or composition for use in any such method, the fact that the substance or composition forms part of the state of the art shall not prevent the invention from being taken to be new* ***if the use of the substance or composition in any such method does not form part of the state of the art****.*
>
> *(4) In the case of an invention consisting of a substance or composition for a specific use in any such method, the fact that the substance or composition forms part of the state of the art shall not prevent the invention from being taken to be new* ***if that specific use does not form part of the state of the art****.*

Parts (2), (3) and (4) of Section 4A make it clear that the exclusion does not apply to substances or compositions which are for use in the treatment of the human or animal body. Part (3) covers the first medical use of the substance or composition, Part (4) covers the second and any subsequent medical use of the substance or composition.

21 Not all methods of treatment of the human or animal body are excluded; only those that fall within the scope of the terms "therapy" or "surgery". In the present case we are concerned with methods of treatment by surgery.

22 Section 130 of the Act, entitled 'Interpretation', makes clear, in part 7 of this section, that section 4A is one of those sections of the UK Act identified *"to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provision of the European Patent Convention … have in the territories to which those conventions apply*".

23 When construing a section of the Act identified by Section 130(7) to have, as nearly as practicable, the same effects as the corresponding provisions of the European Patent Convention (EPC), the House of Lords in *Merrell Dow Pharmaceuticals Inc. v H.N. Norton & Co Ltd* [1996] RPC 6, made it clear that the courts in the United Kingdom must have regard to the decisions of the European Patent Office (EPO). Lord Hoffmann said (at page 82): "*These decisions are not strictly binding upon the courts in the United Kingdom but they are of great persuasive authority; first, because they are decisions of expert courts (the Boards of Appeal and Enlarged Board of Appeal of the EPO) involved daily in the administration of the EPC, and secondly, because it would be highly undesirable for the provisions for the EPC to be construed differently in the EPO from the way they are interpreted in the national courts of a contracting state*".

24 The provision under the current version of EPC which corresponds to Section 4A of the Act is Article 53(c)[2].

25 A definition of what constitutes a method of surgery is provided by decision G-01/07 of 15 February 2010 (*Treatment by surgery*/MEDI-PHYSICS)[3] from the EPO Enlarged Board of Appeal (EBoA), hereafter G-1/07:

> *"A ... method ... which comprises or encompasses an invasive step representing a substantial physical intervention on the body which requires professional medical expertise to be carried out and which entails a substantial health risk even when carried out with the required professional care and expertise, is excluded from patentability as a method for treatment of the human or animal body by surgery pursuant to Article 53(c) EPC"*

26 Section 4A(1) states that a patent shall not be granted for an invention of a method of treatment of the human or animal body by surgery (or therapy or a method of diagnosis) performed on the human or animal, but unlike section 1(2) of the Act, there is no proviso in this section of the Act that methods are only excluded "*to the extent*

[2] The current version of the EPC entered into force in 2000 and replaced the previous version of the EPC which entered into force in 1973. The corresponding Article under EPC 1973 was Article 52(4).

[3] For full text of this decision see here; published in Official Journal of the European Patent Office (hereafter OJEPO) 2011, 134.

that a patent or application for a patent relates to that thing as such". In G-1/07, the EPO EBoA, confirming a body of earlier EPO case law relating to Article 54(5), held that any multi-step method which includes a step comprising a method of surgery (or a method of therapy) is excluded from patentability.

27 In decision G-2/08[4], the EPO EBoA confirmed that it is possible to have a claim for a new use of a known substance or composition for treatment of the human or animal body that relates, for example, to a new dosage regime or to a new mode of administration, the novelty of the claim does not have to rely on a new therapeutic use. This was also confirmed by the UK courts in *Actavis v Merck*[5].

28 The examiner has drawn attention to two EPO TBoA decisions, T-0566/07 of 17 May 2010 (*Vital dyes for vitreo-retinal surgery/MELLES*)[6], hereafter T-566/07, and T-1075/09 of 21 October 2013 (*Treatment of anovulatory women*/LABORATOIRES SERONO)[7], hereafter T-1075/09. He has argued that these decisions mean that, if a claim to a second medical use also encompasses a method of surgery step, then the inclusion of this excluded step renders the whole claim non-patentable. This is the basis of his objection to the main request claim set and the first auxiliary claim set

29 The Applicant has referred to EPO TBoA Decisions T-0009/04 (KONINKLIJKE PHILIPS ELECTRONICS), T-1102/02 (MAQUET CRITICAL CARE) and T-663/02 (PRINCE) in support of their view that the claim in question is a second medical use claim and, as all the steps referred to in the claim are an essential part of that use, they do not encompass a separate method step that involves surgery.

Analysis

Main request claim set

30 I note that the same objection is raised by the examiner in relation to the claims of the main request and the first auxiliary request. This is summarised by the examiner as follows (see official pre-hearing report dated 26 October 2017):

> *"My objection is derived from decisions T-0566/07 and T-1057/09 as discussed by the latest Examination Guidelines for Patent Applications relating to Medical Inventions in the Intellectual Property Office. According to these guidelines an objection may be raised against a second medical use claim if the claimed use involves a surgical, therapeutic or in vivo diagnostic step which is not in fact directly connected to the administration of the agent in question. It is my opinion that the step 'controlling the neural activity of said cell with a light beam to modulate the activity of said light-sensitive' is not related to the administration of the recombinant nucleic acid*

[4] G-02/08 (Dosage regime / ABBOTT RESPIRATORY), published in OJEPO 2010, 456.

[5] *Actavis UK Ltd v Merck & Co. Inc.,* [2008] EWCA Civ 444 (21 May 2008); see [2008] RPC 26; for full-text of decision, see here.

[6] T-0566/07 of 17 May 2010, see full-text of decision here.

[7] T-1075/09 of 21 October 2013, see full-text of decision here.

but is considered to be an entirely separate method step which would require surgery to implement."

31 Whereas the applicant argues (see letter from applicant dated 20 October 2017):

> "*In the Main Request, although method steps are recited, they are not directed towards a method per se, but are instead in connection with what is achieved by the administered recombinant nucleic acid. We submit that it is clear that the expression of the recombinant nucleic acid encoding a light-sensitive protein a cell in the DRG, and the light-sensitive protein's ability to be modulated by a light beam, are in fact properties of the recombinant nucleic acid. A surgical step of implanting is not encompassed in the present claim. The use of a light beam is directly connected to the administration of the recombinant nucleic acid since only when a light beam is present is the required therapeutic effect achieved. Thus, we believe that the case law cited by the Examiner does not apply to the present claims."*
>
> *"Regardless of the above, we respectfully disagree with the Examiner's assertion in [….], where it is stated that the invention is not directed to a change in the internal working of a device or any interaction between the device and an operator. We submit that any control of neural activity of a cell with a light beam carried out using an implanted device must require some form of interaction between the device and an external operator in order to control the light switch. It is apparent that claim 1 does not relate to the implantation of a device. Thus, we submit that the claims of the Main Request are in compliance with Section 4A."*

32 In order to determine whether or not proposed claim 1 of the main request or claim 1 of the first auxiliary request includes a method of surgery step, it is necessary to construe the respective claim and consider if all the elements of that claim relate to the substance (or composition) of the method being used to achieve the medical use claimed. As the applicant notes, the claims in question relate to a "*recombinant nucleic acid for use in a method of relieving neuropathic pain…* (my emphasis in underline)" and then they go on to define that method. If there is any doubt that the method steps do not define the medical use of the recombinant nucleic acid and so could include a separate surgery step then, as first stated in EPO TBoA decision T-0182/90[8], "*a single surgical step in a method for treatment of the human or animal body confers surgical character to the method*" and thus the claims relate to a non-patentable subject matter.

33 EPO TBoA decision T-0009/04 notes:

> "*The opinion G 1/04 instructs that medical method claims must be narrowly interpreted."*

34 Of the various EPO decisions referred to by the examiner and the applicant, I consider that the most relevant is TBoA decision T-0566/07. This decision concerned a Swiss-type claim to the "*Use of at least one vital dye for the manufacture of a composition for staining a retinal membrane in an eye to visually distinguish the retinal membrane from the underlying retina in a method for performing retinal membrane removal*". The

[8] Published OJEPO, 1994

TBoA considered that the claim differed from the Swiss-type format in that it broke down into several applications that the dye is to be used in, i.e.:

a) for staining a retinal membrane in an eye

b) for distinguishing the retinal membrane from the underlying retina

c) in a method for performing retinal membrane removal.

35 The TBoA then evaluated how the various applications related to one another and to the dye composition. They concluded that there was a 'causal link' between features a) and b) as b) further specified the staining of the retinal membrane, but that c) was a separate activity. In regard to the latter point, the TBoA stated "*it is reasonable, both technically and in view of the teaching of the contested patent, to regard the staining procedure as a first activity, which is then followed by a second surgical method.*" This second separate activity was not drafted as a Swiss-type claim and was thus excluded from patentability under Article 53(c) EPC.

36 I consider that the fact that the form of claim considered in T-0566/07 was a Swiss-type claim, whereas I am now considering a second medical use claim of the type introduced with EPC 2000, does not have any material effect on the substantive issue I have to decide. What is pertinent is whether, or not, the claims at issue include a surgical step as a separate activity from the new medical use of the substance in question.

37 Considering Claim 1 of the main request (see above), the claim has two parts – a first part which relates to a substance, i.e. a recombinant nucleic acid, and a second part which relates to a method that uses that substance. The method steps are:

a) expressing in a cell of the dorsal root ganglia in a subject the recombinant nucleic acid;

b) controlling the neural activity of said cell with a light beam to modulate the activity of said light-sensitive protein.

38 Were this the extent of the claim then, I would be in agreement with the examiner because a) and b) would clearly be separate activities and I would then need to determine whether b) defined non-patentable matter because "*controlling the neural activity with a light beam*" might implicitly include surgical implantation of an optical source as suggested at paragraphs [0051] and [0143] of the description of this application. However, this is not the whole of the claim. The first part starts with "*A recombinant nucleic acid for use in a method of relieving neuropathic pain*" where said nucleic acid comprises two components and is for use in the steps of the method highlighted above. This is significant because, as noted by the applicant, "*use of a light beam is directly connected to the administration of the recombinant nucleic acid since only when a light beam is present is the required therapeutic effect achieved*". Thus the present situation differs from that considered in T-0566/07 because the therapeutic effect which constitutes the medical use of the claimed invention (the treatment of pain) only occurs when the light is caused to shine. Without the lihjt is there is no treatment. I conclude therefore that there is no separate second activity which could be excluded as a method of surgery. Instead, if "*controlling the neural*

activity of said cell with a light beam" encompasses any surgical step, it would be an integral part of the claimed medical use. Thus, using the term favoured by the TBoA in T-0566/07, I consider that there is a 'causal link' between method steps (a) and (b) referred to above. As a consequence, the claims of the main request do not, in my view, contravene section 4A of the Act.

First auxiliary request claim set

39 Having reviewed the claims of the first auxiliary request also, I consider that the same reasoning applies and that these claims also would not contravene Section 4A of the Act.

Second auxiliary request claim set

40 In the pre-hearing report dated 26 October 2017, the examiner stated that while he maintained an objection against the claims of the main request and first auxiliary request, he had no objection in respect of section 4A against the claims of the second auxiliary request.

41 I agree with the examiner that there is no issue with the second auxiliary request claim set with regards to section 4A of the Act. Claim 1 relates to "*controlling the neural activity of said cell with a light beam delivered transdermally to modulate the activity of said light-sensitive protein".* Regardless of any of the other considerations outlined above in regard to the construction of such claims, the second auxiliary request claim indicates that the light acting on the light-sensitive protein is provided transdermally (i.e. through the skin). Thus, no implantation of a light-producing device is necessary or envisaged. Any other interpretation would be perverse in my view.

Inventive Step – Section 1(1)(b)

The Relevant law

42 Whether the invention involves an inventive step concerns sections 1(1)b and 3 of the Act.

43 Section 1 of the Act reads as follows:

> *1(1). A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say:*
>
> *(a) …;*
> *(b) It involves an inventive step;*
> *(c) …;*
> *(d) ….*

44 Section 3 of the Act, entitled 'Inventive Step' reads:

An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of Section 2(2) above (and disregarding Section 2(3) above).

45 Section 2(2) of the Act, which refers to the state of the art, reads:

The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.

46 The approach to assessing inventive step is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 ("*Windsurfing*") as modified by Jacobs LJ in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588 ("*Pozzoli*"). This approach involves the following steps:

(1) (a) Identify the notional "person skilled in the art"
(b) Identify the relevant common general knowledge of that person;
(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

47 Sections 125(1) and 125(3) of the Act concern claim construction. They read:

"(1) For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly

….

(3) *The Protocol on the Interpretation of Article 69 of the European Patent Convention (which Article contains a provision corresponding to subsection (1) above) shall, as for the time being in force, apply for the purposes of subsection (1) above as it applies for the purposes of that Article."*

Analysis

48 In the objection raised by the examiner, they contend that the application as filed does not have an inventive step over the disclosure in WO 2010/011404 A1, referred to hereafter as WO404. I note that the applicant of the present application, EOS Neuroscience Inc., is also the holder of WO404.

49 I note that in the correspondence between the applicant and the examiner there appears to have been some confusion on the part of the applicant as to the relevance of the 'other citations' referred to by the examiner. These 'other citations' identified by the examiner in relation to inventive step were cited to illustrate the common general knowledge (CGK) of the 'person skilled in the art', see, for example, the official examination report dated 4 July 2017 and the pre-hearing report dated 26 October 2017. I will consider the relevance of these documents further below.

50 To determine whether (or not) the present application has an inventive step over the prior art, I will follow the approach set out in *Windsurfing/Pozzoli* as mentioned above.

Step (1)(a): Identify the notional "person skilled in the art"

51 I am unclear to what extent the examiner and the applicant are in agreement with respect to the nature of the person skilled in the art. I note that the examiner defines the person skilled in the art as "*a biochemist with an interest in the treatment of pain*. The applicant states *"[t]he skilled person here, in view of the Examiner's comments, appears to understand the field of pain circuits, pain molecular biology, optogenetics and gene therapy*". I do not know if the latter comment means that the applicant does actually agree with the examiner's assessment.

52 However, on the basis of the material before me, I consider that the "person skilled in the art" is represented by a team of scientists with an interest in the treatment of pain, in particular, chronic or neuropathic pain. This team will have a knowledge and understanding of the molecular biology of pain including the types of pain and how they arise (e.g., nociceptive pain, inflammatory pain, neuropathic pain, chronic pain), and how pain is recognised and dealt with in the body (e.g., pain circuits, transmission of messages about pain in the body through the nervous system). This team would also have a knowledge and understanding of gene therapy and optogenetics, including how to prepare nucleic acids encoding light sensitive proteins that are operatively linked to regulatory sequences.

53 I use the term 'pain circuit' to refer to the process of how pain information is modulated within the peripheral nervous system (PNS) and central nervous system (CNS) and how pain is transmitted and controlled within the body.

Step (1)(b): Identify the relevant common general knowledge of that person

54 Given that there appears to have been some confusion regarding the common general knowledge (CGK) in this case, I consider that it is appropriate to remind ourselves what the CGK is. As the IPO Manual of Patent Practice, at para 3.29 indicates, "*Common general knowledge can, perhaps, be summarised as a part of the mental equipment or mental toolkit needed so as to be competent in the art concerned. It is what makes the skilled person skilled.*"

55 In *Raychem Corp's Patents* [1998] RPC 31, Laddie J, as he then was, explained CGK as follows:

> *"The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material he has memorized and has at the front of his mind. It includes all that material in the field he is working in which he knows exists, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art. This does not mean that everything on the shelf which is capable of being referred to without difficulty is common general knowledge nor does it mean that every word in a common text book is either. In the case of standard textbooks, it is likely that all or most of the main text will be common general knowledge. In many cases common general knowledge will include or be reflected in readily available trade literature which a man in the art would be expected to have at his elbow and regard as basic reliable information."*

This knowledge is kept up to date, includes material that is known in the UK , and, as noted by Sales J in *Teva v AstraZeneca*[9], the relevant CGK can include material that would be readily identified by searches of databases of published journal articles.

56 The CGK has to be distinguished from what is public knowledge. It is not enough for the matter to be known or disclosed, say in a patent specification or a journal article that is widely read or published in a journal that is widely circulated[10]. Something more is required. A piece of knowledge will become general and part of the common knowledge when "*it is generally known and accepted without question by the bulk of those who are engaged in the particular art, in other words, when it becomes part of their common stock of knowledge relating to the art.*[13]

57 In establishing what the CGK is, it is necessary to distinguish it from the state of the art. Although a feature, item or concept may be well-known to a few experts or within certain companies or organisations, it is not part of the CGK unless it can be shown to be known to and accepted more widely than that, i.e., by the large majority of those skilled in the art[11]. As noted by Aldous LJ in *Beliot v Valmet*:

> *"It has never been easy to differentiate between common general knowledge and that which is known by some. It has become particularly difficult with the modern ability to circulate and retrieve information. Employees of some companies, with the use of libraries and patent departments, will become aware of information soon after it is published in a whole variety of documents; whereas others, without such advantages, may never do so until that information is accepted generally and put into practice. The notional skilled addressee is the ordinary man who may not have the advantages that some employees of large companies may have. The information in a patent specification is addressed to such a man and must contain sufficient details for him to understand and apply the invention. It will only lack an inventive step if it is obvious to such a man.*

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9 *Teva UK Limited & Anor v AstraZeneca AB* [2014] EWHC 2873 (Pat), see especially para 60

10 *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd* [1972] RPC 457, see especially para 482-483

11 *Beloit Technologies Inc & Anor v Valmet Paper Machinery Inc & Anor.,* [1997] EWCA Civ 993; reported as [1997] RPC 489

It follows that evidence that a fact is known or even well-known to a witness does not establish that that fact forms part of the common general knowledge. Neither does it follow that it will form part of the common general knowledge if it is recorded in a document."

58 As noted above, in addition to WO404, the examiner referred to a number of 'other citations' as part of his inventive step objection in order to demonstrate the CGK of the person skilled in the art. For the avoidance of doubt, and given the confusion experienced by the applicant in dealing with these citations, the examiner has made clear that these additional documents are examples only that show the CGK of the relevant skilled person (see for example, official examination report dated 7 July 2017).

59 In the examiner's view, the skilled team would, based on their CGK, be aware that:

- one is able to treat pain by targeting cells of the DRG (as demonstrated, for example, by US 2010/284977 A1;

- that substance P is involved in pain perception and is expressed from cells of the CNS such as DRG cells, (as demonstrated, for example, in both the Journal of Comparative Neurology, Vol 497 No 1, 2006, "*Time Course of Substance P Expression in Dorsal Root Ganglia Following Complete Spinal Nerve Transection*", pages 78-87, and in the Journal of Neurophysiology, Vol 91 No 5, 2004,"*Characterization of Wide Dynamic Range Neurons in the Deep Dorsal Horn of the Spinal Cord in Preprotachykinin - A Null Mice In Vivo*", pages 1945-1954).

60 The applicant has argued that the examiner has not given appropriate recognition to the complexity of neuropathic pain and how it develops; that substance P is broadly expressed in the body and not just in DRG cells; and that there is not such a straight-forward link between substance P and DRG or between substance P and neuropathic pain as proposed by the examiner. In their official response, dated 11 October 2017, the applicant refers to three documents: WANG, COSTIGAN and LATREMOLIERE – all journal articles, including two review articles - to illustrate that the CGK is not quite so straightforward as proposed by the examiner[12,13,14].

61 I have considered the documents identified by the examiner and by the applicant to illustrate the CGK in this field. On the basis of the information provided therein and bearing in mind the above discussion regarding what constitutes CGK, I will set out

[12] Wei Wang., Wen Wang., Xiaopeng Mei, Jing Huang, Yanyan Wei, Yayun Wang, Shengxi Wu*, & Yunqing Li; (2009); "*Crosstalk between Spinal Astrocytes and Neurons in Nerve Injury-Induced Neuropathic Pain*", PLoS ONE 4(9): e6973. doi:10.1371/journal.pone.0006973 (referred to as WANG).

[13] Michael Costigan, Joachim Scholz, & Clifford J. Woolf; *Annu Rev Neurosci*. 2009 volume 32; "Neuropathic Pain: A Maladaptive Response of the Nervous System to Damage": pages 1–32 [doi:10.1146/annurev.neuro.051508.135531] (referred to as COSTIGAN).

[14] Alban Latremoliere & Clifford J. Woolf; *J Pain*. 2009; Volume 10(9), September: "Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity"; pages 895–926 [doi:10.1016/j.jpain.2009.06.012] (referred to as LATREMOLIERE).

below what I consider to be some of the key points regarding the common general knowledge (CGK) of the skilled team.

The Nervous System and Pain

62 The nervous system comprises two main parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the brain and spinal cord and the PNS comprises all the nerves outside those structures. The PNS is divided into the somatic nervous system and the autonomic nervous system. The nervous system comprises two types of cells: neurons, which transmit information through electrical and chemical signals; and glial cells, which support and protect neurons. Neurons have a cell body which includes the nucleus of the cell and long narrow fibre like extensions from the cell body, called axons, which travel from the periphery (tissue, organs, muscles) to the spinal cord.

63 The somatic nervous system is involved in the detection of noxious stimuli. It consists of sensory (or *afferent*) neurons, which transmit impulses from the PNS to the CNS and motor (or *efferent*) neurons, which transmit impulses from the CNS to the PNS. Various types of neurons are responsible for transmitting information about different types of stimuli from the PNS to the CNS. These include Aα, Aβ, Aδ and C fibres which are known as primary sensory neurons: Aα and Aβ fibres transmit information about low intensity innocuous stimuli such as touch, pressure and vibration; Aδ fibres transmit information about non-painful cold, painful mechanical and heat stimuli; and C fibres transmit information about noxious heat and mechanical or chemical stimuli.

Nociception and Nociceptors

64 A *nociceptor* is a sensory neuron that responds to damaging or potentially damaging stimuli by sending “possible threat” signals to the spinal cord and the brain. If the brain perceives the threat as credible, it creates the sensation of pain to direct attention to the body part, so the threat can hopefully be mitigated; this process is called nociception.

65 In mammals, nociceptors are found in any area of the body that can sense noxious stimuli. External nociceptors are found in tissue such as the skin (cutaneous nociceptors), the corneas, and the mucosa. Internal nociceptors are found in a variety of organs, such as the muscles, the joints, the bladder, the gut, and the digestive tract. The cell bodies of neurons are usually located in the dorsal root ganglia or, in the case of nerves for the face, the cell bodies are located in the trigeminal ganglia. The axon extends at one side of the cell body to the spinal cord where it terminates in the dorsal horn, and at the other side towards the periphery (tissue, organs, muscles) where it terminates in branches to form a receptive field. Such afferent nociceptive neurons (located in the periphery) are also referred to as first order neurons.

66 The dorsal horn of the spinal chord is a complex, multi-layered structure of neurons in which different fibres terminate at different layers. The cells of the dorsal horn are divided into physiologically distinct layers, referred to as laminae. The different primary sensory neuron types form synapses in different laminae - Aδ neurons form synapses in laminae I and V, C fibres connect with neurons in lamina II, Aβ fibres connect with lamina I, III, & V. These sensory neurons use either glutamate or substance P as the neurotransmitter to transmit nerve signals across the synaptic cleft and so communicate with the neurons on the other side of the synapse which are part

of the CNS. After reaching the specific lamina, within the spinal cord, the first order neurons connect with second order neurons, also referred to as wide dynamic range (WDR) cells. The second order neurons then send their information via two pathways to the thalamus in the brain: via either the dorsal column medial-lemniscal system or the anterolateral system. The latter is reserved for pain sensation, the former handles non-painful sensation. Upon reaching the thalamus, the information is processed in the ventral posterior nucleus and sent to the cerebral cortex in the brain, via nerves in the posterior limb of the internal capsule. As there is an ascending pathway to the brain that initiates the conscious realisation of pain, there is also a descending pathway which modulates pain sensation. The brain can request the release of specific hormones or chemicals that can have analgesic effects which can reduce or inhibit pain sensation. The area of the brain that stimulates the release of these hormones is the hypothalamus.

Dorsal Root Ganglion/Ganglia (DRG)

67 The Dorsal Root Ganglion (DRG), also known as the spinal ganglion, or posterior root ganglion, lies close to the base of each individual branching spinal nerve, close to the spinal cord itself (but not in the spinal cord). The cell bodies of the sensory afferent neurons (i.e., Aα, Aβ, Aδ and C neurons) that bring information from the periphery to the spinal cord, are located in the DRG. The ganglion forms a little bulge at the base of each spinal nerve.

68 The cell bodies that make up the DRG are, in effect, bifurcated with one branch extending toward the periphery and the other branch extending, via the dorsal horn, to the spinal cord.

69 While the DRG are a part of the system of the PNS, they lie very close to the spine and spinal cord, and therefore to the CNS, which means that they are an important connection between the two. The neurons that make up the DRG transmit messages of pain and touch very quickly from the periphery to the spinal cord, rather than all the way back to the brain and this shorter distance allows for a very rapid response to a painful stimulus.

Neurotransmitters and Substance P

70 Neurons communicate with each other using neurotransmitters. A neurotransmitter is a chemical messenger that carries, boosts, and balances signals between neurons and between a neuron and other cells such as a muscle cell or gland cell. The endings of nerve cells have specific protein receptors which bind neurotransmitters and cause the membrane to depolarise. This, in turn, leads to the opening of voltage-gated sodium channels, allowing the influx of Na^+ ions into the cell, which causes an action potential to be set up. The action potential is transmitted along the length of the axon (past the cell body) to the axon terminal where it depolarises the membrane, leading to the opening of voltage-gated calcium channels. Calcium ions (Ca^{2+}) flood into the terminal through these channels and, in turn, trigger the release of neurotransmitters into the synaptic cleft between neurons. The neurotransmitters bind to receptors in the membrane of the adjacent neuron, either exciting or inhibiting it.

71 There are a number of different families of neurotransmitters, including amino acids (such as glutamate), monoamines (such as dopamine), purines (such as adenosine),

gasotransmitters (such as nitric oxide) and peptides. Substance P is a member of the peptide family of neurotransmitters. Although it was discovered in 1931, its role as a neurotransmitter was not unravelled until the 1950s. It is a polypeptide that consists of 11 amino acid residues and, given its role, is also referred to as a neuropeptide or neuromodulator. It is one of a number of polypeptides that form the tachykinin neuropeptide family which all have similar and related properties. Neurokinin A is also a member of this family.

72 Substance P amplifies or excites most cellular processes. It is present in neurons located throughout the CNS that play a role in pain, stress, and anxiety. It is also present in the limbic system of the CNS, including the hypothalamus and amygdala, which mediates emotional behaviour. In addition to pain perception, it also has a role in dealing with stress and anxiety

73 Substance P is present in the nervous system and gastrointestinal tract where, in addition to acting as a neurotransmitter in the transmission of signals from pain receptors (transmitting sensory information from periphery to the CNS - a sensory neuron action), it also modulates the contraction of smooth muscle and dilation of blood vessels (transmitting response information from the CNS to the periphery – a motor neuron action).

74 The receptor for substance P, the neurokinin-1 (NK-1) receptor, is also distributed over cytoplasmic membranes of many cell types (neurons, glial cell, endothelial cells of capillaries and lymphatic vessels, fibroblasts, stem cells, white blood cells) in many tissues and organs.

75 Substance P coexists with the excitatory neurotransmitter glutamate in primary sensory afferents that respond to painful stimulation. Substance P and other sensory neuropeptides can be released from the peripheral terminals of sensory nerve fibres in the skin, muscle, and joints.

Types of pain

76 A number of different types of pain are generally recognised.

(a) Nociceptive/Inflammatory pain.

77 Nociceptive pain is the most common type of pain and is caused by the detection of noxious or potentially harmful stimuli by the nociceptors around the body. In the normally functioning human body, nociception plays a bio-protective role: it alerts the brain to the presence of a noxious stimulus so that appropriate avoidance measures may be taken. Noxious stimuli such as heat, extreme cold, intense mechanical pressure and chemicals stimulate the Aδ and C nociceptors. Those afferent sensory neurons then transmit information about these stimuli via the spinal cord for onward transmission to the brain where they are perceived as pain and an appropriate response is decided. This is referred to as *nociceptive pain*.

78 *Inflammatory pain* is a type of nociceptive pain. The inflammatory response to an injury involves the release of various chemical mediators, e.g. cytokines which increase the sensitivity of nociceptors, causing pain both at the site of injury and in the surrounding

area. Inflammatory pain also plays a bio-protective role in that it promotes healing by causing the body to rest or isolate the injured part so as to minimise contact with it.

79 One of the features of nociceptive/inflammatory pain is that it resolves with treatment of the underlying cause. For example a swollen finger will no longer hurt once the inflammation has died down; gout pain will be resolved by treating the gout; post-operative pain will usually resolve once the surgical wound has healed; and the pain associated with sunburn will subside once the burn has subsided.

(b) Neuropathic pain.

80 In contrast to nociceptive/inflammatory pain, *neuropathic pain* does not serve a bio-protective function and it is pathological. Neuropathic pain is associated with damage to the neurons in the body (i.e., neuropathy), following an infection or injury to the area, which results in messages of pain being sent to the CNS and brain regardless of noxious stimuli. Neuropathic pain is caused by damage to the somatic nervous system itself. It can be defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system. When the lesion or dysfunction occurs in the PNS it is referred to as peripheral neuropathy resulting in peripheral neuropathic pain; when it occurs in the CNS, it is referred to as central neuropathy and results in central neuropathic pain or central pain. This lesion or dysfunction causes changes both at the site of damage and centrally in the CNS, typically, resulting in neuronal hyper-excitability, i.e. increased sensitivity of the neuron to the particular type of noxious stimulus. Whereas nociceptive pain subsides either when the noxious stimulus is removed or when the originating injury heals, neuropathic pain usually persists for long periods, sometimes for years or for life, even though the causative factor is no longer present. It is thus chronic rather than acute in nature.

81 The symptoms of neuropathic pain are quite different to those associated with nociceptive/inflammatory pain. Patients report a different quality of pain - they use terms such as “raw”, “gnawing”, “burning’ and “deep aching” to describe such pain – and also report shooting or electric-shock like pains. Unlike nociceptive/ inflammatory pain, there is often a delay in the onset of neuropathic pain after the initiating injury (although this is not always the case). Given its chronic nature, neuropathic pain is debilitating and it is often accompanied by other conditions or disorders such as depression, anxiety, sleep disturbance, social isolation, reduced employment prospects and drug misuse.

82 Example of neuropathic pain include pain resulting from infections e.g. herpes zoster (shingles), HIV, Lyme disease; or pain caused by injury, e.g. post-amputation phantom limb pain, diabetes, multiple sclerosis, cancer treatment.

83 The skilled team will thus be aware that the origin and treatment of pain is complex. The treatment of pain requires an understanding of how nociception works in terms of detecting and responding to noxious stimuli and how that is experienced as pain. Perception and experience of pain in humans is complex and is influenced by factors such as prior experience of, and the context within which, a noxious stimulus occurred. In addition, the pain response is also influenced by a person’s emotional state. The response to pain thus varies from subject to subject and the symptoms of neuropathic pain can also vary between two subjects in the same diagnostic category.

84 The skilled team would also be familiar with the techniques of optogenetics, i.e. those techniques necessary to prepare a recombinant nucleic acid comprising a fragment encoding a light sensitive protein, such as an opsin, and a fragment that is capable of directing expression of the light sensitive protein. They would be familiar with the types of light-sensitive proteins that can be used, such as the microbial opsins, channelrhodopsin (ChR2), halorhodopsin (NpHR), and archaerhodopsin (Arch) and how to activate them directly by light to switch on and off neuronal activity. This team would also be aware that it is necessary to direct the light sensitive protein to the nerve cells of interest and would thus be aware of the methods and techniques necessary to do so. They would be aware that experimentation would be necessary to prepare the recombinant nucleic acid, deliver it to the site of interest and show that it is being expressed.

Step (2): Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

85 The examiner identifies the inventive concept of claim 1 of the main request as a recombinant nucleic acid for use in a method of treating neuropathic pain, the recombinant nucleic acid comprising a fragment encoding a light sensitive fragment and a regulatory nucleic acid fragment capable of directing expression of the light sensitive protein in a cell of the DRG and controlling the neural activity of this cell with light.

86 I do not find anything in the correspondence from the applicant to suggest that they disagree with this characterisation of the inventive concept proposed by the examiner. I too agree with this assessment.

87 Two further points are relevant to the identification of the inventive concept, in my view. Firstly, in the application as filled (see para [0003] for example), it is stated that there is a need for "*selective methods of targeting signalling pathways for treatment of pain"*. In particular, the debilitating chronic pain that results from traumatic and non-traumatic injuries, nerve lesion, amputation, diabetes, HIV/ AIDS, alcoholism, and nerve compression. Such chronic pain can have a significant adverse effect on the quality of life and productivity of the person affected. The examples referred to are those that commonly result in neuropathic pain. Hence, I consider that the reference to chronic pain would be understood as a reference to neuropathic pain.

88 Secondly, I note that in claim 1 of the main request, currently on file, the recombinant nucleic acid for use in the method of the claim comprises *a "nucleic acid fragment encoding a light-sensitive protein; and a regulatory nucleic acid fragment that is capable of directing selective expression of said light-sensitive protein* ***in a cell of the central nervous system (CNS)*** (my emphasis added in **bold**)*",* yet the claim goes on to say that the method comprises "*expressing in a cell of the dorsal root ganglia in a subject the recombinant nucleic acid*". While, the latter expression may be a slightly unusual way to characterise this element of the claim, I consider that what it is referring to is that the recombinant nucleic acid of the method is expressed in a cell of the dorsal root ganglia (DRG). As I have mentioned above in my summary of some of the ley points of the CGK, the DRG are part of the PNS and not the CNS. Thus, I consider that there is, at the very least, an inconsistency, if not an error, in claim 1 of the main

request, as currently on file. Based on the correspondence between the applicant and examiner referred to above and my consideration of the application, I conclude that the invention is directed to the expression of the claimed nucleic acid in cells of the DRG of the PNS (peripheral nervous system).

Step (3): Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed

89 The examiner considers that WO404 represents the state of the art for the purposes of establishing whether or not the present application has an inventive step.

90 WO404 is directed toward methods for controlling, regulating and/or driving specific neural circuits so as to mediate natural neural responses and the perception and control of these responses which can be used in therapy. It discloses gene based therapies to treat diseases that are not based on treating the underlying genetic mutation but rather are focused on controlling, regulating or driving the specific neural circuits that mediate the natural responses. The description in WO404 refers to the use of the various compositions and methods disclosed therein to treat a range of diseases and disorders of the peripheral and central nervous system. The detailed examples given in this application refer to diseases and disorders of the eye.

91 The patent discloses a recombinant nucleic acid comprising a nucleic acid encoding a light-sensitive protein, such as channelrhodopsin (ChR2) operatively linked to a regulatory sequence or fragment of a promoter as the means to exert such control. The promoter may be a cell specific promoter such as GRM6 which is a regulatory sequence of metabotropic glutamate receptor 6 (mGluR6), a G-protein coupled receptor. This is specifically expressed in photoreceptor cells in the eye, specifically, the ON bipolar cells of the retina. Alternatively, the promoter may be a non-cell specific promoter such as the CBA promoter (see Figure 7, para [0096] and Examples 5 and 6) which is made up of a viral enhancer (a CMV immediate early enhancer) and a beta-actin (CBA) promoter of bovine or chicken origin.

92 A number of viral vector constructs based on adeno-associated virus, in particular, serotype 5 (AAV5), serotype 7 (AAV7) or serotype 8 (AAV8), were prepared as means to deliver these light-sensitive protein-encoding polynucleotides to a retinal cell, e.g. AAV7-GRM6-ChR2; AAV5-CBA-ChR2; AAV8 mutant Y733F-GRM6-ChR2. They were prepared as injectable solutions and applied to retinal cells in mice by injection directly into the vitreous of the eye or into the sub-retinal space of the eye (see Example 1). These treated mice exhibited different types of blindness based on different gene mutations (*rdl, rdl6, rho*) which cause photoreceptor disease.

93 Using a test based on the time taken to find a target illuminated by a light source, mice treated with a channelrhodopsin (ChR2) containing construct, such as those mentioned above, showed they were able to learn using visual information. This indicated that expression of the ChR2 containing protein results in, at least, some restoration of visual function (see Examples 5 and 6 and Figure 12).

94 Although a large number of diseases and disorders are referred to in WO404 as capable of being treated using the compositions and methods of the patent, I note that only those that affect photoreceptor cells, such as the retina of the eye, were exemplified. WO404 discusses how to transduce a retinal bipolar cell (such as ON or OFF retinal bipolar cells; rod and cone bipolar cells) by introducing a vector comprising an exogenous nucleic acid comprising a light-sensitive protein operatively linked to a regulatory sequence.

95 For the purposes of the present case, the examiner has identified paragraph [00114] of WO404 as being particularly relevant. This paragraph reads:

> *"[00114] In another aspect,* ***the compositions and methods of this invention are utilized to treat peripheral injury, nociception, or chronic pain****.* ***Nociception (pain) for prolonged periods of time can give rise to chronic pain and may arise from injury or disease to visceral, somatic and neural structures in the body.*** *Although the range of pharmacological treatments for neuropathic pain has improved over the past decade, many patients do not get effective analgesia, and even effective medications often produce undesirable side effects.* ***Substance P (SP) is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain.*** *It has been theorized that it plays a part in fibromyalgia. A role of substance P in nociception is suggested by the reduction in response thresholds to noxious stimuli by central administration of NK1 and NK2 agonists. Pain behaviours induced by mechanical, thermal and chemical stimulation of somatic and visceral tissues were reduced in the mutant mice lacking SP/NKA. In one embodiment light-sensitive proteins can silence the activity of over-active neurons (i.e., substance P expressing peripheral neurons) due to peripheral injury or chronic pain using NpHR or eNpHR. NpHR/eNpHR can be genetically targeted to substance P expressing cells using the substance P promoter sequence. In another embodiment light-sensitive proteins enhance the activity of neurons that are inactive due to peripheral injury or chronic pain."*
> (my emphasis added in **bold**)

96 WO404 would have been worthy of the attention of the skilled team with an interest in treating neuropathic pain using optogenetc techniques. The description in WO404 refers to use of the constructs and methods disclosed to treat peripheral injury, nociception or chronic pain by targeting substance P. While it does not refer to neuropathic pain explicitly I consider that the skilled team would note the reference to chronic pain, fibromyalgia and silencing over-active neurons and the related discussion in this paragraph and be satisfied that this approach could be used for treating neuropathic pain. I consider that the reference to chronic pain would be understood to include neuropathic pain.

97 While I acknowledge that this is not part of the main disclosure in relation to targeting disorders associated with the retina, it is more than just part of a broad list of possible applications where the invention of WO404 might be useful. The additional information provided in this paragraph is sufficient in my view to suggest to the skilled team that it could be useful to treat neuropathic pain using an optogenetc approach combining a

light sensitive protein with a regulatory fragment that is targeted at substance P. Substance P is worth exploring because of its possible role in fibromyalgia which gives rise to neuropathic pain and because there is a "*reduction in response thresholds to noxious stimuli*" when agonists to Neurokinin 1 and Neurokinin 2 receptors – which both bind substance P to different degrees – are administered centrally[15].

98 Furthermore W0404 does indicate that halorhodopsin (NpHR), or an enhanced form of this opsin, eNpHR, can be used to "*silence the activity of over-active neurons (i.e., substance P expressing peripheral neurons) due to peripheral injury or chronic pain*", the opsin being targeted to Substance P by including the substance P promoter sequence in the construct.

99 However, I note that there is no reference in WO404 to targeting cells in the DRG. The examples in WO404 show the targeting of optical neurons and the description refers to targeting neurons of the peripheral nervous system.

Step (4): Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

100 The examiner, referring to the whole document and paragraph [00114] in particular, states that the skilled team would be taught that "*light-sensitive proteins can silence the activity of over-active neurons due to peripheral injury or chronic pain using NpHR or eNpHR. NpHE/eNpHR can be genetically targeted to substance P expressing cells using the substance P promoter sequence*". Using its CGK, the skilled team would know to target cells which produce substance P and which are known to be involved in nociception pathways. Thus, the skilled team would consider it logical to target cells of the dorsal root ganglia (DRG). Therefore, in the examiners view claims 1-7 and 9-12 of the main request are considered to lack an inventive step over the document WO404.

101 Furthermore, in relation to the specific promoters referred to in claim 8 of the main request - PPT and Scn10a, the examiner points out that these are both known to drive the expression of genes in the DRG as a response to a pain stimulus, with PPT being a precursor to substance P[16]. Therefore, in the examiner's view, it would be obvious to the skilled team, to use these promoters to specifically express the recombinant nucleic acid described in WO404 in cells which produce substance P and are known to be involved in nociception. Therefore, claim 8 is considered to lack an inventive step.

102 On the other hand the applicant argues that, without knowledge of the invention as claimed, it is a leap too far to imagine that the skilled worker, reading the one paragraph from WO404 ([00114] quoted above) as part of the whole disclosure of this

[15] Although the main endogenous receptor for substance P is Neurokinin 1 receptor (NK1-receptor, NK1R), it also binds to other neurokinin receptors, such as neurokinin 2 receptor (NK2-receptor, NK2R) which belong to the tachykinin receptor sub-family of metatrophic G-Protein Coupled Receptors (GPCRs)s.

[16] PPT is pre-pro-tachykinin-A

document, would consider that treatment of neuropathic pain by targeting DRG cells would be obvious or likely to succeed. They argue thus:

> *"There is no suggestion in WO 2010/011404 that the method could be feasible in DRG cells in particular. Nor is there any mention of treating neuropathic pain or any data to substantiate this.*
>
> *"The Examiner asserts that optogenetics is a well-established field of study and therefore there would be no bias against the skilled person believing they would have a reasonable chance of success of performing the method on DRG cells in view of the teaching in WO 2010/011404. However, the skilled person would know that due to differences in the nature of the different cell types, their pliability and receptivity to manipulation could also differ greatly. Without extensive experimentation, the skilled person would not reasonably expect that the method would apply in the same effective way in DRG cells as it would on retinal cells."*

In the view of the applicant, the skilled team reading WO404 is presented with methods looking to restore some sort of function to eyes by applying these recombinant nucleic acid techniques alongside which are listed a series of avenues in which the same sort of techniques might prove useful under the heading "conditions amenable to treatment" see paragraphs [00106]-[00120]. Viewed without knowledge of the present invention, why would the skilled team necessarily choose to target DRG cells specifically as a means to treat neuropathic pain when it is known that substance P is expressed in a number of different cell types (not just DRG cells)?

103 The examiner considers that the skilled person would be aware from their CGK that Substance P is produced by the cells of the DRG and so targeting cells of the DRG would be an obvious step for a team interested in treating neuropathic pain. I consider that this is an over-simplification of the situation.

104 While, as I have mentioned above, I am satisfied that the skilled team would be aware that targeting substance P would be a useful approach to targeting neuropathic pain. I do not consider that it would be obvious to conclude that this could be achieved by targeting cells of the DRG. The DRG comprises the cells bodies of primary afferent nociceptors that transmit sensory information about pain from the periphery back to the spinal cord. While substance P is a known neurotransmitter that plays a role in nociception, it is also involved in other biological processes in the body and it is also found in the cells of the CNS as well as the PNS. In my view, the skilled team, aware of the possibility that Substance P could be targeted as a means to treat neuropathic pain, would not conclude, as a logical next step, that the light sensitive protein with associated regularity fragment directed to Substance P should be targeted at cells of the DRG. There would be no motivation from the disclosure and the CGK to focus on DRG cells specifically.

105 In seeking to decide if the invention as claimed is obvious, the examiner has considered "is it obvious to try?" and has come to the conclusion that it is. The Court of Appeal has recently (*Actavis Group PTC EHF & Anor v Teva UK Ltd & Ors* [2017] EWCA Civ 1671) warned against over-elaboration of obvious-to-try, Floyd LJ stating that "*there are some steps which can be characterised as so routine that the skilled person would carry them out simply because they are routine"*. In such a situation,

these steps are obvious to try. However, I do not consider that the necessary steps in the present case are "so routine". I note the statement of Kitchen LJ in *Medimmune v Novartis*[17]:

> "*One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.***"**

106 I am satisfied that the skilled team would consider that targeting substance P has a sufficient prospect of success to merit investigation, however I do not think that this also means that they would conclude that the construct comprising the fragment encoding for the light sensitive protein and the fragment targeting substance P should thus be directed at the neurons that make up the DRG. While I accept that it is known that substance P is produced in the neurons of the DRG, it is also present in neurons of the CNS and in those that carry out motor functions as well as sensory functions.

107 Thus I am satisfied that that the skilled team would not be led to target cells of the DRG based on their CGK and the disclosure of WO404. As a result, I conclude that the invention as claimed does possess an inventive step.

Conclusion

108 Taking account of all of the above, I consider that the main request claim set, as currently on file, does not define a non-patentable method of therapy by surgery under section 4A of the Act. For the same reason, I am also satisfied that the first auxiliary request claim set does not define a non-patentable method of therapy by surgery under section 4A of the Act.

109 For the avoidance of doubt, I agree with the conclusion of the examiner that the second auxiliary request claim set does not define a non-patentable method of therapy by surgery under section 4A of the Act

110 In addition, I consider that the application as claimed in the main request claim set, currently on file, does not lack an inventive step under section 1(1)(b) of the Act. However, claim 1 of this claim set lacks clarity in so far as it refers to targeting cells in the 'central nervous system' but then identifies these target cells as cells of the dorsal

[17] *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd & Ors* [2012] EWCA Civ 1234.

route ganglion which are, as noted already, part of the peripheral nervous system. I note that the first auxiliary request claim set does not appear to suffer from this lack clarity as it refers to the targeting cells of the DRG throughout.

111 I am remitting the application back to the examiner to complete the examination process for this application. In this regard, I note that the period, under Section 20 of the Act, for determining whether this application complies with all the requirements of the Act expired on 20 November 2017. Thus, the question for the examiner to consider is whether the application was in order for grant at this date.

Appeal

112 Any appeal must be lodged within 28 days after the date of this decision.

Dr L CULLEN

Deputy Director, acting for the Comptroller