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Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP 1 831 699 B1
Application No.	05820913.1
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	11.11.2009
Title of the invention	Determination of neutrophil gelatinase-associated lipocalin (NGAL) as as diagnostic marker for renal disorders

II. Proprietor of the patent

first named in the patent specification	Antibodyshop A/S
Opponent's or representative's reference (max. 15 keystrokes)	M/51140-OPPO

III. Opponent

Name	Getica AB
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State of residence or of principal place of business	Sweden
Nationality	Sweden
Telephone/Fax	
Multiple opponents (see additional sheet)	☐

Zur Kasse
705 €

IV. Authorisation

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Additional representative(s) on additional sheet/see authorisation	☒

Opponent's reference M/51140-OPPO

EPO 2300.1 04.08

2. Name(s) of employee(s) of the opponent authorised to act in these opposition proceedings under Art. 133(3) EPC

Authorisation(s) to 1./2.

not considered necessary ☒

has/have been registered under No. ☐

is/are enclosed ☐

V. Opposition is filed against

• the patent as a whole ☒

• claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC) ☒

• it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒

• patentability is excluded on other grounds, i.e. Article ☐ Art.

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC) presented in support of the opposition are submitted herewith on a separate sheet (annex 1) ☒

VIII. Other requests:

On an auxiliary basis, oral proceedings according to Art. 116 EPC are requested, in the event that the opposed patent is not revoked on the basis of the present written submissions.

Opponent's reference M/51140-OPPO

IX. Evidence presented

Evidence is enclosed ☒

will be filed at a later date ☐

A. Publications:

1

Particular relevance (page, column, line, fig.): WO2004/088276
Ex. 5., Figures

2

Particular relevance (page, column, line, fig.): WO2005/121788
Ex. 3, Figures

3

Particular relevance (page, column, line, fig.): Mishra et al, The Lancet, (2005) 365, 1231
Summary, Figure 2

4

Particular relevance (page, column, line, fig.): Mishra et al, J Am Soc Nephrol (2003) 14:2534-2543
pp. 2541, 2542, 2534

5

Particular relevance (page, column, line, fig.): Mishra et al, Am J Nephrol (2004) 24: 307-315
entire document

6

Particular relevance (page, column, line, fig.): Xu S and Venge P, Biochimica et Biophysica Acta 1482 (2000) 298-307
pp. 303, 304

Continued on additional sheet ☒

B. Other evidence

Continued on additional sheet ☐

Opponent's reference M/51140-OPPO

X. Payment of the opposition fee is made

- as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010) ☒
- via EPO Online Services ☐

XI. List of documents

Enclosure No.

0 Form for notice of opposition ☒

1 Facts (see VII.) ☒

2 Copies of documents presented as evidence (see IX.)

a Publications D1-D10 ☒

b Other documents ☐

3 Signed authorisation(s) (see IV.) ☐

4 Voucher for payment of fees and costs (see X.) ☒

5 Additional sheet(s) ☒ Number of sheets 2

6 Other ☐

Please specify here:

XII. Signature of opponent or representative

Place: Munich

Date: August 2, 2010

Signature: 

Name (block capitals): Georg Schweiger

In case of legal persons, signatory's position within company:

Opponent's reference M/51140-OPPO

Opponent: Getica AB
Our Ref.: M/51140-OPPO

Additional Sheet I
Opposition against EP 1831699

Continuation of IX., A

7. Uttenthal, L.O. CLI 2005
Particular relevance (page, column, line, fig.): entire document

8. Helge Erik Solberg: "Establishment and Use of Reference Values." Chapt. 13 in Tietz Textbook of Clinical Chemistry, 2nd Edition, ISBN 0-7216-4472-4, W. B. Saunders Company, United States of America, 1994
Particular relevance (page, column, line, fig.): pp. 454-457

9. Xu, S.Y. et al., Scand.J.Clin.Lab. Invest (1995) 55:125-131
Particular relevance (page, column, line, fig.): pp. 125, 127, 130

10. Mori, K. et al., The Journal of Clinical Investigation (2005) 115: 3, 610-621
Particular relevance (page, column, line, fig.): p. 611, Fig. 1

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Our Ref.: M/51140-OPPO

Additional Sheet II
Opposition against EP 1831699

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Munich, 02.08.2010

Our Ref.: M/51140-OPPO

Re.: **European Patent EP-B1-1 831 699 (DETERMINATION OF NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN)**
Patentee: Antibodyshop A/S
Opponent: GETICA AB

Annex 1

Facts in Support of the Opposition

A. Cited References

In our subsequent submissions, we will refer to the following references:

No.	Reference	Publication date
D1	WO2004/088276 (= D1, Exam)	14.12.2004
D2	WO2005/121788 (= D4, Exam)	22.12.2005
D3	Mishra et al, The Lancet, (2005) 365, 1231	April 2, 2005
D4	Mishra et al, J Am Soc Nephrol (2003) 14:2534-2543,.	2003
D5	Mishra et al, Am J Nephrol (2004) 24: 307-315	May 12, 2004
D6	Xu S and Venge P, Biochimica et Biophysica Acta 1482 (2000) 298-307	2000

D7	Uttenthal, L.O. CLI 2005	November 2005
D8	Helge Erik Solberg: "Establishment and Use of Reference Values." Chapt. 13 in Tietz Textbook of Clinical Chemistry, 2nd Edition, ISBN 0-7216-4472-4, W. B. Saunders Company, United States of America, 1994.	1994
D9	Xu, S.Y. et al., Scand.J.Clin.Lab. Invest (1995) 55:125-131	1995
D10	Mori, K. et al., The Journal of Clinical Investigation (2005) 115: 3, 610-621	March 2005

B. The Claimed Subject Matter

Claim 1 of the opposed patent refers to the following subject-matter:

No.	Feature
1	A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being,
2	wherein said method discriminates between a renal disorder and another condition that does not affect the kidney, said method comprising the steps of
3	i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of bodily fluid from the human being,
4	ii) comparing said concentration with a predetermined cut-off value,
5	said cut-off value being 250 ng/ml or a higher value,
5a	such as a value between 250 and 525 ng/ml
6	chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cut-off value is indicative of a renal disorder

In our subsequent submissions we will adhere to the numbering of the features as stated in the above table.

Subclaims 2 to 17 further specify the analytical method as claimed in claim 1.

C. Revocation under Art. 100 c) EPC – Added Subject Matter (Art. 123 (2) EPC)

1. Claim 1

The patentee entered the European phase of International Patent Application WO 2006/066587 on the basis of an amended set of claims which previously had been submitted with a letter dated October 19, 2006. Said amended set of claims comprised a modified main claim representing a combination of original claim 1 and the specific cut-off-values as disclosed in original claims 2 and 3. Said modified main claim is identical with granted claim 1.

A careful analysis of the original disclosure of the original application text (WO 2006/066587) leaves no doubt that the wording of the granted main claim extends beyond the original disclosure of said application text.

In particular, as a result of said modification the specific cut-off-values of "250 ng/ml", such as those between "250 ng/ml and 525 ng/ml" (see features 5 and 5a) which, according to the original disclosure of the application text, had been disclosed exclusively and **specifically for urine samples** (see original claim 2) **or plasma or serum samples** (see original claim 3) have been inadmissibly **generalized**, as they now refer, according to the wording of the allowed main claim (see feature 3), **to any bodily fluid sample**.

It is well-established that the term "bodily fluid" is understood by a skilled reader broadly, and encompasses **other** bodily fluids as, for example, sputum or spinal fluid, and is not understood be limited to "urine, plasma or serum". As no specific definition for "bodily fluid" is given in the application text, a skilled reader will apply said broader interpretation of said term "bodily fluid", and will note that there is not the slightest basis for extending the specific cut-off-values (as disclosed in original claims 2 and 3 merely for urine, plasma or serum samples) to any other bodily fluid samples, as for example sputum or spinal fluid.

Consequently, claim 1 violates Art. 123 (2) EPC and justifies revocation of the opposed patent under Article 100 c) EPC.

2. Claim 13

The amended set of claims filed with letter of October 19, 2006 also comprised a modified claim 13 which corresponds to granted claim 13. Said claim 13 refers to a specific embodiment of the method of claim 1 and encompasses a further step of comparing the observed NGAL concentration with a second cut-off-value. Granted claim 13 explicitly teaches:

> *"...said second cut-off-value being chosen to exclude lower concentrations of NGAL* ***not associated with a degree of renal disorder that requires treatment*** *of the patient by dialysis, wherein a concentration above the cut-off-value* ***is indicative of a renal disorder*** *requiring treatment by dialysis."* **[emphasis added]**

Contrary to this, the original disclosure of the corresponding passage of original claim 13 reads as follows:

> *"..said second cut-off-value being chosen to exclude lower concentrations of NGAL* ***associated*** *with a degree of renal disorder* ***that is unlikely to*** *require treatment of the patient by dialysis, wherein a concentration above the cut-off-value* ***is indicative of a severe degree of renal disorder that is highly likely to*** *require treatment by dialysis."* **[emphasis added]**

There can be no doubt that the specific methods of granted claim 13 and original claim 13 are completely different, as the obtained final analytical result is completely different. While the method of claim 13 as granted teaches to select a second cut-off-value which specifically and **without any uncertainty** will be indicative of a renal disorder requiring treatment by dialysis, while the explicit teaching of claim 13 as originally filed refers to a second cut-off-value that is **associated with some uncertainty** of interpretation because it is indicative to those patients for which it is merely **highly likely** (i.e. associated with some uncertainty) to require treatment by dialysis.

Moreover, claim 13 as originally filed refers to patients with a "severe degree with renal disorder" while granted claim 13 does not refer to any specific degree of renal disorder and just states that said patients, which will require treatment by dialysis, suffer from "a renal disorder". This means that, according to the teaching of granted claim 13 a much broader group of

patients (patients suffering from a renal disorder) is now encompassed while, according to the teaching of original claim 13, merely such patients with "a severe degree of renal disorder" are evaluated.

There can be no doubt that claim 13 as granted refers to a completely different analytical method if compared to the method of claim 13 as originally disclosed.

Consequently, claim 13 as granted contravenes Article 123(2) EPC and justifies revocation of the opposed patent under Article 100 c) EPC.

D. Revocation under Art. 100a) EPC - Lack of Patentability (Art. 52 to 57 EPC)

1. Invalidity of the Priority Claims

The opposed patent claims priorities of:

- USSN 60/637,503, December 20, 2004, subsequently designated **"P1"** and

- USSN 60/719,307, September 21, 2005, subsequently designated **"P2"**.

It will be explained below that at least claim 1 and claim 13 of the granted set of claims refer to subject-matter **for which neither the priority of P1 nor of P2 can be validly claimed**.

1.1 Claim 1

As can be taken from the above listing of features, the method of claim 1 is based on a determination of human NGAL in a bodily fluid sample (feature 3) and on determining a cut-off-value being 250 ng/ml or higher (feature 5), such as between 250 of 525 ng/ml (feature 5a).

In the subsequent table, said features of granted claim 1 are compared to the corresponding disclosure of claims and/or description of the two priority documents P1 and P2.

EP-B1-1 831 699	P1 (Dec.20, 2004)		P2 (Sept.21, 2005)	
any body fluid	urine	plasma/serum	urine	plasma/serum
≥250 such as 250-525	no specific cut-off claimed	no specific cut-off claimed	claim 2 ≥1500, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000	claim 3 ≥300, 350, 400, 500, 600, 700, 800, 900,
	p.12 one single cut-off disclosed: **about 1000**	no specific cut-off disclosed	p.7 between 500 – 10.000, such as 1000,1500, 2000, 3000, 4000,5000, 6000, 7000, 8000, 9000, 10000	p.7 between 300 –900 such as 350, 400, 500, 600, 700, 800, 900

Values stated in ng/ml

As can be taken from said table, priority document P1 discloses **one single** cut-off-value of **about 1000 ng/ml** obtained from **urine** samples. At the end of page 12 P1 literally teaches:

> *"These results suggest that a cut-off-value of about 1000 ng/ml (1 µg/ml) defines the urinary concentration of NGAL above which it becomes indicative of clinically significant renal affection. In an established case of ATN, the value is expected to be much higher."*

Evidently, priority document P1 does not disclose the cut-off-values (≥250 or 250 to 525 ng/ml) as claimed in allowed claim 1 and correlated to any bodily fluid sample.

An analysis of the disclosure of priority document P2 allows the following conclusions: While sets of cut-off-values (one for urine, and one for plasma and serum) have been disclosed, said two sets of cut-off-values are

considerably different and **appear to be unique** for either urine samples or plasma and serum samples. Moreover, neither the specific cut-off-value of 250 ng/ml nor said range of 250 to 525 ng/ml as stated in allowed claim 1 of the opposed patent is specifically disclosed in P2. Nor is there any disclosure for cut-off-values valid for "any bodily fluid".

Evidently the subject-matter of allowed claim 1 of the opposed patent can't rely on the priority dates of P1 and P2.

1.2 Claim 13

As stated above, the subject-matter of allowed claim 13 refers to a specific embodiment of claim 1 characterized by determining a second cut-off-value allowing to distinguish between patients with renal disorders that require treatment of the patient by dialysis and those patients suffering from a renal disorder which do not require treatment by dialysis. While priority document P1 does not teach said specific embodiment (determining a second cut-off value at all), the disclosure of priority document P2 (see claim 12) is limited to such second cut-off-values:

> *"... being chosen to **exclude** lower concentrations of NGAL associated with renal disorders that are not acute tubular necrosis or acute tubulo-intestinal nephropathy, wherein a concentration above the cut-off-value is **indicative of acute tubular necrosis or acute tubulo-intestinal nephropathy**."* **[emphasis added]**

Choosing a second cut-off-value that allows distinguishing between diseased patients requiring by dialysis or not, is not supported by the disclosure of P2.

Consequently, the specific subject-matter of claim 13 is not supported by each of the two priority documents P1 and P2.

1.3 Conclusion

As a consequence of the above-discussed invalidity of any of the two priority claims, **the actual filing date of the opposed patent is December 20, 2005,** i.e. the international filing date of WO 2006/066587. Thus, any prior art reference with an effective date before the filing date of December 20, 2005

has to be considered during the subsequent discussion of novelty and/or inventive step of the claimed subject-matter.

2. Lack of Novelty and Inventive step

2.1 NGAL - a well-established and well-characterized biomarker

Document D4 (Mishra et al,: J Am Soc Nephrol 14:2534-2543, 2003) identifies NGAL as a novel early biomarker for ischemic renal injury.

In the "Results" section on page 2538, it is described how NGAL is an early biomarker of renal ischemic injury, which easily is detected in urine in rats and mice by Western analysis (an antibody based solid phase immunoassay technique). In Fig. 9 on page 2541, it is illustrated that cis-platin induced kidney injury in mice leads to early presence of NGAL in the urine. On page 2542, of D4, right col. l.6 to 9 it is concluded:

> *"Thus, the upregulation and urinary excretion of NGAL may represent a rapid response of renal tubule cells to a variety of insults."*

In lines 21 and 22, right col. on page 2541, it is noted that the NGAL secretion in urine is not related to any neutrophil granulocytes present, indicating that NGAL levels observed there were not related to inflammation.

Thus D4 demonstrates that NGAL is an early marker of kidney injury of different etiologies, suggests its use as a general early urine marker of kidney injury, and teaches that NGAL levels are not related to inflammation. It also teaches that the marker can be quantified in the urine by the use of antibodies.

Document D5 (Mishra et al, Am J Nephrol 2004;24:307-315. May 12, 2004) also refers to NGAL as an early urinary biomarker for cis-platin nephrotoxicity.

In the first column of page 309, an antibody immunoassay method for quantisation of NGAL in urine is taught. Fig. 5 displays the results from quantisation of urinary NGAL following cis-platin exposure. On page 313, the paragraph bridging the first and second column, the authors teach that urinary NGAL excretion following cis-platin exposure is dose and duration dependant.

In the second paragraph of page 313, it is stated that

> *"In the post-ischemic mature kidney, NGAL is markedly up-regulated in proximal tubules, where it co-localises at least in part with proliferating epithelial cells. In the present study, a similar pattern of proximal tubular NGAL expression was noted following nephrotoxic injury. These findings suggest that NGAL may be expressed by the damaged tubule in order to induce re-epithelialization."*

This is definitely not an inflammatory process.

Most importantly, in the last paragraph of the article (on page 314) it is pointed to that

> *".....it is acknowledged that the clinical utility of detecting NGAL may currently be limited by the presence of co-morbid conditions (such as acute bacterial infections, kidney ischemia, and other nephrotoxins) and by the time factor.....The establishment and validation of an ELISA procedure, and eventually a point-of-care test for urinary NGAL determinations, are envisioned to represent significant advances in the field of biomarker discovery for early renal injury."*

Here the authors teach and propose that validation of quantitative methods and further investigation of the concentration ranges is the way forward to assess the clinical utility. In other words they propose to do exactly what was taught in the opposed patent

Document D6 (Xu S & Venge P: "Lipocalins as biochemical markers of disease." Biochimica et Biophysica Acta 1482 (2000) 298-307) teaches a sensitive immunoassay for NGAL. It is silent about NGAL concentrations in urine. It demonstrates serum concentrations mostly below 500 µg/l in acute bacterial infections, and below 200 µg/l in healthy subjects (see D6, p.304, Fig. 1).

Document D1 (WO2004/088276) teaches in Figures 11,12,13,14, 15 and 16 the quantisation of NGAL in urine from cis-platin-induced renal injury. Assay methods, time-dependant urine sampling and methods to find concentration ranges of interest are taught:

"Using the methods and techniques described herein, both the quantitative level of the RTCI biomarker present in the urine can be analysed and estimated, and a quantitative level of RTCI biomarker present in the urine can be analysed and measured. The clinician would select the qualitative method, the quantitative method, or both, depending of the status of the patient." See D1, [0043]

It also states that

"It is believed that the detected NGAL induction represents a novel intrinsic response of the kidney proximal tubule cells to renal tubular cell injury, including both ischemic and nephrotoxic injuries, and is not derived merely from activated neutrophils." See D1, [0054]

Thus, it is taught that NGAL levels may not result from inflammation. Furthermore, it teaches that

"Urinary NGAL is evident even after mild "subclinical" doses of cisplatin, in spite of normal serum creatinine levels." See D1, [0058]

This teaches that elevated urine NGAL is **unrelated to inflammation**.

Throughout the experimental section of D1 the clinical responses of increased NGAL in urine are described, and taught to be different from inflammatory conditions. See for example D1, [0098]:

"Also, urine from patients with urinary tract infections and kidney transplant rejection (two neutrophil-related disorders) contained only minimal quantities of NGAL (not shown), easily distinguishable from the significantly greater quantities in cadaveric kidney transplants (> 100 ng/ml). These data demonstrate that NGAL is a novel early urinary biomarker for acute renal injury following kidney transplantation."

2.2 Lack of Novelty

At least claim 1 lacks novelty over **Document D10** also published before the filing date of opposed patent

D10 discloses in Figure 1, diagrams C and D human urinary and serum NGAL-levels observed for normal individuals, individuals suffering from chronic renal failure (CRF) as well as patients suffering from ATN. Pictures A and B show immunoblots of urinary and serum samples from normal, ATN, CRF patients and other patients (with liver cirrhosis, hemochromatosis, or pancreatic carcinoma).

In the "Results" section (page 611, right column) a statistically significant urinary NGAI level of 557 ng/ml is disclosed, which distinguishes these patients over normal (22 ng/ml) and CRF patents (119 ng/ml), and obviously also patients with liver cirrhosis, hemochromatosis, or pancreatic carcinoma (the "others" group, for which in said immunoblots no or relatively low NGAL lavels were observed).

It is concluded, that :

"[t]hese data correlate Ngal expression with acute kidney damage.."

Thus said graphical illustrations directly and unambiguously provide a skilled reader with exactly the same teaching as claimed in claim 1 of the opposed patent.

In particular, the selection of an cut-off value in the claimed range is directly and unambiguously derivable from D10 in view of the experimental evidence illustrating said significant differences between NGAL-levels of patients with acute renal diseases like ATN and patients with chronic renal failure, normal patients or those suffering from certain non-renal diseases (with liver cirrhosis, hemochromatosis, or pancreatic carcinoma).

2.3 Lack of an Inventive Step

2.3.1 The closest prior art and the problem to be solved

The closest prior art is represented by **Document D7** by Dr. L.O. Uttenthal, one of the present inventors, published in CLI, November 2, 2005 and entitled "NGAL: a marker molecule for the distressed kidney?".

Said article reviews the prior art knowledge about NGAL, in particular the correlation between NGAL in inflammation or infection, the correlation of NGAL and neoplasia as well, and in particular, the correlation between NGAL and diseased kidney.

At the end of the section "NGAL and the kidney" it is literally stated:

> *"It is therefore apparent that a large variety of renal disorders are associated with raised plasma and urinary levels of NGAL. While plasma and urinary NGAL levels are closely correlated in acute conditions, it is to be expected that urinary NGAL levels will* ***be particularly high after ischemic renal injury severe enough to result in acute real failure, acute tubular necrosis or acute tubulo-interstitial nephropathy.*** *However, the use of urinary NGAL as a potential marker for these conditions is subject to the proviso that the presence of* ***concurrent conditions that are independently associated with raised NGAL-levels are taken into account."*** [emphasis added]

Evidently, said passage discloses exactly the concept of the claimed analytical method of the opposed patent: It is suggested to use NGAL as analytical marker for detecting acute clinical conditions associated with particularly high NGAL-levels. Said conditions are the same as literally stated, for example in section [0001] of the opposed patent, i.e. acute renal failure (ARF), acute tubular necrosis (ATN) or acute tubulo-interstitial nephropathy (ATIN).

In addition, the concept as disclosed by D7 also encompasses the proviso that the analytical results have to be evaluated in the light of **"concurrent conditions"** which also cause increased NGAL-levels, which, however, are not related to said renal pathological conditions. These concurrent conditions are also mentioned in D7 in the preceding sections, namely "inflammation or infection" as well as "neoplasia".

Consequently, the only difference between the teaching of D7 and claim 1 of the opposed patent can be seen in the statement of said specific cut-off-values (see claim 1, features 5 or 5a) which are used to "discriminate" between said "renal" and said "concurrent" conditions.

Therefore, from an objective point of view, the problem to be solved by the opposed patent is reduced to the trivial mental step of defining suitable cut-off-

values, allowing discriminating between renal disorders like ARF, ATN or ATIN, and other diseases, also associated with increased NGAL-values but not affecting the kidney.

2.3.2 Claim 1 lacks an inventive step

(1) Claim 1 is made obvious by D7

As confirmed by the inventor in his own review article **D7**, the scientific community, at the filing date of the present invention **was fully aware** of the particular situation that the proper assessment of NGAL levels requires the ability to distinguish between increased serum, plasma or urinary levels of NGAL associated with severe renal disorders on the one hand and NGAL-values originating from **unrelated** disease conditions like inflammation, infection or neoplasia. However, for determining a suitable cut-off or reference value prerequisite for making said distinction between those groups of NGAL level-increasing disease states nothing else but routine experimentation is required.

This fact is further illustrated by **Document D8**, an excerpt from Tietz Textbook of Clinical Chemistry, 2nd edition, explaining in chapter 13 that establishment and use of reference values (like cut-off values) **is one of the basic principles of establishing a diagnostic test system**.

D8 is cited as just one example of the many textbooks in clinical chemistry teaching how a reference range of a biomarker concentration in patients with a clinical condition has to be established. On page 454, Section "Interpretation by Comparison" is taught,

> *"to relate, in one way or another, observed data to reference data."*

On page 456, under the section "Concept of Reference values" it is taught:

> *"A reference value may then be defined as a value obtained by observation or measurement of a particular type or quantity on a reference individual."*

Furthermore, on page 457, the selection of reference individuals is taught:

"A set of selection criteria determines which individuals should be in the group of reference individuals. Such selection criteria include statements describing the source population, specific criteria for health, or disease of interest."

On page 456 is further taught:

"The observed value is defined as a value of a particular type of quantity, obtained by observation or measurement and produced to make a medical decision. Observed values can be compared with reference values, reference distributions, reference limits, or reference intervals."

D8 thus teaches how to determine cut-off values, which are diagnostic decision values.

The same method is applied in the opposed patent to determine cut-off values for NGAL in urine as a diagnostic tool for kidney damage.

(2) Claim 1 is made obvious by D7 in combination with D6, D9 or D10

There is numerous prior art available which states statistically significant values for urinary or serum NGAL-levels associated with diseases states different from ARF, ATN or ATIN.

For example, **Document D6** discloses on page 303 and in Figure 1, page 304, NGAL-values for normal serum as well as serum obtained from patients with bacterial infection. As can be taken from Figure 1, urine of such patients is characterized by NGAL-levels in the range of about 200 to 500 µ/l [i.e. ng/ml]. Defining a cut-off-value above 250 ng/ml as, for example, between 250 and 525 ng/ml as defined by features 5 and 5a of the claim 1 of the opposed patent must be considered as logical consequence of the disclosure of D6 in an attempt to distinguish patients suffering from ARF, ATN or ATIN over patients suffering from such bacterial infection.

A similar information can be taken from **Document D9**, in particular Figures 1 and 2 illustrating serum and plasma levels of NGAL (designated there as HNL). As illustrated by said Figures 1 and 2 bacteria induced levels of NGAL

in serum and plasma are predominantly below a cut-off-value falling within the range of cut-off-values as defined in claim 1 of the opposed patent.

Finally, reference shall be made to **Document D10** as discussed above disclosing in Figure 1, A, B, C and D human urinary and serum NGAL-levels and corresponding immunoblots observed for normal individuals as well as individuals suffering from ATN and other non-renal diseases. Said graphical illustrations provide experimental evidence for the prior art knowledge about significant differences between NGAL-levels of patients with acute renal diseases like ATN and patients with non-renal diseases or normal patients. Thus, D10 provides evidence that in view of the significant elevation of urinary or serum NGAL-levels associated with ATN, a skilled reader will have a reasonable expectation of success to establish a cut-off-value allowing discriminating between ATN and other disease states associated with less pronounced NGAL-level increases.

Consequently, a skilled reader aware of the concepts as disclosed in D7, would have easily and without inventive effort arrived at the claimed subject matter upon consideration of the specific experimental evidence as disclosed in anyone of the prior art references D6, D9 or D10.

(3) Claim 1 lacks clarity to an extent that it encompasses trivial diagnostic methods

While clarity per se is not a ground of opposition it is nevertheless established practice to consider clarity issues in combination with issues of inventive step or sufficiency of disclosure.

In the present case, for example the above mentioned feature 2 of claim 1 as granted is so unclear and imprecisely worded (in particular the partial feature *"another condition which does not affect the kidney"*) does not exclude healthy individuals. Thus, claim 1 encompasses diagnostic methods which distinguish healthy individual from those suffering from renal disorders. Such diagnostic methods have to be considered as trivial to a skilled reader, who is aware of the fact that normal NGAL serum or urine levels are in the range of 20 ng/ml, and setting a cut-off level of at least 250 ng/ml will not solve any problem.

Thus claim 1 encompasses trivial subject matter so that said claim lacks an inventive step in total.

2.3.3 Claims 2 to 17 are not inventive as well

The modifications of the basic method of claim 1 as defined by subclaims 2 to 17 of the opposed patent do not contain additional technical features which might contribute to an inventive step.

The specific embodiments of claims 2 and 3 (making use of urine, plasma or serum, samples) just reflect the typical samples as used in any of the above NGAL-related references (see for example D1, D3, D4, D5, D6, D7, D9 and D10).

Applying the claimed method with the aim to discriminate a renal disorder from other conditions as defined in subclaims 4, 5 and 6 is also made obvious by the teaching of D7 (see discussion above) or by the teaching of D1 (as discussed above).

Modifying the method of claim 1 by repeating the analytical steps as defined in claims 7 to 9 is made obvious by D7. D7 teaches at the end of the section "NGAL as a potential diagnostic marker" that:

> *"It is to be expected that **serial** rather than isolated single measurements of NGAL, whether in urine or plasma, will provide the most useful data for patients with several concurrent pathologies."* **[emphasis added]**

Making use of the claimed method for diagnosing renal disorders as stated in claims 10 to 12, follows exactly the proposals made in D7 (see section "NGAL and the kidney").

A person of ordinary skill in the art aware of the fact that NGAL-levels are closely related to the severity of the renal disease causing said increase of NGAL-levels (and are particularly high for severe diseases) will expect that particularly severe states will damage the kidney and, ultimately, will require treatment by dialysis. Obtaining and defining such a second, higher, cut-off-value for NGAL-levels as stated in claims 13 and 14 is, therefore, nothing but

a straight-forward modification of the basic analytical method of claim 1 and can't be considered as inventive.

Making use of a binding molecule that specifically binds to NGAL in order to measure NGAL, as defined in claim 15 represents the standard analytical method used throughout the cited prior art documents, see for example D1, section [0079] or D3, page 1232, right column, 2nd paragraph.

For the same reasons as stated above for subclaims 2 and 3, the subject-matter of claims 16 and 17 cannot be regarded as inventive.

E. Revocation under Art. 100b) EPC – Lack of Sufficient Disclosure (Art. 83 EPC)

Article 83 EPC requires that a European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

These requirements are not met by the opposed patent.

Claim 1 is directed to a method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being, wherein said method shall **discriminate between a renal disorder and a condition that is not affecting the kidney.** The "discriminator" as specifically defined by the technical teaching of claim 1 is said cut-off-value being 250 ng/ml or higher such as a value between 250 and 525 ng/ml.

As explained in the introductory part of the specification (see section [0001]):

> *"The methods are particular useful for the detection of the renal response to ischemic injury, the clinical or pathologic consequences of which are typically acute renal failure (ARF) acute tubular necrosis (ATN) or acute tubulo-interstitial nephropathy (ATIN) ..."*

It is also explicitly stated in section [0001] that the abnormal concentration of NGAL to be determined is

"...indicative of a disease or group of diseases, in this instance disorders of the kidney resulting in decreased renal function, including those caused by ischemic injury (due to impaired blood supply of the kidney) or exposure to nephrotoxic agents or rejection of a transplanted kidney."

On the other hand, as it is evident from the experimental results disclosed in **Document D2** (WO 2005/121788) (see in particular figure 6 and example 3, pages 27 and 28 of D2) in said experiment patients receiving a cardial pulmonary by-pass (CPB) were investigated whether or not they subsequently developed acute renal injury. It was observed that all patients who subsequently developed acute renal injury displayed a post-operative urine NGAL level above an arbitrary **cut-off-value of 50 ng/ml**, whereas only one out of 51 patients of the control group showed a urinary NGAL-value above this arbitrary cut-off. In other words, a cut-off-value of only 50 ng/ml is, according to the teaching of D2, sufficient to "discriminate between a renal disorder and a condition that is not affecting the kidney" as required by claim 1.

The same results as disclosed in D2 are also published in **Document D3,** see in particular summary as well as Figure 2.

On the other hand, upon following the teaching of claim 1 of the opposed patent and selecting a **cut-off-value of 250 ng/ml** would automatically categorize most or all of said 20 patients of said experiments of D2 as patients showing a condition that is **not (!)** affecting the kidney. Such an outcome illustrates that the alleged invention as described in granted claim 1 is not sufficiently described and consequently contravenes Article 83 EPC.

F. Summary

The claims of the opposed patent violate in part Article 123(2) EPC.

The opposed patent does not validly claim the priority dates of December 20, 2004 and September 21, 2005.

The entire set of claims lacks patentability, and in particular, lacks novelty and an inventive step over the cited prior art.

Moreover, the alleged invention as described in claim 1 of the opposed patent is not sufficiently disclosed in the opposed patent.

The opposed patent, therefore, has to be revoked as requested.

(Georg Schweiger) gs