Intellectual Property Office

BL O/604/19

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PATENTS ACT 1977

APPLICANT	The Scripps Research Institute
ISSUE	Whether patent application GB1609984.8 complies with the requirements of section 14(3) and 14(5)(c)
HEARING OFFICER	Dr L Cullen

DECISION

1 This decision concerns patent application GB1609984.8 entitled "*Gene expression profiled associate with sub-clinical kidney transplant rejection*" (hereinafter "the application"), and whether the specification discloses the invention in a matter which is clear and complete enough to enable the invention to be performed by a person skilled in the art, as required by Section 14(3) of the Patents Act 1977 (hereinafter "the Act"), and whether the claims are adequately supported by the description, as required by Section 14(5)(c) of the Act,

Background

2 The application was filed on 22 May 2015, in the name of The Scripps Research Institute (hereinafter "the applicants"), claiming an earliest priority date of 22 May 2014. It was published as international application WO 2015/179777 on 26 November 2015, and republished as GB 2538006 on 2 November 2016, following its entry into the UK national phase. The compliance date has been extended through a series of discretionary extensions under rule 108(3) of the Patents Rules 2007 (hereinafter "the Rules"), following the as-of right extension under rule 108(2) of the Rules. The compliance date is currently 22 July 2019.

3 An objection to lack of support due to the excessive breadth of the claims was raised initially in the examiner's first official examination report, dated 28 November 2016. This objection was maintained by the examiner through subsequent rounds of amendment and correspondence with applicant. In his examination report dated 1 March 2019, the examiner has maintained this objection to lack of support and sufficiency. Given the nature of the objection and the lack of a satisfactory response from the applicants to address this issue, the examiner informed the applicants that he was of the view that the application should be refused, in his official letter dated 30 April 2019. With the matters unresolved, the applicants requested an oral hearing.

4 The examiner has set out his objection in his pre-hearing report dated 28 May 2019. Following a review of this pre-hearing report and of the application as a whole, the office wrote to the applicant on 12 July 2019, requesting that the applicants be prepared to address some specific issues at the hearing. However, the attorney representing the applicant responded, in an email dated 12 July 2019, that they had been instructed not to attend the hearing and that they would not be filing any further arguments. As a consequence, the decision below is based on the correspondence on file. I was assisted in this matter by senior examiner Rowena Dinham, acting as assistant to the hearing officer.

The Invention

5 The application relates to the detection of subclinical acute rejection (subAR) in a kidney transplant patient. Existing methods rely upon serum creatinine levels, which can lag renal injury and therefore detect kidney graft rejection only after the initial injury has started, whereas the present invention relies upon a peripheral blood gene expression signature that can distinguish between subAR, well-functioning normal transplant (TX) and acute rejection (AR), i.e., which can distinguish between these situations before initial injury has started. The invention itself relies upon an analysis of gene expression profiles in samples taken from transplant patients, and the identification of probe sets that can classify samples as subAR, AR and TX with a high degree of accuracy.

The Claims

6 The set of claims currently on file consists of 19 claims, with a single independent claim, claim 1, which reads:

> *A method of detecting subclinical acute rejection (subAR) in a kidney transplant recipient comprising:*
>
> *(a) obtaining nucleic acids of interest, wherein the nucleic acids of interest comprise mRNA extracted from a blood sample from the kidney transplant recipient or nucleic acids derived from the mRNA extracted from the blood sample from the kidney transplant recipient;*
>
> *(b) detecting expression levels in the subject of at least four genes using the nucleic acids of interest obtained in step (a), wherein the at least four genes are capable of specifically detecting subclinical acute rejection (subAR) in a kidney transplant patient with a stable or normal serum creatinine level; and*
>
> *(c) detecting subAR in the kidney transplant recipient from the expression levels detected in step (b),*
>
> *wherein the expression levels are detected by using a microarray or sequencing assay;*
>
> *wherein the at least four genes are selected from Table 14; and*

wherein the method has a negative predictive value (NPV) of at least 75% for subAR.

Matters to be decided

7 There are two issues to be decided:

(i) Is the application disclosed sufficiently across its entire breadth, as required by Section 14(3) of the Patents Act 1977; and

(ii) Are the claims supported fully by the description, as required by Section 14(5)(c) of the Patents Act 1977.

In effect, I must determine whether, or not, there is enough information in the specification as filed that allows the invention to be performed across its entire breath.

The Law

8 Section 14 of the Act, entitled "*Making of Application*", refers to certain requirements that the specification and its associated claims must meet to be allowable. In this instance, we are concerned with Sections 14(3) and 14(5).

Section 14(3)

9 Section 14(3) relates to the specification and reads as follows (my emphasis added):

> ……
>
> *(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****.*
> ……

10 As set down in Section 130(7) of the Act, Section 14(3) is intended to have, as nearly as practicable, the same effect as the corresponding provisions of the European Patent Convention (EPC) and the Patent Cooperation Treaty (PCT). Article 83 EPC and Article 5 PCT require the invention to be disclosed *"in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art"*. An objection under this section of the Act is often referred to as "*sufficiency of disclosure*" or "*sufficiency*". This pre-grant provision concerning the patent application accords directly with section 72(1)(c) of the Act which sets out the same requirement for the validity of the granted patent. Thus, while much of the case law relating to sufficiency derives from proceedings concerning granted patents under section 72, the principles set out in these cases are pertinent to section 14(3). It is the responsibility of the applicant to ensure that, at the time of filing the application, the disclosure is clear enough and complete enough in respect of the invention claimed in each of the claims. If it is not, then the application shall be refused or, if it is possible to do so, the claims must be restricted or amended to that matter which has been adequately disclosed, i.e., that for which there is an enabling disclosure. Deficiencies in the disclosure cannot be rectified subsequently by adding matter because of the prohibition under section 76(2) of the Act.

11 The overall purpose of Section 14(3) is to prevent the patent applicant from claiming products or processes which the teaching of the specification does not enable the skilled person to perform. In effect, one is being asked to determine if there is enough information in the specification as filed by the applicant to allow the person who has a reasonable knowledge and understanding of the technical area described to carry out the invention as defined in the claims.

12 Kitchin J provided a summary of the relevant principles to be applied when assessing sufficiency (at [239]) in *Eli Lilly v Human Genome Sciences,* [2008] RPC 29 (hereafter *Eli Lilly*):

> *"The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:*
>
> *(i) the first step is to identify the invention and that is to be done by reading and construing the claims;*
>
> *(ii) in the case of a product claim that means making or otherwise obtaining the product;*
>
> *(iii) in the case of a process claim, it means working the process;*
>
> *(iv) the sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;*
>
> *(v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;*
>
> *(vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;*
>
> *(vii) the specification must be sufficient to allow the invention to be so performed without undue burden."*

13 Construction of the claims is approached, as set out in Section 125 of the Act, in a purposive manner and interpreting them in the light of the description and drawings.

14 For the purposes of s.14(3), the skilled person is seeking to make the patent work and does so with the common general knowledge at the time the patent was filed. The skilled worker has the patent in front of them, and thus is "*trying to carry out the invention and achieve success, ... not searching for a solution in ignorance of it*." (see *Zipher Ltd v Markem Systems Ltd.,* [2009] FSR 1 at page 50, hereafter *Zipher*).

15 Whilst there is only one provision under the Act, it is well established in UK law that the understanding of what sufficiency is - in terms of the disclosure being clear and complete enough for the invention to be performed by the person skilled in the art - can be approached in three different ways, i.e.:

1) Classical insufficiency

2) Insufficiency by ambiguity
3) Insufficiency by excessive claim breadth

A summary of what should be understood by each of these approaches to sufficiency was provided by Floyd J (as he then was) in *Zipher* (see paragraphs 361 to 454, but especially paras 367-373 & 440-454). For the purposes of the present case we are concerned with the third approach to sufficiency outlined above

16 The House of Lords in *Biogen Inc v Medeva plc* [1997] RPC 1 (hereafter *Biogen*) held that for the purposes of sections 14(3) and 72(1)(c), the disclosure must be enough to enable the full width of the claimed invention to be performed, and that the disclosure of a single embodiment will not always satisfy this requirement regardless of the width of the claim. In particular, Lord Hoffman pointed out (at page 51, line 1 - page 52, line 8), that the extent of the patent monopoly as defined by the claims should not go beyond the technical contribution of the invention:

> *"…. there is more than one way in which the breadth of the claim may exceed the technical contribution to the art embodied in the invention. The patent may claim results which is does not enable, such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made. Or it may claim every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which makes no use of the invention."*

17 This type of insufficiency, arising from a disclosure which does not enable the invention to be performed across the entire width of the claim, is thus sometimes referred to as '*Biogen insufficiency'*.

Section 14(5)

18 Section 14(5) relates to the claims and reads as follows (my emphasis added):

> *(5)* ***The claim or claims shall*** *–*
> *(a) define the matter for which the applicant seeks protection;*
> *(b) be clear and concise;*
> ***(c) be supported by the description****;*
> *(d) relate to one invention or to a group of inventions which are so linked as to form a single inventive concept. ….*

In the present case we are concerned specifically with Section 14(5)(c) (as highlighted above).

19 As set down in Section 130(7) of the Act, Section 14(5) is intended to have, as nearly as practicable, the same effect as the corresponding provision of the EPC, Article 84, and of the PCT, Article 6. Both provisions use essentially the same wording as section14(5)(a)-(c).

20 It is established practice in UK law that the form of the claim is a matter for the applicant, and that any claim which fulfils the requirements of the Act is acceptable. The claims should aim to define and delimit the features of the invention, with the independent claims clearly establishing the essential features of the invention as well

as enough details of this inter-relationship, operation or utility to establish that the invention achieves the intended objectives. Section 14(5)(c) requires that the scope of the invention, as defined in the claims, is consistent with what is disclosed in the specification, and not so broad that it goes beyond the invention, yet not so narrow that it deprives the applicant of a just reward for the disclosure of his invention.

Relationship between section 14(3) and section 14(5)

21 The Court of Appeal in *Genentech Inc's Patent,* [1989] RPC 147 noted that lack of support is not a ground which can be addressed after a patent is granted, unlike the provision concerning sufficiency. The comments of Dillon LJ therein (at page 236, line 50 - page 237, line 3) are a useful guide for examiners when considering lack of support:

> *"The Patent Office ought to have very clearly in mind that it is undesirable to allow claims the object of which is to cover a wide and unexplored field or where there is no disclosure in the specification which is in any way coterminous with the monopoly indicated in the claims."*

22 The importance of a correct decision pre-grant on the question of lack of support was further emphasised by Aldous J in *Schering Biotech Corp.'s Application'* [1993] RPC 249 (hereafter *Schering*), and he went on to point out (at page 252, line 53 - page 253, line 2) that the substance of the disclosure, rather than its form, was the key issue:

> *"I do not believe that the mere mention in the specification of features appearing in the claim will necessarily be a sufficient support. The word 'support' means more than that and requires the description to be the base which can fairly entitle the patentee to a monopoly of the width claimed."*

23 He went on to state the even though there were passages in the specification that provided literal support for a feature in the claims, it is the claims that define the scope of the invention and not all that fell within the scope of the claim was included within the patent.

24 It is often the case that the requirements of Section 14(5) of the Act overlap with those of Section 14(3) as both are concerned with the relationship between the extent of disclosure and the scope of the claims. As pointed out by Lord Walker in *Generics v Lundbeck* [2009] RPC 13 (at paragraph 20, hereafter *Generics*):

> *"The disclosure must be such as to enable the invention to be performed…to the full extent of the claims. The question of whether there is sufficient enabling disclosure often interacts with a question of construction as to the extent of the claims".*

25 This is particularly apparent in applications where the claims are unduly broad and speculative, as argued by the examiner in the present case, and therefore objections can be raised under both Section 14(3) and Section 14(5)(c). Therefore, whilst I will deal with these sections of the Act individually below, there will inevitably be some overlap in the reasoning.

26 Taking all the above into account, I consider that the law requires me to determine, based on the information in the application and taking account of the views of the examiner and applicant during the examination process, whether the application provides enough detail to support the invention as claimed.

Analysis

27 Taking note of the principles for assessing sufficiency set down in *Eli Lilly* (see above), the first step is to construe the claims, as it would be understood by the skilled person, interpreting them in light of the description and any drawings in the application as filed, as instructed by Section 125(1) of the Act, taking into account the Protocol to Article 69 of the EPC. To do so I first need to identify the skilled person. I note that there has been no discussion of who the skilled person would be by either the examiner or the applicant during the prosecution of this application.

28 I consider the skilled person to be a team comprising a *molecular biologist* familiar with the identification of genes differentially expressed in normal and diseased patients, who would be aware of different methods that could be used to detect these differences, including microarray analysis and next generation sequencing (NGS); and a *clinician* who has a knowledge of kidney damage during transplant rejection and is aware of existing methods of detecting such kidney damage, as well as the limitations of these methods.

29 Turning to claim 1, it can be construed in a straight-forward manner. It is directed to a method for the detection of subAR in a kidney transplant recipient who has a stable or normal serum creatinine level, by determining the expression levels of **at least 4 of the genes listed in Table 14**, where this method has a negative predictive value (NPV) of at least 75% for subAR. The term negative predictive value or NPV refers to the likelihood of a person testing negative truly not having subAR. Table 14 lists a total of 818 different genes.

30 Example 3 of the specification discloses the methods to detect AR, subAR and TX phenotypes in the blood samples of 68 kidney transplant patients. Paragraph [00205] specifically refers to Table 14, and states that this table depicts the full 818 probe sets used in this analysis, ranked by p-value (i.e., by higher statistical significance). The passage goes on to state that the '*best performing probe set*' gene signature is listed in Table 15. This consists of 61 genes, and presumably represents the genes which are most likely to provide the desired result of detecting subAR with the NPV of at least 75%. However, there is little or no overlap between the genes listed in Table 14 and those listed in Table 15. In fact, only 6 of the genes listed in Table 15 (and deemed to be best performing) are listed in Table 14. Nevertheless, this overlap of 6 genes does indicate that there are 6 genes listed within Table 14 that *may* be used in a method to detect subAR to the degree of accuracy required of claim 1. Thus, I am satisfied that there is an example of one way of performing the invention disclosed in the application, even if it is not immediately apparent because of the small degree of overlap between the genes listed in Table 14 and those listed in Table 15. I note that the examiner has observed (in the official examination report dated 20 April 2019) that this example provides an enabling disclosure and so the claimed invention cannot be regarded as insufficient in this regard, i.e. so-called classical sufficiency does not arise. I agree with this view. I am satisfied that if all the genes in Table 15 are analysed they will fall within the scope of claim 1.

31 The examiner referred to the *Biogen* decision from the House of Lords, where it was held that, for the purposes of Section 14(3), the disclosure must be enough to enable the whole width of the claimed invention to be performed, and therefore the disclosure of a single embodiment may not always be enough to satisfy the sufficiency of disclosure requirement. The examiner argues that one gene set of 61 genes (from Table 15) does not enable the skilled person to develop a diagnostic test for subAR with the required degree of accuracy using a panel of biomarkers comprising any number of combinations of at least 4 of the 818 genes listed in Table 14, without an undue burden of research.

32 Having considered the correspondence on file, the only argument that the applicant has put forward to show that the invention as claimed is supported across its full breath is that in the letter from their attorney, dated 21 March 2019, where they state that paragraph [00205] of the application as filed discloses that the biomarkers have been shown to differentiate between AR, subAR and TX. It is clear, in their view, that the biomarkers of Table 14 can be used to distinguish all three phenotypes. As such, according to the applicants, the invention is sufficiently disclosed (and the claims supported across their entire breadth).

33 Claim 1 encompasses the use of any combination of any 4 of the 818 genes listed in Table 14 to detect subAR with sufficient degree of accuracy. However, I can see nothing in the specification that suggests that only 4 of these genes is needed and can in fact be used to detect subAR with an NPV of at least 75%. Furthermore, there is no disclosure that would enable the skilled person to identify which combination of 4 genes would in fact detect subAR with any degree of accuracy, let alone with the specific requirement of an NPV of at least 75%. The only disclosure that does provide any assistance to the skilled person in selecting which genes can be used to differentiate between subAR, AR and TX patients is the panel of 61 genes listed in Table 15. However, as I discussed above, only 6 of these genes are present in Table 14, and therefore this single example of how to perform the invention does not help the skilled person determine how to choose a combination of **any 4 genes** from Table 14 to detect subAR patients and distinguish them from AR and TX patients. Thus, I am of the view that this single example is not enough to enable the skilled person to work the invention across its entire breadth and does not meet the requirements of Section 14(3) of the Act.

34 Nevertheless, I am also mindful of the reasoning in the *Biogen* and *Generics* cases that the monopoly conferred by the patent should correspond to the technical contribution to the art. As I have discussed above, I consider that the technical contribution in this case lies in the identification of a **specific set of genes** that enable the distinguishing of subAR, AR and TX between transplant patients with an NPV of greater than 75%. As such, I would expect some disclosure in the specification to support a claim that all the genes listed in Table 14 could be used in a combination of 4 or more to distinguish subAR, AR and TX with an NPV of greater than 75%. There is not enough information in the application to tell the skilled person that any four or which sets of four genes listed in Table 14 have the claimed property

35 The applicants appear to suggest that the invention lies in the general principle of distinguishing between subAR, AR and TX in kidney transplant patients with a normal level of creatinine by gene expression analysis. However, this general principle of gene expression analysis to identify such patients is already known (see WO

2014/074501, cited in the official examination report, dated 21 January 2019), and therefore this cannot be the technical contribution of this patent application to the art.

36 The applicants point out in the letter from their attorney, dated 15 January, that the present invention provides an inventive step over the prior art because it would not be obvious to search for alternative genes that enable this detection. They refer to the disclosure of *Alakulppi et al., Transplantation* Vol 86 (2008), pp 1222-1228 (hereafter referred to as *Alakulppi,* it was cited during prosecution of the corresponding EP patent EP3146076 and was referred to in the above-mentioned letter from their attorney). This document teaches that gene expression analysis of blood samples failed to identify suitable markers to detect subAR. The applicants in the present case appear to argue that there would have been no expectation of success in using **any** genetic marker to detect subAR with the desired NPV, based upon what was disclosed in *Alakulppi*. From this line of argument, it appears that it is not possible to predict which differentially expressed markers could be used to detect subAR kidney transplant patients and distinguish them from AR and TX kidney transplant patients. It therefore follows that it may not necessarily be possible to predict which differentially expressed markers identified in Table 14 could be used to distinguish subAR patients from AR and/or TX patients. Given that the applicant pointed to this prior art to illustrate how difficult it is to achieve the invention as claimed, this also, in my view, points to the fact that the limited disclosure in the application as filed does not provide the skilled person with enough information to work the invention across the breath of this claim.

37 The examiner has also objected that the claims as currently drafted lack support across their full breadth, as required under s.14(5)(c). This objection is based on the interpretation of the words "*supported by the description*" given by the Court of Appeal in *Schering*, in which it was held that mere mention in the specification of features appearing in the claim is not necessarily sufficient support: "*The word 'support' means more than that and requires the description to be the base which can fairly entitle the patentee to a monopoly of the width claimed.*" The reasons why the examiner considers that claim 1 is not supported across its full breadth are the same as those already discussed in relation to the application being insufficient due to undue claim breadth. Although, the description lists genes that may be used to detect subAR, AR and TX in kidney transplant patients with an NPV of greater than 75%, it goes no further than identifying these **possible** genes. It does not show that all combinations of 4 of these genes in Table 14 could be used in such a method. Therefore, I am of the view that the claims of the application as currently on file lack support across their entire breadth and so they do not meet the requirements of Section 14(5)(c).

Conclusion

38 Taking account of all the above, as well as the correspondence on file, I am satisfied that patent application GB1609984.8 does not disclose the invention in a manner which is clear enough and complete enough to enable it to be performed by a person skilled in the art. Therefore, I find that the application does not meet the requirements of Section 14(3) of the Act.

39 Furthermore, I find that the claims are not fully supported by the description, and therefore the application also does not meet the requirements of Section 14(5)(c) of the Act.

40 I therefore refuse the application for failure to comply with the requirements of the Act under Section 18(3) of the Act.

Appeal

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

Dr L Cullen

Deputy Director, acting for the Comptroller