Intellectual Property Office

BL O/681/18

30 October 2018

PATENTS ACT 1977

APPLICANT	Attomarker Limited
ISSUE	Whether patent application GB1012376.8 complies with Section 14(3) of the Act
HEARING OFFICER	Dr C L Davies

DECISION

Introduction

1 This decision concerns patent application GB1012376.8 which was filed on 23 July 2010 by the University of Exeter but has since been assigned to Attomarker Limited. The title as filed is "Data processing systems". The applicant, in response to an objection raised by the Examiner in his first examination report dated 1st February 2017, amended the title to read "Data processing systems for predicting the response of a patient to surgery using complement cascade pathway biomarkers".

2 In that first examination report, the Examiner also raised objections that the invention was excluded having regard to section 1(2) of the Act and that the invention lacked an inventive step. These objections however were not pursued in subsequent examination reports, with the Examiner instead focussing on what he considered a more fundamental objection. Accordingly, in all subsequent examination reports dated 27th September 2017, 5th February 2018 and 3rd April 2018, the Examiner objected to the application not complying with Section 14(3) of the Act, objecting that the application is classically insufficient.

3 At an interview between the inventor, Dr Andrew Shaw and the Examiner held on 7th June 2018, Dr Shaw sought to clarify what the patent application taught and how it may be implemented. A report of this interview was sent to the Attorney who, in a letter dated 22nd June 2018, provide further evidence as to how the skilled team would understand the invention as disclosed in the context of their common general knowledge. In that letter, the Attorney also confirmed the Applicant's request for a Hearing Officer to decide on the papers whether the application should be allowed as it then stood. The Examiner's final communication with the Applicant was a pre-hearing report dated 31st July 2018. At the time of preparing this decision the compliance period prescribed by rule 30 for this application has been extended to 1 October 2018.

The invention

4 The invention concerns a system for characterising different types of infection in a patient after surgery, the system comprises an analytical device, at the heart of which, is a plasmon-resonance based sensor array to detect multiple blood born biomarkers implicated in complement cascade pathways. The system interrogates each of the following complement cascade pathways - the alternative pathway, the classical pathway, the lectin pathway and the lytic pathway. This is achieved by analysis of the change in concentration of certain biomarkers associated with each pathway to determine if that pathway is activated or not, the level of activation of a pathway, also termed it's 'flux' in the description, is abbreviated J_a for the alternative pathway, J_c for the classical pathway, J_L for the lectin pathway and J_{ly} for the lytic pathway. The description and claims propose that it is possible to differentiate gram positive, gram negative and viral infection types from certain patterns of activation, or the absence of activation in the complement cascade pathways. These patterns of activation, or as they are termed in the description, the 'model' of the complement cascade can be refined by further clinical data such as to distinguish the effect on the complement cascade of an initial surgical insult from an infection response or be updated with actual patient outcomes.

The claims and description

5 The latest set of claims were filed on 5th March 2018. There are 7 claims, with claim 1 being the only independent claim. I will base my decision on this set. I will also work from the latest version of the description filed 30th June 2017, where the Attorney has provided clarifying amendments in response to the Examiner's first examination report.

Claim 1 reads as follows:

"1. A system for determining infection in a patient who has undergone surgery, the system comprising:

a multianalyte detector to analyse a sample of blood from said patient to determine, substantially in parallel, concentration data for each of a set of biomarkers of a set of complement cascade pathways, wherein said multianalyte detector is configured to determine said concentration data within a time duration of less than one hour;

wherein the multianalyte detector comprises a plasmon-resonance based sensor array for plasmon resonance-based sensing of a plurality of different biological targets simultaneously, the biosensor array comprising a transparent substrate bearing a plurality of electrically conductive assay regions,

a system to flow a sample of bodily fluid of 1ml or less over said biosensor array,

an illumination system to illuminate the biosensor array such that total internal reflection of light at a wavelength at or near a plasmon resonance results in dark-field scattered light modulated by binding of said biological targets,

an image sensor to capture an image of said dark-field scattered light from said biosensor array; and

a data analyser, coupled to said multianalyte detector, to receive and analyse said concentration data, and having a user interface;

wherein said complement cascade pathways include the lytic pathway, the lectin pathway, the classical pathway and the alternative pathway having respective fluxes J_{Ly}, J_L, J_C, and J_A, and wherein the sets of biomarkers comprise:

C5a and C6-C9 for said lytic pathway,

C2b for said lectin pathway,

C4a, C1, and C1q for said classical pathway, and

C3a, C3 for said alternative pathway;

wherein said data analyser is configured to capture a time series of said concentration data to differentiate a response in the lytic pathway resulting from an initial surgical insult from an infection response in one or more of said lectin pathway, said classical pathway, and said alternative pathway,

wherein said data analyser stores model data defining a calibrated model calibrated with absolute concentrations of said biomarkers representing said fluxes in said complement cascade pathways for determining relative fluxes in said complement cascade pathways from concentrations of said biomarkers over time;

wherein said data analyser is configured to process said concentration data using said calibrated model to determine probability data representing likely infection of the patient; and

an output device, coupled to said data analyser, to provide to a user an outcome of the determination of said infection;

wherein processing said concentration data using said calibrated model to determine probability data comprises determining of one or more of the following conditions:

$J_A + J_L > J_C$, elevated J_{Ly}

$J_A > J_L + J_C$, elevated J_{Ly}

$J_C > J_A + J_L$, depressed J_{Ly}

which respectively determine gram+ bacterial infection, gram- bacterial infection, and viral infection."

Issue to be decided

6 The issue to be decided, as summarised in the pre-hearing report, of 31 July 2018, is whether the application is classically insufficient. I will therefore need to decide whether the application complies with Section 14(3) of the Act. If I find the application to be sufficiently disclosed, I will remit it back to the Examiner for further processing. If I do not find the application to comply with Section 14(3) I will refuse it.

The law

7 Section 14(3) of the Act states:

"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."

Relevant precedent

8 There is significant case law on sufficiency. In recent years the reasoning that should be used to assess whether an application satisfies section 14(3) of the Act has relied predominantly on *Eli Lilly v Human Genome Sciences* [2008] RPC 29 (hereafter *Eli Lilly*) particularly paragraph [239] wherein Kitchen J gave the following summary of the relevant principles to be applied:

> *"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."*

9 Furthermore, In *Zipher Ltd v Markem Systems Ltd* [2009] FSR 1, (hereafter *Zipher*) the objection to classical insufficiency is summed up as follows:

> *"Classical insufficiency arises where the express teaching of the patent does not enable skilled addressee to perform the invention. This type of insufficiency requires an assessment...of the steps to which it would be necessary for the skilled reader or team to take in following the teaching of the specification and in order to arrive within the claim. Plainly the steps should not include inventive ones. But a patent can also be found insufficient if the steps can be characterised as prolonged research, enquiry or experiment."*

10 I note that of the above only *Zipher* has been raised by the Examiner, basing his analysis of sufficiency on the reasoning in *Kirin-Amgen Inc v Hoechst Marion Roussel [2005] RPC 9 (hereafter Kirin-Amgen)*, this states:

> *"Whether the specification is sufficient or not is highly sensitive to the nature of the invention. The first step is to identify the invention and decide what it claims to enable the skilled man to do. Then one can ask whether the specification enables him to do it."*

Kirin-Amgen and *Eli Lilly* (and for that matter *Zipher*) share common themes in how they formulate the question of what constitutes a sufficient disclosure, such as determining what the skilled person/team is taught to do, this further requiring determination of the skilled person/team and their common general knowledge. I note that both the Attorney and Examiner have formulated their arguments around these common themes. Given the common themes in *Eli Lilly* and *Kirin-Amgen* I do not consider the Applicant has been disadvantaged by not having had the opportunity to specifically formulate their arguments having regard to *Eli Lilly*. I will therefore assess the application based on *Eli Lilly* and *Zipher*

11 I note that it is well established, such as in *Biogen Inc v Medeva plc [1997] RPC 1* that I am to determine sufficiency by considering the state of the art at the filing date of the application and I will do so accordingly.

Argument and analysis

12 In order to apply the principles in *Eli Lilly* I must identify the invention by construing the claims (step i) and do so having regard to the common general knowledge of the skilled person or team at the filing date of the invention (step v). Therefore I will first determine what constitutes the common general knowledge of the skilled team.

The common general knowledge of the skilled team

13 The Examiner in his pre-hearing report dated 31st July 2018 stated that he broadly agreed with the Applicant as to the nature of the skilled team and their common general knowledge. On page 2 of their letter dated 5th March 2018, the Attorney indicated that, *"The relevant skilled person would generally be a skilled team comprising, for example, a surgeon trained in the evaluation of complement cascade biomarkers (taught at undergraduate level), a clinical chemist, and a physicist or physical chemist"*. I agree with this analysis of the composition of the skilled team and I will adopt it.

14 I consider the skilled team (using only their common general knowledge) would be able to construct analytical systems comprising the plasmon-resonance detector with associated optics, a sample delivery unit and data analyser in order to perform a multi-analyte detection assay for specified biomolecules. I also consider that the skilled team would be aware of suitable reagents to facilitate binding and thereby analysis of the particular biomarkers of the complement systems indicated in the description, these being well characterised molecules. I have carefully considered the letter (dated 2 March 2018) from Mr I Daniels Consultant Surgeon at the Royal Devon and Exeter NHS trust, particularly with a view to determining the common general knowledge of the skilled team. Mr Daniels proposes that the skilled team would be knowledgeable about the complement cascade and would also have been taught about biomarkers associated with these pathways, and their analysis. Mr Daniels also proposes that the skilled addressee would be able to use the lab data concerning the absolute level of a biomarker to determine the activation level or flux in a particular complement cascade pathway. By this I take it that Mr Daniels proposes that the skilled team would be able to associate a change in the concentration of certain biomarkers with activation of a complement cascade pathway and that the absence of a change would indicate a lack of activation of the

relevant complement cascade pathway. I agree that all of this knowledge would be within the common general knowledge of the skilled team.

Construing the claims

15 I will now identify the invention by construing the claims (principles (i)-(iii) in *Eli Lilly*). I note the claims have been considerably amended when compared to those originally filed. I note the Examiner has not objected that amendments have added matter and as such I note this is also not an issue before me to decide. I have considered the claims as filed on 5 March 2018 and do not consider they add matter.

16 I construe the claims as proposing an analytical system and its use in a process for determining / distinguishing different infections in a patient in the post-operative period. The analytical system is used in a process wherein the concentrations of certain biomarkers are measured. Combining how the biomarker's concentrations change in the post-operative period is used to assess the activation of complement cascade pathways as a function of time. In turn this activation data is fed into a model of the complement cascade which is characteristic of the infection, to thereby provide an output of the probability of the infection type present.

17 I should note at this stage that I have to determine if the skilled person is able to perform the invention having regard to what is taught by the specification as a whole [principle (iv) in *Eli Lilly*], which I take as a reminder that the teaching of the specification can only be determined from the matter therein, and that I must not rely on detail given in evidence provided by the Attorney/inventor to determine what is taught by the application. Indeed the Attorney has reminded me, in their letter of 22nd June 2018, that the evidence provided with that letter aims *"to convey information about the skilled team's understanding of the subject matter"*. I have considered all the evidence submitted by the Attorney/inventor in this way.

18 So turning to principles (vi) and (vii) of *Eli Lilly* I will consider if the system and use, comprised in the invention can be performed over its entire scope without undue burden. As I have construed it the invention comprises two aspects; an analytical system and the process for its use. I consider the construction of the analytical system would be within the common general knowledge of the skilled team particularly as directed by the schematics of Figure 3 (a)-(c) and the admitted art on page 1 of the specification. Having found it is possible for the skilled person/team to implement the analytical system, I will not consider it further.

19 Whereas it is not in contention that the analytical system of claim 1 is enabled by the specification, it is not readily clear to me that the skilled team, even with the benefit of their common general knowledge, is able to perform the process of the invention wherein the concentrations of certain biomarkers are measured and combined to assess the activation of complement cascade pathways as a function of time, and where in turn this activation data is fed into the model of the complement cascade which is characteristic of the infection, to thereby provide an output of the probability of the infection type present, as required by claim 1. Indeed, I note that it is in this regard that the Examiner proposed the specification to be classically insufficient.

20 The heart of the invention concerns how the concentration data of certain biomarkers are combined to assess activation of the complement cascade and wherein this

activation data is fed into the model of the complement cascade to provide an output of the probability of the infection type. How this is performed is set out on page 8 of the description, reproduced below for convenience, and in claim 1 (see paragraph 5 above):

> *"**First Differential Diagnosis - time evolution***
>
> *G+ infection $J_A + J_L > J_C$, elevated J_{LY}*
>
> *G-infection $J_A > J_L + J_C$, elevated J_{LY}*
>
> *Viral $J_A, > J_C + J_L$, depressed J_{LY}*
>
> *Fungal $J_A + J_L > J_C$, depressed J_{LY}*
>
> *Antibody response $J_C > J_A + J_L$ elevated J_{LY}"*

For ease of reference I will refer to the above statements as "diagnostic statements" hereafter. These statements are qualified on page 8 of the description by certain statements showing what constitutes activation of each complement cascade:

> ***"Serum Concentration markers - time evolution***
>
> *J_C activation - increasing C4a, depletion Cl, Clq, increasing CRP*
>
> *J_L activation -increasing C2b, depletion factor H, Factor I*
>
> *J_A activation -increasing C3a, decreasing C3, decreasing fH, fI, fD, decreasing properidin initially then rising.*
>
> *J_{LY} - increasing C5a, decreasing C6-C9"*

For ease of reference I will refer to these statements as "serum marker statements" hereafter.

Also relevant to understanding the serum marker statements is the passage at the foot of page 7 of the description:

> *"**Markers of activation***
>
> *Flux through each of the activation pathways J_A, J_C, J_L and the lysis pathway J_{LY} will be measured by the changes of the components of the pathway with respect to one another."*

For the avoidance of doubt, I take the "markers" of page 8 of the description to be synonymous with the "components" of page 7 of the description. In my view, I consider the skilled person/team seeking to work the invention is able to look at the serum marker statements and recognise the relevance of the markers to the activation of the complement cascade pathways and thereby know what measurements the invention proposes they make to determine if the complement cascade pathways were activated.

21 The "diagnostic statements" (which I note rather confusingly in the description, precede the "serum marker statements" which are used to calculate them), provide a model of the relationship between the fluxes in the complement cascade arising from certain infection statuses/ antibody response. The passage titled *First Differential Diagnosis - time evolution* on page 8 of the description and claim 1 itself teaches the skilled person to combine the fluxes according to the relationships therein and if those relationships are satisfied the skilled team would understand they have followed the diagnostic statements, and on the face of it, this would enable the infection status to be assigned to the patient. I have come to this conclusion based on the process set out in the description at page 8 and that of the claim as amended on 5 March 2018 and both lead me to the same conclusion. I note however that my conclusion differs somewhat from the Examiner's conclusion. The Examiner was of the opinion, and I quote from paragraph 10 of their pre-hearing report of 31st July 2018, that *"The application is not clear when it comes to instructing the unimaginative skilled person/team as to what* must *be measured (i.e. the biology) and how a comparison between the fluxes through the various complement pathways is to be made"* (emphasis added by the Examiner).

22 I am satisfied that the "diagnostic statements" enable the skilled person to assign an infection status to a post-operative patient using the changes in certain biomarkers indicated, albeit there would be some difficulty in making this assignment as the "diagnostic statements" and "serum marker statements" are rather obscure. However, I have construed the claims as requiring more than a mere assignment of a patient to different infection groups. Rather, in my opinion, the invention is in "determining / distinguishing different infections for a patient in the post-operative period", and the doubt I have over the sufficiency of the disclosure subsists in whether or not the skilled person is actually enabled to determine which infection is present with any certainty. In my view, this is because the "diagnostic statements" (provided under the heading *Differential Diagnosis* in the description and in claim 1 expressed as *'conditions'*) are a "black box" – with as far as I can determine, there being no evidence in the specification to justify whether or not they result in determining the infection status of the patient. In the absence of evidence, it is my contention that the "diagnostic statements" do not determine the infection status as the skilled person would have no reason to believe the statements were anything but speculative.

23 To test this, I have looked for disclosure/evidence in the specification to show that the "diagnostic statements" are not speculative. For example, I have looked at whether the specification might show the "diagnostic statements" to be an aspect of the prior art. Alternatively, whether the "diagnostic statements" could be derived empirically, which could be done by comparing the infection status assigned according to the invention with those determined by other means and showing that the probability of assigning patients to the correct diagnostic group, as confirmed by other means, is better than chance. I have therefore considered in particular the references in the description to the prior art and the experimental section of the description.

24 As regards the prior art references, I can find no indication that the diagnostic statements are known in the prior art, I have considered both the specification and admitted art with this purpose.

25 As regards the experimental evidence disclosed in the description, I note this relates to the change in log C-reactive protein (CRP) over time both before and in the first few days of the post-operative period (as shown in Figure 1). It is somewhat unclear what is shown in Figure 2. Whilst the figure legend for Figure 2 on page 5 lines 26-27 indicates that the Figure shows post-operative white blood cell count (WBC), the Y axis of Figure 2 is labelled as log CRP and the passage discussing Figure 2 on page 9 line 7-9 indicates a trend in CRP. Even if I were to conclude that the figures show how CRP and WBC count change in the post-operative period, I can find no assertion that this data facilitates determining the infection status in the post-operative period. Indeed the description at page 10 lines 12-17 appears to infer that this data does not allow the infection status to be determined:

> *"…… We analyzed the diagnostic accuracy of serial CRP and WBC measurements to detect infectious complications after colorectal resections.*
>
> - *However, CRP levels change considerably during the postoperative course in both uncomplicated and complicated cases, and they are not specific to any one kind of complication."*

Ultimately changes in CRP and WBC count do not appear to establish evidence for the “diagnostic statements” as the latter rely on several fluxes which are in turn derived from the "serum marker statements" (as set out on page 8 of the description and as referred to in paragraph 21 above), wherein the “serum marker statements” comprise many markers in addition to CRP and do not mention WBC at all.

26 On considering the specification, I have also been struck by the use of terms in the description which imply “what is to be done” rather than “what has been done”. For example in the section entitled "DEATILED DESCRIPTION OF PREFERRED EMBODIMENTS" (starting at the bottom of page 5 and which includes the passages I have already quoted from page 8), it is notable that the “diagnostic statements” are introduced as being "postulated" and relate to a "first differential hypothesis". I shall quote from page 6 lines 10-18 of the description to illustrate this:

> *"The CC [complement cascade] forms part of the innate response to infection providing two defence processes: opsonisation and the membrane attack complex. Early detection proteins trigger the remainder of the cascade providing primitive of [sic] antigen recognition of the surface of pathogens with some discrimination. Additional factors moderate the CC response providing a multiplexed response to an infection with postulated characteristic responses of the CC.*
>
> ***First Differential Hypothesis** requires that the CC response is differential towards Gram+, Gram-, viral and fungal pathogens."*

(my underlining for emphasis)

Use of the words *"postulated"* and *"hypothesis"* in my opinion indicate that the complement cascade changes in the post-operative period have not been measured and therefore the “diagnostic statements” are yet to be established in fact, or in other words, are speculative. This further dissuades me from finding that the “diagnostic statements” are not speculative.

27 I have found no evidence in the specification, either in the prior art references or the experimental section which show the “diagnostic statements” not to be speculative. To diagnose patients with any certainty using the process of the present claims as I have construed them would require the “diagnostic statements” to be tested and in my view, this would place an undue burden on the skilled person, [principle (vii) of *Eli Lilly*] or require prolonged research, enquiry or experiment [as in *Zipher*].

28 To summarise, I have used the teaching of *Eli Lilly* to formulate the question as to whether or not the invention is sufficiently disclosed. From this perspective, I consider that both the analytical system and its use in a process for assigning patients to different infection groups in the post-operative period are sufficiently described, but in my opinion assigning patients to different infection groups does not amount to "determining / distinguishing different infections for a patient in the post-operative period", with this being required by the claims as I have construed them. Insofar that I consider the “diagnostic statements” that underlie the assignments of patients to certain infection groups to be speculative, the skilled person would in my view conclude the assignments to infection groups to be speculative, with no confidence that a diagnosis had been made. I have sought evidence from the specification and the admitted prior art to consider whether the “diagnostic statements” are not speculative but I have not found any.

29 It is my opinion that the specification does not allow the invention to be performed over the whole scope of claim 1 as I have construed it, [as required by principle (vi) of *Eli Lilly*] and cannot be performed without undue burden [as required by principle (vii) of *Eli Lilly* or *Zipher*]. The specification appears to comprise an invitation to test a hypothesis proposed in the “diagnostic statements”. I therefore consider the invention to be classically insufficient.

Conclusion

30 Having carefully considered the information available to me, I conclude that the specification of GB1012376.8 does not 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, as required by Section 14(3) of the Act. There is no apparent way of curing this deficiency without contravening section 76. Therefore I refuse this application.

Appeal

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

Dr C L Davies

Deputy Director, acting for the Comptroller