INTELLECTUAL PROPERTY OFFICE

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PATENTS ACT 1977

APPLICANTS	Yung-Hsiang Liu, Wing-Yee Chan, Yuan-Feng Lin
ISSUE	Whether patent application GB1010504.7 complies with Sections14(3), 14(5)(c) and 18(5)
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1. The application in question in this case is a divisional application lodged on 22 June 2010 that claims the filing date, 1 June 2006, of the parent application, GB0610836.9. In turn, the parent application claims priority from Taiwanese patent application TW094118270 which has a priority date of 2 June 2005. The parent application was granted on 15 December 2010 and published as GB2426765B.

2. The issues to be resolved in relation to this case are sufficiency and lack of support under Section 14, and conflict with the granted parent application under Section 18, of the Patents Act 1977 (the "Act"). These matters came before me at a hearing on 6 January 2011.

3. The compliance date for the application was 22 January 2011. Since the hearing, a further two month discretionary extension to the compliance date until 22 March 2011 has been agreed under rule 108(3) of the Patents Rules 2007 (the "Rules").

4. The applicants were represented by Mr Adrian Bradley of Cleveland, assisted by Mr Nick Bennett. Also present at the hearing were my assistant, Dr Jim Houlihan, and the examiner, Dr Rowena Dinham. In addition, two patent examiners observed the hearing for training purposes.

5. No skeleton argument was filed prior to the hearing. Mr Bradley presented two different sets of claims for discussion at the hearing on an informal basis.

These were referred to as ‘version 1’ and ‘version 2’. In a letter following the hearing, dated 19 January 2011, the applicant indicated that ‘version 1’ is intended to replace the claims presently on file. This letter also indicated that the applicant had not yet decided on the status of ‘version 2’ of the claims but did confirm that it was not intended to replace those claims currently on file. It may be submitted formally at a later date in the event of an appeal.

6. At the beginning of the proceedings, Mr Bradley referred to the examiner’s most recent report, dated 17 December 2010, which set out the issues that were outstanding on the application and acknowledged that these were objections under sufficiency, lack of support and conflict with the granted parent application. Mr Bradley asked whether it was appropriate to consider ‘version 1’ of the amended claims first which he considered were relevant to the examiner’s objections, especially in relation to the potential conflict with the parent under section 18(5).

7. I considered that it was best to proceed by considering the lack of support and sufficiency issues in relation to the set of claims dated 16 November 2010 which were those currently on file and were the subject of the examiner’s above mentioned report dated 17 December 2010. The amended claims referred to as ‘version 1’ could then be considered, if necessary, in the context of those objections and in view of the section 18(5) objection.

8. This decision is therefore given in respect of the set of claims dated 16 November 2010 which consists of 19 claims; claims 2-19 being dependent on claim 1. I also considered informally whether ‘version 1’ of the claims brought to my attention at the hearing offered a fruitful way to address the deficiencies identified in this decision (see below). I did not consider ‘version 2’ of the claims brought to my attention at the hearing.

The Application

9. The application entitled the “*The Preparation of Multipotent stem cells and the use thereof*” lies in the field of producing stem cells for clinical applications which have the broad capacity to give rise to many body tissues from a particular cell type (multipotent stem cells are abbreviated to “P-stem cells” in the application and in this decision). The progressive differentiation of cells with specific characteristics and functions (phenotypes) from precursor cells which are less differentiated is well established in contemporary biology. In contrast, this patent application concerns de-differentiation, which as the term suggests, is the process by which cells with more generic potential are derived from cells of a narrower, more particular function, in effect, working backwards to the normal biological process.

10. In particular, the application relates to the generation of autologous (from the same individual) multipotent stem cells from CD14+ peripheral monocytic cells by treating the cells with a modulator of protein kinase C (PKC). Monocytes represent about 10% of the white cell population in humans. PKC is an enzyme that plays a central role in signal transduction by controlling other proteins

through phosphorylation. Signal transduction is the mechanism by which signals are transmitted from outside the cell to intracellular molecules which then generate a response.

11. The statement of invention reads *"in the first aspect, the present invention provides a P-stem cell obtainable by exposing a mononucleated cell to a protein kinase C modulator"*.

12. The original set of claims filed with the application were all based on claim 1 which reads as follows:

> "*A P-stem cell is generated from one of mononucleated cells treated with a protein kinase C (PKC) modulator for activating intracellular* PKC-β2 *of the mononuclear cells*"

13. As a result of correspondence and amendments from the applicant, in response to objections raised by the examiner in official reports dated 8 July 2010 and 25 October 2010, claim 1 under consideration at the hearing (submitted on 16 November 2010) reads as follows:

> "*A process for multipotent stem cell generation comprising the treatment of a mononucleated cell with a PKC modulator which only activates the intracellular* PKC-β2 *iso-form"*

14. It is also necessary for the purpose of this decision to consider claims 2 and 7, in particular, as these claim two mechanisms for activating the PKC-β2 iso-form.

15. Claim 2 reads:

> "*The process of claim 1 wherein the treatment comprises the steps of pre-treating a mononucleated cell with Go6976 followed by incubation with Bryostatin-1.*"

16. Claim 7 reads:

> "*The process of claim 1 wherein the treatment comprises the step of exposing a mononucleated cell to a combination of GM-CSF and SDF-1."*

17. The other dependant claims, claims 3-6 dependant on claim 2 and claims 8-19 dependant on claim 7, detail additional parameters, conditions and uses. As these were not referred to specifically in the hearing they are not formally considered here.

18. I will now briefly outline the examples in the application which are relevant to the question of support and sufficiency and which were specifically drawn to my attention by Mr Bradley.

19. Practice Example 1.1 details a method for culturing mononuclear cells with sequential doses of Go6976 and Bryostatin-1. In particular, I note that these

cells were incubated with Go6976 for 30 minutes and then Bryostatin-1 was added. The cells were then cultured for 15-21 days.

20. Practice Example 9 describes a Western Blot analysis. The results are shown in Figures 3 and 4. Figure 3 shows the constitutive expression of a number of PKC iso-forms, including PKC-β2. Figure 4 shows that the sequential use of Go6976 and Bryostatin-1 of Example 1.1 activates only the PKC-β2 iso-form. This result is particularly important to this decision. I accepted that it provides evidence for the specific activation of the PKC-β2 iso-form by the treatment of mononuclear cells by incubating them with Go6976 for 30 minutes followed by Bryostatin-1.

21. Example 9 concludes with the assumption that it demonstrates that activation of PKC-β2 is capable of inducing differentiation of P-stem cells. Practice Example 1-3 says "*in the above Practice Examples, the PKC modulator is not limited to Go6976, Bryostatin-1, GM-CSF, SDF-1, collagen, or fibronectin. Substances modulating PKC activity are capable of inducing the generation of P-stem cells from their progenitor cells*" but I note there is no evidence in the application in respect of the factors other than Go6976/Bryostatin-1 or GM-CSF/SDF-1.

22. I also outline Practice Example 1.2 which is relevant to claim 7. In this Example, mononuclear cells were treated with a combination of GM-CSF and SDF-1 for 3-7 days "*after which the mononucleated cells were fully differentiated into P-stem cells*". I note in particular that Practice Example 1.1 details the sequential application of Go6976 and Byrostatin-1 to the mononuclear cells, whereas Practice Example 1.2 describes the addition of a combination of factors, GM-CSF/SDF-1, in a single application.

23. Practice Examples 3 to 8 describe methods for the differentiation of P-stem cells into certain different cell types and refer to the identification of the differentiated cells in Figures 2A-F. In particular, Practice Example 3 describes methods for the differentiation of P-stem cells into osteoblasts; Practice Example 4 refers to the identification of osteoblasts in Figures 2A and 2B. Similarly, Practice Example 5 describes the differentiation of P-stem cells into another bone-related cell type, chrondocytes, and Practice Example 6 describes the identification of chrondocytes in Figures 2C and 2D. Practice Example 7 refers to the differentiation of neurons from P-stem cells and Practice Example 8 describes the identification of neurons in Figures 2E and 2F.

24. The second paragraph of Practice Example 8 claims that P-stem cells can differentiate into a variety of cells, for example, skeletal myocytes, cardiomyocytes, renal cells, pulmonary cells, hepatocytes, and adipocytes, and it describes a set of conditions and factors to differentiate P-stem cells into each of these cell types. There is no accompanying data or figures to show the actual production of these different cell types.

25. The description suggests, by implication, that because the cell population generated by the sequential application of Go6976 and Bryostatin-1 in Practice Example 1.1 is capable of differentiating into the different cell types shown in

Practice Examples 3 to 8, the Go6976/Bryostatin-1 treatment of mononuclear cells generates P-stem cells. However, the specification does not actually state from which of Practice Examples 1.1 and 1.2 the P-stem cells were derived.

The Law

26. This case concerns whether or not the claims at issue are sufficient, supported by the description and whether or not they relate to the same invention as the parent application. These are provided for by Sections 14(3), 14(5)(c) and s18(5) of the Act, respectively, which read as follows:

Section 14

…….

(3) The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.

……

(5) The claim or claims shall –

(a) …;

(b) …;

(c) be supported by the description; ..

(d) ….

Section 18

…….

(5) Where two or more applications for a patent for the same invention having the same priority date are filed by the same applicant or his successor in title, the comptroller may on that ground refuse to grant a patent in pursuance of more than one of the applications.

27. The Examiner cited five authorities in relation to support and sufficiency which are as follows:

*Mycogen Plant Science Inc. EPO Technical Board of Appeal [1996] T694/92 (hereafter "*Mycogen")

Biogen Inc. v Medeva PLC [1997] RPC 1 (hereafter "Biogen")

Schering Biotech Corp.'s Application [1993] RPC 249 (hereafter "Schering")

American Home Products Corporation v Novartis Pharmaceuticals UK LTD [2001] RPC 8 (hereafter "AHP v Novartis")

DSM NV'S Patent [2001] RPC 35 (hereafter "DSM")

During the hearing Mr Bradley referred to a decision of the EPO Technical Board of Appeal in relation to conflict of claims between a divisional and its parent application as follows:

Komag Inc. EPO Technical Board of Appeal [2000] T587/98 (hereafter Komag*)*

Argument and Analysis

The Examiner's Arguments

28. The examiner's arguments are laid out clearly in her official report of 17 December 2010 already mentioned above and which I have summarised below.

29. The examiner accepted that the application provides evidence for the specific activation of the PKC-β2 iso-form by the sequential application of Go6976 (a well known PKC-α, PKC-β1 and PKC-γ inhibitor) and Bryostatin-1 (a wide-ranging PKC agonist) to mononuclear cells over a 24 hour period. The evidence of Example 9 and Figure 4, taken together with Practice Example 1.1, led her to conclude that it "*can reasonably be assumed that the activation of the* PKC-β2 *forms part (my emphasis) of the signalling pathway utilised during the generation of the multipotent stem cells from mononucleated cells by Go6976/Bryostatin-1 treatment*".

30. She did not, however, accept that the mechanism of action of the combination of GM-CSF and SDF-1 was through the same intracellular signalling pathways utilised by the cells treated with Go6976 and Bryostatin-1 as there was no evidence for this in the application. Notably, she says "*it cannot be assumed that the action of GM-CSF and SDF-1 is via the specific activation of PKC*-β2".

31. The examiner went on to say "*Consequently there is no evidence to suggest that the activation of PKC-β2 is an essential step in the generation of the multipotent stem cells, rather it forms part of the signalling cascade initiated by the pre-treatment of mononuclear cells with Go6976 for 30 minutes, followed by incubation with Bryostatin-1 for at least a further 24 hours".*

32. She also surmises that the differences in culture conditions in the GM-CSF/SDF-1 experiment (Practice Example 1.2) and Go6976/Bryostatin-1 (Practice Example 1.1) "*suggest that the process for multipotent stem cell generation from mononuclear cells by GM-CSF and SDF-1 is via a different signalling cascade".* I would agree with the examiner that the GM-CSF/SDF-1 experiment opens the possibility that derivation of P-stem cells from mononuclear cells could take place through a mechanism that does not involve PKC-β*2*.

33. In relation to claim 7, the examiner concludes "*the assertion in claim 7 that the use of GM-CSF and SDF-1 can activate PKC-β2 alone is wholly unsupported".*

34. The nub of the examiner's argument in relation to support is that there is only *"support for a process for multipotent stem cell generation comprising the treatment of a mononucleated cell where the PKC modulator is Go6976 followed by incubation with Bryostatin-1".* Consequently, she asserts that claim 1 lacks support across its whole breadth and cites *Schering* and *Mycogen* in doing so.

35. The examiner also considered that the claims are insufficient and cited *Biogen* to support her argument. In her view the facts in *Biogen* could be compared to the facts of the present application. She says "*the technical contribution in Biogen was in how the product was made, and therefore for sufficiency purposes, the process of making the product is important and therefore the patentee was only entitled to claim one way of making it. The same can be said of the present application; the invention is in the process of making the cells, not in the cells per se*".

36. In the context of insufficiency, the examiner also cites *AHP v Novartis* and *DSM* in respect of the issue of undue burdens of experimentation and expense and labour to perform an invention. She considered that a skilled person, seeking to perform the process of claim 1, would be under an undue burden in needing to "*go to the expense and labour of trying to ascertain which PKC modulators specifically activate the PKC-β2 iso-form in mononuclear cells and go on to produce a multipotent stem cell, other than the use of Go6976 followed by Bryostatin-1*".

37. The examiner considered that claim 2 of the present claims is coterminous with claim 1 of the granted parent application which reads "*A process for multipotent stem cell generation comprising the steps of pre-treatment of a mononucleated cell with Go6976 followed by incubation with Bryostatiin-1*". She concluded that present claim 1 therefore falls foul of section 18(5) of the Act.

The Applicants' Arguments

38. In opening, Mr Bradley reiterated claim 1 and said that it was "*common ground between the parties that the specification details how to identify a PKC modulator which only activates the PKC-β2 iso-form*" which is illustrated by Practice Example 9. He said that Go6976 followed by Bryostatin-1 was one example of activation and pointed to Practice Example 1 which showed dedifferentiation of mononucleated cells to give multipotent stem cells using these compounds.

39. Mr Bradley submitted that Practice Example 9 "*contains a methodology to determine whether or not a set of conditions activates solely the PKC-β2 iso-form*".

40. Mr Bradley said the general question to be answered is - what is the scope of claim the applicants are entitled to? I agree. He submitted that the applicants' technical contribution to the art goes far beyond the Go6976/Bryostatin-1 experiment. He said that to deny that is to deny the applicants a reasonable reward for their inventive contribution. His argument was that they should be entitled to claim all obvious variations of the teaching which they were claiming. He submitted that if the claims were limited to a certain set of conditions it would be easy for a third party to circumvent the claims while taking advantage of the actual technical contribution.

41. A central limb of Mr Bradley's argument, which he submitted at various times during the proceedings, was that the "kernel" or "essence" of the invention is as follows:

> "*the actual technical contribution is the surprising observation that only the PKC-β2 iso-form is implicated in the dedifferentiation of mononucleated cells*".

He emphasized that this had not been disclosed in the prior art. He pointed out that a finding of other ways of generating multipotent stem cell which did not involve PKC-β*2* activation would not fall within the scope of the claims in question.

42. Another key limb of Mr Bradley's submissions is that the application did not impose an undue burden on the addressee to identify compounds which could specifically activate PKC-β*2*. He said the application "*provides a complete set of instructions for identifying whether any particular set of conditions would have the result*" of activating PKC-β*2* and that this gave the reader the ability to determine whether or not a particular reagent would activate PKC-β*2* by routine trial and error.

43. Mr Bradley's submission that the disclosure of "*one particular condition for this activation*, *PKC-β2"* was sufficient to support the generality of claim 1 neatly focused the question of both support and sufficiency. Looking at this question in more detail, I would say that one has to take account of two issues in coming to an answer:

    (i) does the disclosure of a method for generating multipotent stem cells from mononuclear cells **which involves the activation of the PKC-β2 iso-form by the sequential application of two particular reagents** (emphasis added) provide sufficient support for the full breadth of the claim relating to the modulation of the PKC-β*2* iso-form *per se*; and

    (ii) does the application provide a sufficient disclosure to enable the full breadth of the invention to be performed?

44. Mr Bradley considered the relevance of the authorities which the examiner cited to support her objections. He contended that the present case was distinguished from *Schering* because that case concerned structural features, whereas the present case concerned features that define the function of the

invention and provided specific guidance of how perform the invention. He also said that while it was accepted in *Schering* that some of the structural features claimed would not work, there is no evidence in the present case that PKC-β*2* modulators would not work.

45. *Schering* was one of the first cases in the field of biotechnology before the Patents Court to consider the question of support under the Act. The claim at issue in *Schering* related to a vector with a cDNA insert capable of producing a protein possessing multi-lineage cellular growth activity (MCGF) or nucleotide sequences of at least 75% homology to the specified cDNA. The *Schering* specification discussed at some length, and in some detail, various interleukins possessing MCGF activity; however only one, IL3, was exemplified. In his finding of lack of support, Aldous J commented that some of the features claimed "*included within the claim a large number of sequences which have not been explored…….and which, if used, might produce polypeptides having the claimed activity but not as yet known and certainly not described in the description*". Aldous J distinguished between theoretical references in the description which he termed "*verbal support*" from the substance of the invention described in the patent. While he accepted that claims do not have to be restricted to a specific embodiment, the width of the claim must be properly supported by the description of the invention in the specification.

46. For clarification, I questioned whether claim 1 in suit defined a result, not how to achieve that result. Mr Bradley said that a functional definition, a PKC-β*2* "modulator", is perfectly legitimate which I was content to accept.

47. In his analysis of *Mycogen*, Mr Bradley said that it was a case where the broad principle was known and there were serious doubts about whether the whole ambit of the invention claimed would work, a point reinforced by Mr Bradley's assistant, Mr Bennett, when asked to comment. In contrast, Mr Bradley submitted, the broad principle in the case in suit, i.e. that PKC-β*2* activation results in dedifferentiation of mononuclear cells, was not known in the art and therefore the applicants were entitled to a correspondingly broad claim. He also said that in the present case there was no evidence that serious doubts existed about this activation mechanism.

48. I did not entirely agree with Mr Bradley's analysis of this decision. While it is true that *Mycogen* indicates that the existence of serious doubts about whether the invention can be worked across the full range of application of the invention is an important consideration, I do not consider that the situation in relation to the present case can be distinguished in as clear cut a manner as Mr Bradley suggests.

49. I do not consider that the absence of negative data correlates with proof of the broad principle as suggested by Mr Bradley. It could simply mean that such evidence does not presently exist rather than it cannot exist. As the saying goes "*the absence of evidence is not the evidence of absence*". A fundamental point made in *Mycogen* reads: "*the guiding principle is always that the skilled person should after reading of [sic] the description, be able to readily perform the invention over the whole area claimed without undue burden and without*

needing inventive skill". A question also posed in *Mycogen* is whether more than one example and more technical details were necessary to provide support for a claim where the essence of the invention was the achievement of a given technical effect by known techniques in different applications. It is also worth noting that in *Mycogen*, the EPO Technical Board of Appeal considered the claims lacked support despite the existence of "*formal support*" in terms of general statements in the description. A critical feature in their decision was the lack of actual examples in relation to the wider ambit of the claim beyond a single example. This supports the distinction referred to earlier in *Schering* in relation to theoretical references in the description or "*verbal support*" as distinct from the substance of the invention described in the patent.

50. Furthermore, my view of *Mycogen* is that the general principle had not necessarily been established; it was not immediately clear in the art at that time that the broad principle of genetically modifying a plant with the general features claimed would work; the prior art taught the general principle which *Mycogen*'s application took a step further. To me, there are clear similarities to the process claim at issue here. In the case in suit the prior art teaches that the derivation of multipotent stem cells from mononuclear cells by using a PKC modulator was known and the present case indicates that PKC-β*2* specifically is involved in this process. It is not immediately certain, however, that the sequential application of two specific modulators of PKC-β*2 extends to a* general principle that activation of PKC-β*2* by any method involving modulators of that protein would generate multipotent stem cells from mononuclear cells.

51. In response to my questions relating to *Mycogen*, Mr Bradley said that the "*entire inventive activity resides in the observation that only the PKC*-β*2 iso-form is necessary*" for dedifferentiation. He contended that this was equivalent to a selection invention over the prior art and "*a principle of general applicability*".

52. In concluding his submissions in relation to support Mr Bradley referred to the GM-CSF/SDF-1 experiment in relation to claim 7. It is appropriate for me to deal with this issue at this juncture because Mr Bradley acknowledged the examiner's objection in relation to these claims which he agreed to withdraw.

53. The experiment in Practice Example 1.2 showed the production of multipotent stem cells but, as discussed above, the examiner contended this did not provide evidence that this was achieved through PKC-β*2* iso-form activation. I questioned Mr Bradley on the difference in the time it took to differentiate the cells in the GM-CSF/SDF-1 experiment (Practice Example 1.2), where cultures were maintained for 3 to 7 days, in contrast with the prolonged cultures of 15 to 21 days in Practice Example 1.1 after the application of Bryostatin-1. As I have mentioned above, I find the argument presented by the examiner that Example 1.1 indicates that GM-CSF/SDF-1 might be not be working through a pathway that involves PKC-β*2* a persuasive one.

54. Mr Bradley admitted that the GM-CSF/SDF-1 protocol (Example 1.2) provided "*less evidence*" for PKC-β*2* activation. While Mr Bradley did not concede that the GM-CSF/SDF-1 did not work to advance the case, he acknowledged there

was a limited amount of data regarding these products and was prepared to withdraw the claims (claims 7-9) relating to GM-CSF/SDF-1.

55. Mr Bradley then referred to the *Biogen* case which he considered indicated that a broad claim was justified where the invention relates to a general principle of application. While to some extent this is true, *Biogen* is more commonly regarded as establishing the principle that substantial disclosure in the description beyond formal support is necessary to provide an enabling disclosure and support for a claim to a broad principle. Mr Bradley reiterated his point that the general principle of application in the case in suit is the surprising inventive observation that PKC-β*2* activation results in dedifferentiation of mononucleated stem cells. He also made the point that third parties armed with the knowledge of the application would be able to take advantage of this in other uses and circumvent the present claims.

56. *Biogen* is a landmark case from the UK House of Lords concerning the principles of support and sufficiency which arose in the field of genetic recombinant technology. Although support is not formally grounds for invalidity post grant it was nevertheless considered germane by the House of Lords in *Biogen* in the context of sufficiency. In his judgment Lord Hoffmann said "*the requirement of an enabling disclosure in a patent application is a matter of substance and not form*". In forming its judgment the House of Lords drew an important distinction between a claim which related to a new idea and a claim relating to finding a way of achieving a particular idea where the idea or goal was known. An oft-quoted (and by now famous) phrase from Lord Hoffmann's judgment reads "*It is not whether the claimed invention could deliver the goods, but whether the claims cover other ways in which they might be delivered; ways which owe nothing to the teaching of the patent or any principle which it disclosed"*. His Lordship also referred to the EPOs Technical Board of Appeal decision in *Exxon/Fuel Oils* (T-409/91) [1994] which reaffirmed the principle of what amounts to sufficiency in disclosure first set down in the earlier Technical Board of Appeal decision in *Genentech I/Polypeptide* (T-292/85) [1985]. When discussing Article 84, the relevant article of the European Patent Convention (EPC, 1977 version) that corresponds to Section 14(5)(c) of the Act, the Board stated:

> "*Furthermore, Art. 84 EPC also requires that the claims must be supported by the description, in other words it is the definition of the invention in the claims that needs support. In the Board's judgment, this requirement reflects the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported, or justified*".

This point is also made explicitly in *Mycogen*.

57. It seems to me that, as Mr Bradley also suggests, the point at issue in *Biogen* is similar to that in the present case. In my view, while the present case provides evidence to suggest that activation of the PKC-β*2* iso-form with specific reagents could generate multipotent stem cells it does not preclude the fact that there might be other ways of doing so. Mr Bradley responded that the PKC-β*2*

iso-form is essentially a selection invention; PKCs were known in the art to be involved in dedifferentiation but the present application is based on the finding about the effect of PKC-β*2*.

58. The second limb of Mr Bradley's argument in relation to sufficiency was essentially that the test is whether the skilled person could work the full breadth of the claim through routine trial and error without undue burden. I accept this view. The kernel of Mr Bradley's argument in relation to the "undue burden test" was that "PKC inhibitor" and "PKC activator" are known terms in the art and that Example 9 provided the "*complete protocol, a routine test"*, which enables the reasonable person to determine which compounds, or set of compounds, would fall within the scope of the claim, for example by high throughput screening (HTS). He submitted that no inventive activity would be required to do this. He emphasized there was no requirement to develop an assay or synthesise compounds in the present case. He said this distinguished the case in suit from *AHP v Novartis* because, in the present case, there was not a requirement to develop new compounds. Accordingly, he argued, that claim 1 is "classically sufficient" in the *Biogen* sense.

59. In considering this argument from Mr Bradley, I am unable dismiss the concern about the burden imposed to establish modulators of PKC-β*2* raised by the examiner in her official report of 17 December 2010 (see paragraph 14) and again at the hearing when I invited her to comment following Mr Bradley's submissions on this point. In the examiner's view the routine screening process for finding PKC-β*2* modulators was not as simple as Mr Bradley suggested - the mere testing for modulators of PKC-β*2* in a single step. She pointed out that the screening method disclosed in the application which gave rise to the PKC-β*2* activation is a two-step screening process. It would appear from the teaching of the specification, Dr Dinham surmised, that the skilled person would have to perform these two steps. While Dr Dinham was satisfied that Example 9 provided a test to determine which chemicals activated PKC-β*2*, she was concerned that PKC inhibitors and activators are likely to have different effects under different conditions. There is nothing to suggest that mere testing of modulators in single step would produce the result in Fig 4. To me, it seems that this would entail a much bigger set of experiments than Mr Bradley is suggesting. The skilled person would have to screen compounds to inhibit all PKCs and then use a specific up-regulator of PKC-β*2*. Mr Bradley submitted that this was nonetheless still a routine experiment having been taught by the protocol of Example 1.2 to select PKC inhibitors and PKC activators.

60. Also among the examiner's concerns were the claimed effects of the GM-CSF/SDF-1 experiments which suggested that mononuclear cell dedifferentiation might work through a mechanism that does not involve PKC-β*2*. On this particular point, Mr Bradley responded that the focus should be on the examples that do work on PKC-β*2.* I was willing to accept this particular point because Mr Bradley had already indicated he was willing to set aside the GM-CSF/SDF-1 experiments and claims relating them (see above).

61. These points regarding the extent of the technical disclosure in the application in relation to the identification of modulators of PKC-β*2* and the ability of

identified modulators to differentiate mononuclear cells to P-stem cells go to the heart of the question of sufficiency and support and were explored in some depth.

62. In relation to sufficiency I am minded to refer to the examiner's comments in her pre-hearing report which read "*You have disclosed only one way of activating PKC-β2, and without any further disclosure of PKC-β2-specific activators, or any indication in the prior art of what such activators might be, a skilled person would not be able to work the invention by any means other than the single means disclosed in your specification*".

63. In responding to the examiner's comment about the undue burden of the screening process, Mr Bradley submitted that the application provided a complete set of instructions in the Practice Examples, with which by routine trial and error one could determine whether only the PKC-β*2* iso-form was activated by a variety of reagents. This he said could be done, for example, by using HTS.

64. Mr Bradley, expanded on this argument by saying there is in one example, Example 1, and this provides "*evidence in black and white*" that the invention works. He reasoned therefore the claim is "classically" sufficient in the Biogen sense because the skilled person is taught a "*starting point, a road map which a robot could perform and make the invention work*".

65. While on the face of it, it might seem reasonable that the application provides a road map, I am not satisfied that there is any guidance as to where the skilled person might begin with a certain set of compounds; the number of compounds that needs to be tested is potentially infinite. To me, the question is whether someone would know what a PKC-β*2* modulator is. I was not convinced by Mr Bradley's argument that one could find this out from the specification and pointed to Example 1. To my mind, that is a circular argument. It is not consistent with Mr Bradley's analogy that one would know what SSRIs are or what a steroid is. The latter are examples of single compounds but the application in suit only provides evidence for the activation of a PKC-β*2* modulator by a combination of compounds, and also in a particular sequence. However, I do accept that those skilled in the art would know what PKC inhibitors and PKC activators are but these compounds might only achieve their effect in activating PKC- β*2* as claimed in claim 1 through the two step process and certain conditions described in Example 1.1.

66. It seems to me that there are actually two different concepts at issue here. Mr Bradley claims that both are enabled and supported by the application. The first is that the skilled addressee could determine any type of PKC-β*2* modulation protocol, for example by the application of a single modulator, from the teaching of the application, Example 9. Consequently, Mr Bradley suggests, the addressee could work claim 1.

67. The second concept is the more specific two step activation of PKC-β*2*. This is narrower than the first concept but still more general in nature than the applicants' provide in Example 1.1. Mr Bradley's argument on the second

concept is that Example 1.1 provided clear guidance how to work the invention across the full breadth of the claim admitting that the guidance included a two step test of first applying an inhibitor and then an activator of PKC. He said that Go6976 and Bryostatin-1 were examples of PKC inhibitors and activators and that the addressee could test a variety of other compounds with these properties to achieve PKC-β*2* activation.

68. I can accept to some degree the arguments concerning the two step determination of PKC-β*2* modulator. However, Claim 1 is not limited to a PKC-β*2* modulator identified by a two-step test. Accordingly, what I find difficult to accept is that one skilled in the art could without undue burden determine a single PKC-β*2* inhibitor, or indeed a variety of PKC-β*2* activation protocols, other than by using the combination of methods of Example 1.1 and Example 9. Mr Bradley contended this would not entail undue burden and inventive effort and could for example be carried out through HTS, although he acknowledged this might take some time to achieve.

69. As the examiner indicates in her report of 17 December 2010, *AHP v Novartis* and *DSM* provide guidance about the "undue burden" test which I discuss below. In *AHP v Novartis* (page 177, §40) the Court of Appeal stated:

> "*There is a difference between on the one hand a specification which requires the skilled person to use his skill and application to perform the invention and, on the other, a specification which requires the skilled person to go to the expense and labour of trying to ascertain whether some product has the required properties. When carrying out the former the skilled person is trying to perform the invention, whereas the latter requires him to go further and to carry out research to ascertain <u>how</u> (my emphasis) the invention is to be performed. If the latter is required the specification would appear to be insufficient*".

70. I think this is particularly relevant to the question at issue in the present case. Undoubtedly the contemporary innovation of HTS has made the screening of large numbers of compounds possible. However, I do not think that existence of HTS techniques mean that any compound for any purpose can be arrived at by simple trial and error; otherwise one might expect that HTS would have already resolved the vast majority of molecular challenges in contemporary molecular biology! Rather, I would suggest that the design of HTS experiments is often likely to entail some creativity and ingenuity on the part of the person doing this work.

71. In the case in question I consider that the skilled addressee faces a considerable task of establishing whether a single compound would have the property of PKC-β2 activation. I accept that the specification gives the addressee a starting point and routine test to identify PKC-β2 expression but, in my opinion, it does not give the complete package of information necessary to perform the invention of claim 1. I am inclined to think that considerable labour and expense would be required to establish whether a compound or compounds had the properties accommodated by the full ambit of claim 1. It is

likely in the words of *DSM* that the "*skilled worker would have to depart from the express teaching of the patent*".

72. My view is that Example 1, which produces the result in Example 9, details a particular methodology for activating PKC-β*2.* This example does not necessarily provide a methodology to test all PKC modulators. Furthermore, and as the examiner mentioned, in my view there is only enough evidence to suggest that dedifferentiation of mononuclear cells involves activation of PKC-β2 and that PKC-β2 is capable of being activated by the combined use of Go6976/Brysotatin-1 under the conditions of Example 1.1.

Conclusion

73. The key question I must decide is whether the application provides a sufficient disclosure, in substance, that PKC-β2 activation is a pivotal mechanism, "*a principle of general applicability*" to use Mr Bradley's words, in the dedifferentiation of mononuclear cells to P-stem cells. The disclosure of substance over form is well established by the authorities discussed above. *Biogen, Schering* and *Mycogen* also make the point that a claim to a general principle requires a finding that is consistent with or supports that general principle. The question is not a simple binary one of fact, whether a single example is sufficient to support a general claim, but rather it is whether the application provides a disclosure that is sufficient to enable the skilled addressee to perform the full ambit of the claim without an undue burden.

74. It is useful at this juncture to summarise the teaching of the application and the evidence upon which Mr Bradley and I agree. The application rests on the concept of dedifferentiation of P-stem cells from mononuclear cells. The basis of claim 1 rests on the principle that this is specifically achieved through activation by the PKC- β2 iso-form. Practice Example 1.1, taken together with Practice Example 9 and Figure 4, provides evidence for the specific activation of the PKC- β2 iso-form by the sequential treatment of mononuclear cells with two chemicals, G06976 and Bryostatin-1, to give rise to "P-stem cells". Practice Example 1.2 describes a method for the production of P-stem cells with a combination of GM-CSF/SDF-1 but, in contrast to Example 9 and Figure 4, no supportive evidence for the specific activation of the PKC- β2 iso-form by GM-CSF/SDF-1 is given.

75. Taken together the experiments in Practice Examples 1.1 and 9 and Figure 4 show a relationship between Go6976/Bryostatin-1 administration and activation of PKC-β2. However, I do not believe that these two experiments establish a general principle for the key involvement of PKC-β2 activation in dedifferentiation of mononuclear cells. It might be that the applicants have hit upon a principle of general applicability but the evidence in suit does not make out a sufficient case for that. Accordingly, I hold that claim 1 is not supported.

76. I also do not believe that the application provides a sufficient disclosure to the skilled person to allow them to be able to identify modulators of PKC-β2 as claimed in the generality of claim 1 without an undue burden of labour and

expense. The application has taught one way of modulating PKC-β2 and contains some evidence that de-differentation of mononuclear cells might not involve this protein. Even if I set the potential "counter evidence" of the GM-CSF/SDF-1 experiment aside, the fact remains that the application only provides a single, very specific set of conditions for PKC-β2 activation in mononuclear cells. Accordingly, I hold that claim 1 is insufficient.

77. As I have mentioned above and as Mr Bradley admitted, there is no evidence for the involvement of GM-CSF/SDF-1 in activating PKC-β2 in the application. I therefore hold that claim 7 is insufficient and not supported. I note that Mr Bradley was prepared to withdraw these claims.

78. As I have found that the main claim is not allowable the issue of compliance with section 18(5) becomes less relevant. However, for completeness I shall deal with that here. Mr Bradley made reference to the *Komag* case in the EPO as an authority on this issue. I note that *Komag* was decided in reference to principles for examination in the EPO and that the EPC does not have an equivalent provision to section 18(5). I would agree, however, that in terms of its theoretical scope, claim 1 in suit is not co-terminus with claim 1 of the parent application which is the question to be considered under section 18(5) of the Act. However, as I have found above, because claim 1 is only supported by the Go6976/Bryoststatin-1 experiment it is *prima-facie* co-terminus with claim 1 of the parent application. I note that claim 2 relates to the specific process involving Go6976 and Bryostatin-1 and consider therefore that it relates to the same invention as claimed in claim 1 of the parent application.

79. I should comment on the amended claims labeled "version 1" of the claims informally submitted at the hearing. These exclude claims 2-6 dependant on claim 1 and also claims 7-9 which relate to GM-CSF/SDF-1. While these amendments deal with my objections in respect of claim 7 and resolve the issue of section 18(5) compliance of claim 2, it remains that claim 1 in "version 1" is insufficient and lacks support for the reasons I have outlined above.

80. Mr Bradley did not make any particular submission regarding the other dependant claims, 3-6 and 10-19, which detail particular culture conditions and reagents. Accordingly, I have not considered these claims here.

81. I therefore find that the application in its present form is not in order and remit the case to the examiner in the event that the applicants wish to file amendments. There would appear to be scope for amending the claims currently on file to address the deficiencies I have identified above. While 'version 1' of the claims discussed informally at the hearing would appear to address some of the deficiencies identified as indicated above, it would not address them all. Further amendment would be needed in my view to properly address all the deficiencies identified with this application.

82. If no further submissions are made to the examiner by the compliance date of 22 March 2011, the application will be treated as refused under Sections 14 and 18 of the Act for the reasons I have outlined above.

Appeal

83. Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days of this decision.

Dr L Cullen
Divisional Director acting for the Comptroller