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June 11, 2012

Board of Appeal
EUROPEAN PATENT OFFICE
Erhardtstr. 27
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Via fax and via mail

Our ref.: 4783/SW/bc

Re: Appeal number T 0772/12-3.3.08
European patent EP 1 616 184 B1
European patent application no. 04758356.2
in the name of Children's Hospital Medical Center, *et al*
Opposition by 1) Bioporto Diagnostics A/s
2) Dr. Kilger Ute

Dear Madams and Sirs,

this is to file the Patentee's Statement of Grounds of Appeal in connection with the earlier Notice of Appeal filed against the Written Decision of the Opposition Division (the "OD") dated January 31, 2012 to revoke the above-identified patent.

Patentee submits that the OD was wrong to revoke the above-mentioned patent, and that the patent should have been maintained on the basis of the Patentee's Main Request as filed with its letter dated December 29, 2010.

1. REQUESTS

1.1 Patentee confirms its request for cancellation of the Written Decision of the Opposition Division to the extent that the OD decided to reject Patentee's Main Request as well as each of the Patentee's Auxiliary Requests 1A-1D and 2-6 (as renumbered by the OD as Auxiliary Requests 1-9).

1.2 Patentee again requests the rejection of each of the two oppositions and maintenance of the patent on the basis of the Main Request that was filed with Patentee's letter dated December 29, 2010. The patent in suit, which represents an important technical contribution to the state of the art, satisfies all of the requirements of the EPC. It should therefore be maintained on the basis of the Main Request.

1.3 Patentee hereby requests the appointment of Oral Proceedings under the provisions of Article 116 EPC in the event that the Board of Appeal is

considering *not* maintaining the patent in suit on the basis of the Main Request.

1.4 In addition, Patentee reserves the right to: (i) expand on the present submissions both in writing and at any subsequent Oral Proceedings; and (ii) make amendments to the Main Request in order to deal with any deficiencies which the Board of Appeal considers to be present within an otherwise allowable set of claims; and (iii) file one or more auxiliary requests should the Board of Appeal arrive at an opinion that the patent in suit cannot be maintained on the basis of the Main Request.

2. INTRODUCTION

2.1 In the Written Decision, the OD correctly concluded that Patentee's Main Request fulfils the requirements of Rule 80 EPC and Articles 84 and 123 EPC. Indeed, the Opponents had no objections under any of these provisions (see Section 3 of the Written Decision, on pages 3 and 4). In addition, the OD concluded, once again correctly, that the subject matter of the Patentee's Main Request is novel over the disclosure in the state of the art, and is sufficiently disclosed by the patent in suit, thereby fulfilling the provisions of both Articles 54 and 83 EPC (see Section 4, paragraph 4.9 on page 7 of the Written Decision, and Section 5, paragraph 5.4 on page 8 of the Written Decision).

2.2 In light of the above, there is only one single issue to be addressed in this Statement of Grounds of Appeal, namely the OD's finding that the subject matter of the Main Request (and, by extension, of each of the auxiliary requests) does not reflect the presence of an inventive step. This finding, which led to the revocation of the patent, is clearly incorrect. Thus, as will be established below, the subject matter of the present invention as defined by the Main Request *does* reflect the presence of an inventive step, and the provisions of Article 56 EPC are therefore fully satisfied. The decision under appeal should now be set aside, and the patent should be maintained on the basis of the Main Request.

3. INVENTIVE STEP (Articles 56 and 100(a) EPC)

3.1 In conducting its assessment of whether the subject matter of the granted claims entails an inventive step, the OD's initial finding, that document D15 (Muramatsu *et al.*, 2002) is the closest prior art document, was entirely correct. Specifically, the OD correctly applied the Guidelines for Examination in the EPO, and the case law of the Boards of Appeal, and therefore found that document D15 would have offered the skilled person the most realistic and most promising starting point for further development. As determined by the OD, it is "*directed to a similar purpose and has the most features in common with Claim 1.*" Reference may be made to paragraph 6.1.1 on pages 8 to 9 of the Written Decision.

3.2 In this connection, document D15, like the patent in suit, relates to a method for the early detection of an ischemic renal tubular cell injury ("IRTCI"; hereinafter, an ischemic renal injury or "IRI") by testing the urine of a patient for a protein biomarker. In the case of the patent in suit, the biomarker is neutrophil gelatinase-associated lipocalin ("NGAL"); in the case of document D15, it is cysteine rich protein 61 ("Cyr61"). In further detail, document D15 reports that Cyr61 was detected in the urine at 3-6 hours, and peaked at 6-9 hours, following an ischemic renal injury. It concludes that Cyr61 is "rapidly induced in proximal straight tubules following renal ischemia, and excreted in the urine where it might serve as an early biomarker of renal injury" (see the Abstract of document D15, in the "Results" and "Conclusions" sections).

3.3 Now although the OD correctly identified document D15 as the closest prior art, it erred in its application of the subsequent steps of the problem and solution approach. Firstly, it did not fully understand, or accurately record, the technical problem which underlies the present invention. Then, after having misrepresented the underlying technical problem, it committed a further error by ignoring an aspect of that technical problem, apparently on the basis that the method of Claim 1, in its granted form, could not, as a matter of logic, solve that aspect across all of its claimed embodiments. Now since this was an aspect in respect of which the use of NGAL is, unexpectedly, far superior to the use of Cyr61, this error by the OD resulted in its disregard for the unforeseen advantages that the method of Claim 1 provides over the method disclosed within document D15, which advantages are identified in the patent and evidenced by its examples. Instead, the OD proceeded to reformulate the technical problem as the provision of a *mere alternative biomarker* for an IRI, and then decided, once again in error, that the solution to this reformulated technical problem, as set forth in Claim 1, would have been obvious to the person of skill in the art at the priority date of the present invention. This determination of obviousness was also unjustified because, even if one were to adopt the technical problem *as reformulated by the OD*, the subject matter of the claims should have been considered to be inventive.

3.4 In the following observations, the Patentee will investigate the two main elements of the OD's decision. It will examine in particular: (1) the OD's improper characterisation of the technical problem underlying the present invention, and its subsequent disregard for the unforeseen advantages that arise from the substitution of NGAL for Cyr61 in the method of detection that is described in document D15. These erroneous actions resulted in the OD's reformulation of the technical problem as the provision of a mere alternative urinary biomarker for IRI, which reformulation is incorrect; and (2) the OD's incorrect evaluation of the state of art, and the resulting conclusion that the common general knowledge at the priority date of the present invention would have rendered obvious the use of NGAL, as a mere alternative urinary biomarker to Cyr61, for the detection of an IRI.

3.5 ***The technical problem behind the present invention***

3.6 In relation to element (1), the Patentee will demonstrate as a preliminary matter that the OD has not fully understood, or accurately recorded, the technical problem that underlies the present invention, as set forth during the first instance proceedings. Moreover, whilst the OD would seem to have appreciated that the true technical problem at least involves an aspect of providing for an improvement, over the methods already known in the art, in respect of the early detection of an IRI, and, in particular, for the detection of an IRI even earlier than would be possible than when using Cyr61 as the biomarker (*e.g.* detection in the first 2 hours following the IRI), it would also seem to have disregarded this particular aspect from any further consideration.

3.7 In this regard (and perhaps as a result of its misrepresentation of the technical problem, which recites a 2 hour time point at which NGAL "appears" in the urine of a patient who has suffered an IRI), the OD has suggested that unless the granted Claim 1 is amended to specify that the urine sample is collected within 2 hours after the IRI, this aspect of the technical problem cannot be taken into account. In other words, the OD has concluded that without this amendment, the technical problem that was put forward by the Patentee (and misrepresented by the OD) is inadmissible, because the problem of providing for an improvement, as compared to the use of Cyr61, with respect to the early detection of an IRI, has allegedly not been solved across the full scope of Claim 1. Furthermore, this has resulted in the OD's decision to reformulate the technical problem as the provision of an *alternative urinary biomarker for the detection of an IRI* (see *e.g.* paragraph 6.2.1 of the Written Decision).

3.8 Each of these related points of element (1) will now be discussed in detail.

3.9 First, the OD has misrepresented the technical problem as presented by the Patentee as "... *to provide an early onset biomarker which appears as early as 2h after IRI*" (see *e.g.* paragraph 6.2.2 of the Written Decision). However, in the context of a *method* claim that relates to achieving a technical effect (Claim 1; detection of an IRI), it is clearly improper to formulate the technical problem as "the provision of *a biomarker*": one should at least refer to the provision of an improved *method*. In addition, it is clearly incorrect to refer to an inherent property of the biomarker that was not even recognised at the priority date of the patent: at that date, it was not even known that *there might exist a biomarker* for an IRI which "appears" within the urine as early as 2 hours after the injury. In sum, the OD's characterisation of the technical problem as presented by the Patentee is considered to be improper, and the problem should have been formulated differently so as to refer to the provision of an *improved method for the early detection of an IRI.*

3.10 Also in this regard, this technical problem is considered to be more accurate because it takes account of two important facets of the early detection of an IRI, *i.e.* it not only takes account of:(i) the time taken for the biomarker to "appear" in the sample (*i.e.* for the level of the biomarker to be significantly different from the level that exists in healthy patients); but also (ii) the time taken for the processing of the sample, and for the performance of the assay, before a signal can be measured and hence an IRI can be detected. Both of these facets are important in the early detection of an IRI, which is in turn advantageous because it permits a therapeutic intervention to be initiated as soon as possible after the ischemic event, thereby, *inter alia*, reducing the risk of acute renal failure ("ARF").

3.11 In relation to this more accurate formulation of the technical problem, the application that led to the patent in suit reports, in paragraphs [0003] to [0007] of the description, that:

> "*[the] introduction of therapy early in the disease process will reduce the mortality rate associated with ARF and shorten the time for treatment of various types of renal tubular cell injuries, including ... ischemic ... injuries. The identification of a reliable, early biomarker for a renal tubular cell injury would be useful to facilitate early therapeutic intervention.*"

3.12 The application in suit further reports that the traditional biomarkers that were known in the art at the priority date of the present invention, such as *e.g.* serum creatinine:

> "*... do not allow for early detection of the disease ... Indeed, while a rise in serum creatinine is widely considered as the "gold standard" for the detection of ARF, it is now clear that as much as 50% of the kidney function may already be lost by the time serum creatinine changes.*"

3.13 Moreover, the application identifies two urinary biomarkers for IRI that were known in the state of the art at the priority date of the patent, *i.e.* KIM-1 and Cyr61 (the latter being the biomarker that is described in the closest prior art document, D15). With specific regard to KIM-1, the application notes that it was found to be upregulated only after 24-48 hours after an ischemic renal insult, this rendering KIM-1 a "reliable but *somewhat late marker of tubular cell damage*". As for Cyr61, this was found to be better than KIM-1 since it is "detectable in the urine 3-6 hours after ischemic renal injury in animal models". However, one main disadvantage of Cyr61 is that the assay for detecting it comprises "a bioaffinity purification and concentration step with heparin sepharose beads, followed by a Western

blotting protocol." This means that critical time is lost while the assay is being conducted, thereby delaying any therapeutic intervention which may turn out to be required. In sum, at the priority date of the present invention, there was a need for a biomarker which both "appears" as soon as possible after an IRI has occurred, and, furthermore, whose assay procedure for detection is as simple and rapid to perform as possible. In this regard, the early detection of an IRI is further disclosed in *e.g.* paragraphs [0035], [0036], [0049] and [0051] of the application as filed.[1]

3.14 In light of the above, the OD's characterisation of the technical problem presented by the Patentee, *i.e.* "... to provide an early onset biomarker which appears as early as 2h after [an] IRI", is a misrepresentation. Thus: it refers to the provision of a *molecule*, instead of a *method*; it references a *property* of NGAL, instead of an *objective*; it relies on *hindsight knowledge* of the present invention (the "appearance" of NGAL in the urine in less 2 than hours); and it only refers to the early *appearance* of NGAL, instead of the early *detection* of an IRI, thereby ignoring that part of the technical problem which relates to permitting the early detection of an IRI by improving the simplicity and speed of the assay. In short, the OD's representation of the technical problem as set forth by the Patentee is certainly improper, and the technical problem should more accurately be formulated as *providing for an improved method for the early detection of an IRI.*

3.15 ***The OD's disregard for the temporal aspect of the problem – early detection***

3.16 Now as discussed above, the OD has disregarded the aspect of the technical problem of detecting an IRI as quickly as possible after the ischemic event, and, indeed, *earlier than would be possible using Cyr61 as the biomarker* (*e.g.* within 2 hours from the IRI). In this connection, the OD has implied that unless Claim 1 is amended to require that the urine sample be collected within 2 hours of the IRI, this aspect of the technical problem cannot be considered, because that the advantage of NGAL, as compared to the use of Cyr61, would not be achieved across the full scope of the claim (in the opinion of the OD, "[no] technical effect [would be] associated with this difference", see paragraph 6.2.1 on page 9 of the Written Decision). Now as a result, the unexpected advantages of the method of the present invention, as compared to a corresponding method in which Cyr61 is used as the biomarker (*e.g.* the improvement that the method provides in relation to the early detection of an IRI), have not been taken into consideration. Moreover, the OD decided that the technical problem should be reformulated as the provision of a *mere alternative urinary biomarker* for detecting an IRI (see *e.g.* paragraph 6.2.1 of the Written Decision).

3.17 Now having regard to the true technical problem that is presented above, of providing for an *improved method for the early detection of an IRI*, it is clear that the OD's approach to this matter was flawed.

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1 Having regard to the ability of a detection method based on NGAL to address the technical problem of providing for an improvement with respect to the early detection of an IRI, reference may be made to *e.g.* paragraph [0037] of the application as filed, which discloses a particularly advantageous property of NGAL, *i.e.* the fact that it "appears" in the urine within 2 hours after the onset of an IRI, and, moreover, in the first urine output of a subject immediately *after* the onset of an IRI (this qualifying NGAL as an "immediate" biomarker of an IRI, as well as an "early-onset" biomarker of an IRI). Reference may also be made to paragraphs [0054] and [0060] of the application, and to Examples 5 and 6 and the related Figure 16A. Finally, and with respect to the ability of NGAL to be rapidly measured in a urine sample from a patient, attention is directed to paragraph [0059] of the application as filed. This teaches the ability of NGAL to be "*easily and rapidly detected* as relatively clean immunoreactive peptides in Western blots with as little at 1µl of the very first *unprocessed urine* output following renal ischemia". In short, it is clear from the above that the use of NGAL as a urinary biomarker for IRI, in place of Cyr61 as used in the state of the art, provides for significant improvements in that it appears within the urine more quickly after an IRI has occurred, and it takes less time to detect in an assay. Therefore, NGAL provides for the earlier detection of ischemic renal injuries and, as a direct result, for an opportunity to initiate an earlier therapeutic intervention.

3.18 Thus, to examine the OD's reasoning in detail, its incorrect decision to ignore the aspect of detecting an IRI as soon as possible after the occurrence of an IRI, and earlier than a corresponding method which uses Cyr61 as a biomarker, thereby so as to provide for an improved method for the early detection of an IRI, was based on the fact that the granted Claim 1 does not recite any specific time point, after an IRI, at which the level of urinary NGAL must be determined. In particular, in paragraph 6.2.2 of the Written Decision, the OD states that:

> "*The Patentee defined the problem to be solved as to provide an early onset biomarker which appears as early as 2h after IRI. The Opposition Division observes that claim 1 does not indicate any time point at which NGAL is detected after IRTCI. Hence, such a feature should not be taken into account when formulating the objective technical problem based on the distinguishing features between the claimed invention and the closest prior art.*"

3.19 To further investigate the OD's reasoning, it would seem to have acknowledged that if a urine sample from the patient were to be taken *within 2 hours* after the IRI, then the use of NGAL would be advantageous, as compared to the use of Cyr61, because the level of NGAL in the urine would be detectably different (*i.e.* NGAL would "appear" in the urine) whereas the level of Cyr61 would not. Having said this, the OD would also seem to have concluded that if the urine sample from the patient were to be taken much later, *e.g.* at say 6 hours following the IRI, then the use of NGAL would be *equivalent to, rather than an improvement over*, the use of Cyr61. In this connection, the OD would seem to have concluded that at this later time point, both of the biomarkers will show an elevated level in the urine as compared to their corresponding control values in healthy individuals, and that as a result, both biomarkers will provide, equally, for the detection of the IRI. Thus, the OD found that because the granted Claim 1 does not require the urine sample from the patient to be taken *before* the time point, following an IRI, at which the level of Cyr61 rises to above a normal, healthy value (on the basis of document D15, this is 3-6 hours after the IRI), the advantages of the use of NGAL, when compared to the use of Cyr61, purportedly do not extend across the scope of Claim 1; this permits the collection and testing of the urine sample to occur *after* that time point.

3.20 Now as the Board of Appeal will readily appreciate, the OD's analysis is clearly incorrect.
Firstly, the granted Claim 1 defines "A method for *the detection of* [an IRI]". Accordingly, it is clearly inappropriate to have to recite a specific time point, *after the IRI*, at which the claimed method for *detecting* the IRI should be performed: if a skilled person *knows* that an IRI has occurred in the patient 2 hours earlier, then there is no need to conduct any method for *detecting if an IRI has occurred.*

3.21 Secondly, and, in particular, because a skilled person who practices the claimed method *does not know*, by definition, whether or not an IRI has occurred, the method of Claim 1, in its present format, *does* provide for an advantage, across its full scope, as compared to a corresponding method in which Cyr61 is used as the biomarker (*i.e.* it does provide for an improvement, with respect to the early detection of an IRI, across the full scope of that claim). This is because the claimed method, whenever it is performed, provides for an advantage in this respect: it not only allows for the detection of those ischemic renal injuries which would also be detected using Cyr61, but it also provides for the detection of very recent ischemic renal injuries that would not be detected using Cyr61, *e.g.* those ischemic renal injuries which have occurred only 2 hours previously. In other words, the method of Claim 1 provides for the earlier detection of such ischemic renal injuries than would

otherwise be possible, since when using a different biomarker, such as Cyr61, the injuries would go undetected, and may not be identified until a subsequent testing of the patient's urine, or indeed at the incidence of overt clinical signs of the IRI.

3.22 Now although there may be certain occasions on which carrying out the claimed method, or carrying out a corresponding method in which Cyr61 is used as a biomarker, will both provide for the detection of an IRI that has previously occurred (*e.g.* on occasions when an IRI has, unknowingly, occurred 6 hours earlier), this certainly does not undermine the advantages of the claimed method, or the fact that they extend across the scope of the claim. This is because, when initiating the method of Claim 1, a skilled person does not know whether or not an IRI has occurred but, nevertheless, *on each of those occasions*, the claimed method, as compared to a corresponding method in which Cyr61 is used as the biomarker, *increases the likelihood of any IRI which has occurred being detected*. In particular, NGAL "appears" in the urine at levels that are detectably different from normal control values at time points, after an IRI, at which Cyr61 does not: this can be described as a longer "detection window". Thus, the method of Claim 1, of detecting whether or not an IRI has occurred, is – each and every time that it is performed – highly advantageous over a corresponding method in which Cyr61 is used as the biomarker. In summary, the OD was wrong to disregard the temporal aspect of the technical problem (to provide for an *improved method for the early detection of an IRI*), since the improvement that arises from the use of NGAL as the biomarker, as compared to the use of Cyr61, *does* in fact extend across the scope of Claim 1. The OD's reformulation of the technical problem as the provision of an alternative biomarker to Cyr61 is entirely incorrect, as is its resulting conclusion that the subject matter of Claim 1 would have been obvious.

3.23 ***The alleged obviousness of NGAL as an alternative urinary biomarker for an IRI***

3.24 Patentee turns to element (2) of the OD's reasoning, where the OD would seem to have made an incorrect assessment of the common general knowledge within the state of the art at the priority date of the present invention. Based on this incorrect assessment, and a mistaken reformulation of the objective technical problem behind the present invention, it then arrived at an unjustified conclusion that the use of NGAL, as an *alternative urinary biomarker* to Cyr61 for the detection of an IRI, would have been obvious to the person of skill in the art.

3.25 To consider in more detail the OD's evaluation of the common eneral knowledge in the art, the OD determined that at the priority date of the present invention, a person of skill in the art would *allegedly* have understood that a renal ischemic event results in damage to kidney tissue which causes cellular debris, including proteins, to be released into the urine. Accordingly, the OD argues that the skilled person would have expected that as a result of a renal ischemic injury, a detectable increase in the concentration of the NGAL protein within the urine would be inevitable.

3.26 Furthermore, whilst the OD acknowledges that low-molecular weight proteins ("LMWP") which enter into the tubular filtrate are reabsorbed into the kidney tissue by the proximal tubules, it argues that the person of skill in the art would have expected that the above-mentioned allegedly anticipated increase in the release of NGAL into the tubular fluid, as a result of the kidney damage, would not be offset by increased reabsorbtion. Therefore, the OD opines that a person of ordinary skill in the art would have expected an increase in the level of NGAL, within the urine, as a result of an IRI (see the Written Decision from the first full paragraph on page 11 to the end of the first full paragraph on page 12). In support of this premise, the OD also refers to documents D6 (Weinberg, 1991) and D17 (Racusen, 2001).

3.27 Now as an initial matter, the OD's conclusion in this part of the Written Decision, that any protein that is expressed in kidney tissue will show an increased appearance in the urine as a result of an IRI, is entirely inconsistent with the remainder of the Written Decision. For example, the Patentee has pointed out that in response to an ischemic renal injury, numerous proteins are upregulated in the kidney tissue.[2] However, the OD pointed out, in paragraph 6.3.3 of the Written Decision, that:

> "*There is no doubt that many genes are up-regulated in response to IRI (D21: abstract). Few of the corresponding proteins, if up-regulated in response to IRI, will turn out to be [a] good urinary biomarker for IRI.*"

3.28 Accordingly, this latter acknowledgement, that few of the hundreds of proteins which are upregulated in kidney tissue in response to an IRI will turn out to be an effective urinary marker for IRI, clearly contradicts, and proves the fallacy of, the previous assumptions of the OD, *i.e.* that a skilled person would expect that *any* protein that is upregulated in the kidney tissue will inevitably exhibit a significant and detectable increased appearance in the urine as a result of the damage to the kidney cells which results from an IRI.

3.29 Also in this regard, the OD's finding, that the damage to kidney cells that is caused by an IRI will produce an inevitable increase, in the urine, of any protein which is expressed in kidney tissue, also fails to account for the fact that tissues that are exposed to damaging insults often seek to retain and indeed reclaim valuable nutrients, such as proteins, from the extracellular environment, since the building blocks of those nutrients are needed for tissue regeneration and repair (reference is made to document D23, the declaration from Professor John Kellum, at paragraph 22).

3.30 Turning next to a brief discussion of the cited documents D6 and D17, Patentee submits that the OD's assertions, that a person of skill in the art at the priority date of the present invention would have readily expected that an IRI results in damage to the kidney tissue which causes *any* protein that is expressed in that tissue to be released into the urine, is not supported by these references. As explained in document D17 (see page 1, column 2, in the final paragraph, lines 1-2) "*the process of renal tubular injury and repair is very complex*", which means that the OD's reliance on certain passages in these documents, which passages have been taken out of context, is considered to be unjustified.

3.31 By way of an example, the OD refers to the loss of the apical brush border which occurs in response to a renal tubular cell injury, and asserts that "*at least some of the molecules present in the disappearing apical brush border are released into the urine*" (page 11 of the Written Decision, middle paragraph, lines 8-10, referring to D17 at page 2, column 1, final paragraph). However, the OD fails to note that the molecules that are being referred to are brush border *enzymes* (*i.e.* gamma glutamyl transpeptidase ("GGTP") and alkaline phosphatase), whereas NGAL is not an enzyme. Further, the OD's reference to "*at least some* of the molecules present in the disappearing brush border" only serves to highlight the fact that the OD *itself* believes that *not all of the molecules* that are expressed in the brush border will be released into the urine as a result of an IRI.

3.32 As for the passages which relate to the death of tubular epithelial cells and their release into the lumen (see *e.g.* document D17, page 2, column 2, final paragraph), here the OD is

2 See document D21 (Yoshida *et al.*, 2002): the Patentee was demonstrating that the mere upregulation of NGAL that is reported within document D1 (Matthaeus *et al.*, 2001) does not provide any reasonable expectation that NGAL would serve as an effective urinary biomarker for the detection of an IRI.

overlooking the fact that the document in fact teaches that tubular epithelial cells can be retained in the renal tubules, where they form aggregates or "casts". Further, the OD refers to cellular disintegration and/or fragmentation, and to cellular remnants being shed into the urine, thus implying, without any justification, that dying tubular cells "burst open" and spill all of their protein contents – but only after they have sloughed from the tubular epithelium, and are therefore remote from neighbouring cells which might salvage those protein contents.

3.33 Finally, and importantly, the *timing* of any of the above-mentioned events that allegedly result in the release of the NGAL protein into the urine, in comparison to the occurrence of the overt clinical signs of an IRI, has not been discussed by the OD. Furthermore, the *extent or severity* of those events, and therefore the amount of the NGAL protein that is allegedly released into the urine, has also not been examined. Without any teaching of these factors, however, a person of skill in the art could not have anticipated that NGAL would provide for an *alternative urinary biomarker* to Cyr61, even if he were to assume, that the NGAL protein, because it is expressed in the kidney tissue, will demonstrate at least some increased appearance in the urine as a result of an IRI.

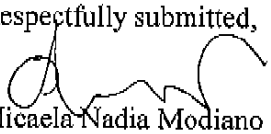
3.34 Specifically, as was set forth during the first instance proceedings before the OD, and as evidenced by the declaration by Professor Kellum (document D23) in paragraph 9:

> "*... the mere possibility of [a] protein finding its way into the urine is not sufficient, by itself, to predict that the protein will be an effective biomarker of an ischemic renal injury. To the contrary, in order to make any such determination, a scientist in the field would need to have observed each of the following properties:*
>
> *(a) that as a result of an ischemic renal injury, there is a change in the concentration of the protein within the urine;*
>
> *(b) that this change is sufficient for patients suffering from an ischemic renal injury to be reliably distinguished from healthy individuals and, ideally, is sufficiently large that the concentration of the protein as a result of the change is well outside of the range observed for healthy individuals and, preferably, different from the values that are observed for individuals who are suffering from renal conditions other than acute kidney injury;*
>
> *(c) that this change in the concentration of the protein is rapid, such that an ischemic renal injury can be detected, and therapeutic intervention can be started, as early as possible, before acute kidney injury is obvious from a clinical perspective, and certainly before acute renal failure ensues;*
>
> *(d) that (in the absence of any therapeutic intervention) the change in the concentration of the protein is sustained, or it does not decline so rapidly that it will not be detected if the assay were not to be conducted immediately after the onset of the ischemic renal event (i.e., there is a reasonable "detection window");*
>
> *and*
>
> *(e) that the candidate protein is stable within the urine such that the assay method does not require any special (or worse still impractical) precautions as to e.g. sample handling or preparation techniques.*"

3.35 In this regard, it should certainly be clear from the Written Decision (see paragraph 6.3.2 and the summary paragraph 6.3.5), that whilst the OD has asserted that a "knowledge of the pathophysiological changes in the renal tubules during IRTCI would lead the skilled person to expect that increases in NGAL expression in the proximal tubule due [to] IRI would also be detectable in urine", the OD has failed to consider the above observations, *e.g.* the skilled person's uncertainty as to whether any anticipated increase in the level of NGAL in the urine would be "*sufficient for patients suffering from an ischemic renal injury to be reliably distinguished from healthy individuals*", and would also be "*rapid, such that an ischemic renal injury can be detected, and therapeutic intervention can be started, as early as possible, before acute kidney injury is obvious from a clinical perspective*". As a result, even if the OD were correct that the person of skill in the art would have expected that an IRI would result in an increase in the concentration of NGAL within the urine, it is certainly not the case that he could have predicted that NGAL would be able to act as a effective urinary biomarker for an IRI.

3.36 In review of the above, even if the technical problem were considered to be the provision of an alternative urinary biomarker to Cyr61 for the detection of an IRI (or the provision of an alternative method of detecting an IRI), the subject matter of the present invention would certainly not have been obvious to a person of skill in the art at the priority date of the present invention. The subject matter that is defined by the Patentee's Main Request represents a valuable technical contribution to the state of the art, and the patent should have been maintained on the basis of that request.

Respectfully submitted,



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