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Datasheet for the decision of 23 April 2018

Case Number: T 0103/13 - 3.3.01

Application Number: 09002897.8

Publication Number: 2071332

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Language of the proceedings: EN

Title of invention:
Method for monitoring persons with IBD using total endogeneous lactoferrin as a marker

Applicant:
TechLab, Inc.

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Beschwerdekammern

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Case Number: T 0103/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 April 2018

Appellant: (Applicant)	TechLab, Inc. 2001 Kraft Drive Blacksburg, VA 24060-6358 (US)
Representative:	Murgitroyd & Company Scotland House 165-169 Scotland Street Glasgow G5 8PL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 23 May 2012 refusing European patent application No. 09002897.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	G. Seufert
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. The decision under appeal is the decision of the examining division, posted on 23 May 2012, refusing European patent application No. 09002897.8.

II. The documents cited in the course of the examination proceedings include:

D1: Database Medline [Online], abstract, accession number NLM9437905, Tabata K. et al. (1997)

D2: Clinical Biochemistry 27(4), 259-264 (1994)

D8: Jpn J Clin Pathol 45(12), 1201-1203 (1997)

D8 is a full English-language copy of the journal article summarised in D1 and contains the text of D1.

III. The decision under appeal is based on a main request and on a first auxiliary request. Claim 1 is identical in both requests and reads as follows:

> "1. An *in vitro* method for monitoring a human patient having inflammatory bowel disease for gastrointestinal inflammation comprising:
>
> diluting a first human fecal sample obtained from a patient at a first time;
>
> contacting said first fecal sample with immobilized polyclonal antibodies to endogenous lactoferrin to create a first treated sample;
>
> contacting said first treated sample with enzyme-linked polyclonal antibodies to create a first enzyme-linked antibody bound sample;
>
> adding a substrate to the first enzyme-linked antibody bound sample to create a first readable sample;
>
> determining the optical density of said first readable sample at 450 nm;

generating a purified lactoferrin standard curve and determining a linear portion of the standard curve;

comparing said optical density of said first readable sample to said standard curve to determine a concentration of the first diluted sample;

determining whether the concentration of the first diluted sample is within the linear portion of the standard curve, and wherein if the first diluted sample is within the linear portion of the standard curve, determining the concentration of total endogenous lactoferrin in said first fecal sample;

diluting a second fecal sample obtained from the patient at a time after the first sample was obtained;

contacting said second fecal sample with immobilized polyclonal antibodies to endogenous lactoferrin to create a second treated sample;

contacting said second treated sample with enzyme-linked polyclonal antibodies to create a second enzyme-linked antibody bound sample;

adding a substrate to the second enzyme-linked antibody bound sample to create a second readable sample;

determining the optical density of said second readable sample at 450 nm;

comparing said optical density of said second readable sample to said standard curve to determine a concentration of the second diluted sample;

determining whether the concentration of the second diluted sample is within the linear portion of the standard curve, and wherein if the second diluted sample is within the linear portion of the standard curve, determining the concentration of total endogenous lactoferrin in said second fecal sample; and

comparing said lactoferrin concentration of the first fecal sample to the lactoferrin concentration of the

second fecal sample for the patient to monitor the inflammatory bowel disease activity of the patient and determine if the patient has had a decrease or increase in gastrointestinal inflammation."

IV. In the decision under appeal, the examining division found that, starting from the teaching of document D1 or D8, the subject-matter of the claims of the main request and of the first auxiliary request did not involve an inventive step within the meaning of Article 56 EPC. It had been known from D1/D8 that inflammatory bowel disease could be diagnosed by measuring lactoferrin in a faecal sample using an ELISA method. Measuring lactoferrin not only once, but again at a later point in time, in order to solve the problem of providing a method to monitor inflammatory bowel disease, was obvious in view of common general knowledge and could furthermore be derived from the statement in D1/D8 referring to the usefulness of measuring the concentration of faecal lactoferrin for non-invasive monitoring of the disease activity.

V. The applicant (appellant) filed an appeal against that decision and, with the statement setting out the grounds of appeal, filed two sets of amended claims as its new main request and first auxiliary request.

VI. The appellant also submitted the following documents:

D9: British Journal of Surgery 96, 663-674 (2009)

D10: Poster presentation; Walker et al.: "Serial Fecal Lactoferrin Measurements are Useful in the Interval Assessment of Patients with Active and Inactive Inflammatory Bowel Disease" (undated)

VII. Claim 1 of the new **main request** reads as follows (the differences from claim 1 of the former main request examined in the decision under appeal are underlined):

"1. An *in vitro* method for monitoring a human patient having inflammatory bowel disease for gastrointestinal inflammation comprising:

diluting a first human fecal sample obtained from a patient at a first time during a single flare of the inflammatory bowel disease;

contacting said first fecal sample with immobilized polyclonal antibodies to endogenous lactoferrin to create a first treated sample;

contacting said first treated sample with enzyme-linked polyclonal antibodies to create a first enzyme-linked antibody bound sample;

adding a substrate to the first enzyme-linked antibody bound sample to create a first readable sample;

determining the optical density of said first readable sample at 450 nm;

generating a purified lactoferrin standard curve and determining a linear portion of the standard curve;

comparing said optical density of said first readable sample to said standard curve to determine a concentration of the first diluted sample;

determining whether the concentration of the first diluted sample is within the linear portion of the standard curve, and wherein if the first diluted sample is within the linear portion of the standard curve, determining the concentration of total endogenous lactoferrin in said first fecal sample;

diluting a second fecal sample obtained from the same patient at a time after the first sample was obtained but during the single flare of the inflammatory bowel disease;

contacting said second fecal sample with immobilized polyclonal antibodies to endogenous lactoferrin to create a second treated sample;

contacting said second treated sample with enzyme-linked polyclonal antibodies to create a second enzyme-linked antibody bound sample;

adding a substrate to the second enzyme-linked antibody bound sample to create a second readable sample;

determining the optical density of said second readable sample at 450 nm;

comparing said optical density of said second readable sample to said standard curve to determine a concentration of the second diluted sample;

determining whether the concentration of the second diluted sample is within the linear portion of the standard curve, and wherein if the second diluted sample is within the linear portion of the standard curve, determining the concentration of total endogenous lactoferrin in said second fecal sample; and

comparing said lactoferrin concentration of the first fecal sample to the lactoferrin concentration of the second fecal sample for the same patient to monitor the inflammatory bowel disease activity of the patient during the single flare of the inflammatory bowel disease and determine if the patient has had a decrease or increase in gastrointestinal inflammation."

VIII. Claim 1 of the **first auxiliary request** is identical to claim 1 of the former main request examined in the decision under appeal (see point III above), except that at the end of the claim, the following clause was added:

"...; wherein the present method is used to follow the lactoferrin levels of a single patient suffering from

ulcerative colitis during a "flare" of active disease through remission."

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or, alternatively, of the first auxiliary request, both submitted with the statement setting out the grounds of appeal.

X. The appellant's arguments may be summarised as follows:

According to document D1/D8, samples from populations of patients having active inflammatory bowel disease were compared with samples taken from healthy control populations to identify groups having normal or abnormal levels of lactoferrin.

The claimed method differed from the disclosure of document D1 in that two or more readings from the same flare of inflammatory bowel disease in a single patient were to be compared with one another rather than with readings from a healthy control, as taught by D1. Thus the monitoring according to the claimed invention was different from the monitoring allegedly taught by D1. At most, D1 only taught the monitoring of patients over a period of time non-related to a single episode or flare.

Not all biomarkers changed in the same way in response to disease activity. Prior to the invention, it had only been known that patients with inflammatory bowel disease had flares and remissions. It had not been known that patients underwent peaks and troughs of activity within single active flares of the disease, and that lactoferrin levels could be monitored within a single flare to identify changes in gastrointestinal inflammation. Longitudinal data obtained subsequent to

the priority date of the invention had shown that there could be significant variation in lactoferrin levels within a short period of time in a patient with acute disease (D9: page 671, column 2, first paragraph).

Further research by the inventors had indicated that not only could monitoring of lactoferrin in an individual patient at serial time points during the disease predict the future onset of flares of inflammatory bowel disease in advance of symptoms (D10: figure 3) but such serial lactoferrin measurements during a flare were effective in predicting clinical relapse of the disease in individual patients following the cessation of drug treatment (D10: figure 5).

The claimed method permitted the clinician to identify exactly what was changing during a single flare of active inflammatory bowel disease, and from this to accurately predict clinical prognosis (relapse or remission) of the disease, for example following drug treatment.

The objective technical problem was how to quantify the progression of inflammatory bowel disease during an active period of the disease, and accurately predict clinical prognosis of the disease in a subject.

The solution to that problem, as defined in claim 1 of the main request and first auxiliary request, was not obvious for the following reasons:

- Only with the benefit of hindsight could it be suggested that document D1 provided an incentive to the person skilled in the art to monitor multiple consecutive readings in a single patient during a single flare.

- Document D2, which had been relied on by the examining division to complement the teaching of document D1/D8, taught away from the claimed method because it did not focus on the comparison of lactoferrin levels in a single patient during the same flare of the disease.

XI. In a communication issued in preparation for oral proceedings and advising the appellant of its preliminary opinion, the board observed that it was inclined to agree with the assessment of inventive step as set out in the decision under appeal. The additional technical features which had been introduced into the claims of the current requests did not appear to provide a contribution which could support an argument in favour of inventive step.

XII. By letter of 19 March 2018, the appellant informed the board that it would not be attending the oral proceedings scheduled for 23 April 2018. It did not provide any further arguments in reply to the board's communication.

XIII. Oral proceedings were held on 23 April 2018 in the absence of the appellant, in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

Reasons for the Decision

1. Inventive step - main request

Content of the application and main request

1.1 The present application (see the description, page 1, paragraph 1) relates to the clinical differentiation and monitoring of gastrointestinal illnesses, and in particular, to a method for quantifying the level of total endogenous human lactoferrin in clinical specimens to monitor gastrointestinal inflammation in patients suffering from inflammatory bowel disease.

1.2 Claim 1 of the main request relates to an *in vitro* method for monitoring a human patient having inflammatory bowel disease for gastrointestinal inflammation.

- The method involves the comparison of the concentrations of lactoferrin determined in a first and second faecal sample, both obtained from a single patient at different times during the same flare of inflammatory bowel disease.

- Claim 1 additionally defines certain method steps, amounting to a typical ELISA assay, to be employed for determining the concentration of faecal lactoferrin.

- The claim further specifies that the comparison serves to monitor the inflammatory bowel disease activity of the patient during the single flare of the inflammatory bowel disease and determine whether the patient has had a decrease or increase in gastrointestinal inflammation.

Starting point in the prior art

1.3 Document D8 and its abstract D1 were used in the decision under appeal as the starting point for the assessment of inventive step. The board has no reason to select a different starting point.

1.4 Documents D1 and D8 report that the usefulness of measuring the faecal concentration of lactoferrin (known as a faecal protein related to inflammation) was evaluated, with a view to providing a non-invasive method for assessing the inflammatory condition of the gastrointestinal system in inflammatory bowel disease. Non-invasive methods for the diagnosis of gastrointestinal diseases are particularly desirable when paediatric patients are to be inspected. Lactoferrin (abbreviated as "Lf") was quantified by ELISA assay in faecal samples from patients with infectious enteritis, Henoch Schönlein purpura and ulcerative colitis, and in healthy control subjects. The faecal lactoferrin levels in the disease groups were significantly higher than in the control group. The abstract of D1/D8 concludes as follows: "These findings suggest that the measurement of fecal Lf concentration is useful for non-invasive monitoring of the disease activity in pediatric patients with gastrointestinal disease (...)."

1.4.1 "Monitoring" is a commonly used term which expresses the concept that the progress of something is observed over time. In particular, the progress of a disease may be observed ("monitored") as part of the typical routine work of a clinical practitioner, which involves repeated diagnosis of a patient and comparison of the results. In the absence of any different definition in D1/D8, the term has to be understood in its usual meaning. Thus the expression "monitoring of the disease

activity" employed in D1/D8, in combination with the idea that the concentration of faecal lactoferrin is a diagnostic parameter useful for such monitoring, implies that measurements of faecal lactoferrin would have to be performed on two or more samples obtained at different times from the same patient, and the results would have to be compared in order to detect changes in the activity of the disease.

1.5 While suggesting the use of the diagnostic method for monitoring of the disease activity, document D1/D8 does not however disclose an instance in which such monitoring was actually carried out.

Technical problem and solution

1.6 Thus the method according to claim 1 of the main request differs from the disclosure of D1/D8 in that the concentration of faecal lactoferrin is determined not only once, but twice in the same patient, and the concentrations are compared. More specifically, the two samples in which the concentrations are to be measured must be obtained at different points in time during the same "flare" of the inflammatory bowel disease.

1.7 The technical effect linked to these distinguishing features and provided by the method of claim 1 is the monitoring of gastrointestinal inflammation in a patient during a flare of inflammatory bowel disease.

1.8 The appellant did not rely on the technical features of claim 1 which define the successive steps of the analytical method to support its case in favour of an inventive step. In any case, the board considers that those features could not contribute to inventive step, since the method steps of claim 1 relating to an ELISA assay are common routine, and an ELISA assay was also

employed in the prior art (see D1/D8: abstract and D8: page 1201: column 2).

1.9 Based on the technical effect mentioned in point 1.7 above, the objective technical problem to be solved is to implement a method for monitoring inflammatory bowel disease.

1.10 The solution to that problem is the method defined in claim 1, which involves the comparison of two values for the faecal lactoferrin concentration determined in samples taken at different points in time during a single flare of inflammatory bowel disease in a patient.

1.11 This is considered a credible solution to the objective technical problem, for the following reasons:

Faecal lactoferrin was known as a marker for active gastrointestinal inflammation (see documents D1/D8 and D2 and the present application: page 3, lines 25 to 31). Its concentration was reported to be higher in patients having active ulcerative colitis and Crohn's disease than in those in the non-active phase (see D2: page 263, column 1, paragraph 3); thus the concentration of faecal lactoferrin reflected the activity of inflammatory gastrointestinal lesions. The results reported in the present application for a single patient (see the paragraph bridging pages 23 and 25) are consistent with that assumption, since the lactoferrin levels observed correlated with disease activity. On that basis, the diagnostic method based on faecal lactoferrin measurement would also appear to be applicable for monitoring disease activity, changing of its own account or in response to medication, during a single flare of the disease.

Obviousness of the solution

1.12 The suitability of the parameter "faecal lactoferrin level" for monitoring purposes was known:

1.12.1 As already mentioned (see points 1.4-1.4.1 above), document D1/D8 suggests explicitly that the measurement of the faecal lactoferrin concentration may be used for non-invasive monitoring of the disease activity.

1.12.2 The teaching of document D2 (see page 263, column 1, paragraph 3) further corroborates the skilled person's expectation that the faecal lactoferrin concentration reflects the activity of inflammatory gastrointestinal lesions. In that context, it is irrelevant that D2 does not specifically mention a method of monitoring, since monitoring is already suggested in D1/D8.

1.12.3 On a still more general basis, non-invasive monitoring methods are in any case sought after in the field of medicine; thus to provide such methods is a technical problem common in that field. It is, furthermore, common general knowledge that a diagnostic method can be used to monitor disease activity if carried out several times in succession, provided that the diagnostic method measures a parameter which varies depending on the activity of the disease. Based on the teaching of D1/D8 and D2, the person skilled in the art would have expected that to be the case in this instance (see points 1.11 to 1.12.2 above and the decision under appeal, reasons 17 and 18).

1.13 The application of the monitoring method to samples taken at specific times was obvious:

1.13.1 The person skilled in the art would have been aware that repeated diagnosis of the same patient is required for the implementation of any method of "monitoring"

and that, therefore, at least two samples taken from the same patient at different points in time must be analysed (see point 1.4.1 above).

1.13.2 It is also self-evident that the progress of a disease which is characterised by intermittent phases of "flares" and remission (such as inflammatory bowel disease) may be observed by analysing samples taken at various points in time during a flare and/or during a phase of remission. Depending on the current activity of the disease in an individual case, samples would be taken at time intervals deemed useful, for example with a view to observing the efficacy of medical treatment.

1.13.3 In that context, the decision to analyse two samples within a single flare of the disease, as defined in claim 1 of the main request, is within the usual professional competence of the person skilled in the art and would be taken without the need for inventive skill.

Additional arguments presented by the appellant

1.14 The appellant also submitted that a flare of inflammatory bowel disease could be characterised by peaks and troughs of inflammatory activity varying significantly in one patient, the claimed method permitting the identification and monitoring of such changes.

1.15 The board has the following observations with regard to this issue:

(a) It can be inferred from the term "flare" itself that, by definition, disease activity must vary during a flare, since such activity will initially increase and later decrease when the flare subsides. Thus it is obvious that different

concentration values may be measured at two different points in time during a flare, which would allow the clinician to determine whether gastrointestinal inflammation at the second point in time has decreased or increased since the first.

(b) Apart from that, no evidence has been provided to show that (multiple) pronounced peaks and troughs will typically occur in one patient during a flare. The text passage of document D9 cited by the appellant (see D9: page 671, column 2, paragraph 1) merely mentions that there can be significant variation of faecal lactoferrin levels within a period of four weeks. It cannot be inferred from that statement that the four weeks necessarily cover a period within a single flare of the disease, or that multiple peaks and troughs occur during that time.

(c) Furthermore, the method according to claim 1 of the main request involves only two measurements, which would not provide sufficient data for identifying and monitoring troughs and peaks of activity. That would only be possible based on multiple serial application of the monitoring method of claim 1. Even then, it would not be surprising by itself that changes can be depicted by a monitoring method, since that is the purpose of monitoring, irrespective of the nature and magnitude of the changes which may occur and be observed.

For these reasons, the appellant's argument that specific changes during a single flare can be monitored by the claimed method cannot establish a contribution to inventive step.

1.16 Referring to data presented in document D10 (figures 3 and 5) in support of the alleged utility of the monitoring method of claim 1, the appellant further contended that the claimed method permitted the clinician to give an accurate clinical prognosis of relapse or remission.

1.17 The conclusions of the board with regard to the alleged advantage of accurate prognosis are the following:

(a) Contrary to the requirement in claim 1 of the present main request, the data presented in figures 3 and 5 of D10 were not obtained during a single flare. Figure 3 of document D10 relates to subjects who were in prolonged remission and subsequently experienced flares preceded by increased lactoferrin levels. Figure 5 relates to elevated lactoferrin levels at discontinuation of steroid medication post-flare, with subsequent relapse. Thus the information presented in document D10 is not relevant to the assessment of claim 1 of the main request. Without further evidence it is furthermore not plausible that the comparison of only two measurements taken at any two points in time during a "flare" of inflammatory bowel disease would necessarily provide information sufficient as a basis for accurate prognosis.

(b) Assuming that the method of claim 1 were to be applied multiple times, thus providing data from more than two measurements, it would nevertheless not be surprising that a prognosis might be derived from any trend in such data. This is at any rate the usual purpose of a monitoring method which records quantitative changes in a parameter correlated to disease activity. The degree of accuracy of such predictions would then have to be

determined by further research within the usual routine of a person skilled in the art. That the outcome of such research is uncertain with regard to the actual degree of accuracy which may be achieved, does not in itself turn the result into an invention.

For these reasons, the appellant's argument that the claimed method predicts disease activity with great accuracy cannot establish an inventive step.

1.18 As a consequence, the board has arrived at the conclusion that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

2. Inventive step - first auxiliary request

2.1 The appellant did not present different arguments in respect of the claims of the first auxiliary request, but stated that the arguments presented for the main request applied equally to the auxiliary request.

2.2 In fact, the added clause relating to a use of the method (see point VIII above: "..., wherein the present method is used to follow the lactoferrin levels of a single patient suffering from ulcerative colitis during a 'flare' of active disease through remission") effectively seems to define a further method wherein the actual monitoring method (which involves comparing the results of two concentration measurements) is reiterated over a period of time which includes a flare of active disease and the subsequent remission period.

2.3 The study reported in documents D1/D8 involved, *inter alia*, patients suffering from ulcerative colitis (see point 1.4 above). Thus, while removing the restriction

that the two measurements which are to be compared must have been taken during a single flare of the disease, amended claim 1 of the first auxiliary request does not introduce any other distinctions relative to the disclosure of D1/D8, except the requirement that the monitoring method is to be used to follow the lactoferrin levels during a flare of active disease through remission.

2.4 Accordingly, the technical effect provided by the method of claim 1 is the monitoring of gastrointestinal inflammation in a patient during a flare of ulcerative colitis through remission.

2.5 On that basis, the objective technical problem to be solved is to implement a method for monitoring ulcerative colitis.

2.6 The solution to that problem consists in monitoring lactoferrin levels during a flare of the disease through remission by serial measurements, as proposed in claim 1 of the first auxiliary request.

2.7 As already mentioned in section 1 above (see in particular point 1.13.2), it is normal practice that monitoring will be carried out depending on the stage of the disease and at time intervals which are deemed useful. Evidently, the person skilled in the art would also consider applying the monitoring method consecutive times in order to get a more detailed picture or to observe disease activity over a longer period of time, e.g. in order to observe the reaction to one or several courses of treatment.

2.8 Taking into account this common general knowledge, the above-mentioned technical effects achieved by

the method (or use) defined in claim 1 of the first auxiliary request are not surprising.

2.9 Otherwise, the findings set out above with regard to claim 1 of the main request apply, *mutatis mutandis*, also to claim 1 of the first auxiliary request (see points 1.12 to 1.13.2, 1.15.(c) and 1.17.(b) above).

2.10 As a consequence, the subject-matter of claim 1 of the first auxiliary request does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow G. Seufert

Decision electronically authenticated