Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2017-01-17
Docket Number / Aktenzeichen:	X ZR 11/15
Name of Decision / Name der Entscheidung:	Borrelioseassay

Arbeitskreis
Patentgerichtswesen
in Deutschland e.V.

Translation downloaded from „patentdecisions.de“.

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 11/15

Pronounced on:
17 January 2017
Hartmann
Judicial Secretary as
Clerk of the court
registry

in the patent nullity proceedings

Borrelioseassay/
Lyme disease assay

EPC Art. 83; Patent Act Sec. 34(4)

An in vitro method in which a polypeptide defined by its disclosed amino acid sequence and the nucleic acid sequence encoding it, or polypeptides encoded by unspecified segments of the nucleic acid sequence in the patent, can be tested for specific immunological binding (herein: for antibodies directed against Borrelia burgdorferi), is disclosed to be executable as a whole if the method can be carried out with a polypeptide corresponding to the full sequence length with a practically useful result, even if better-suited segments cannot be found without inventive effort.

Federal Court of Justice, judgment of 17 January 2017 - X ZR 11/15 –
Federal Patent Court

ECLI:DE:BGH:2017:170117UXZR11.15.0

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 17 January 2017, attended by the presiding judge Prof. Dr. Meier-Beck, the judges Gröning, Dr. Grabinski and Hoffmann as well as the judge Dr. Kober-Dehm

ruled that:

> The appeal against the judgment of the 3rd Senate (Nullity Senate) of the Federal Patent Court of 30 September 2014 is dismissed at the expense of the plaintiff.

By operation of law

Facts of the case:

1 The defendant is the owner of European patent 894 143 (the patent in suit), which was filed on 20 February 1997, claiming the priority of a U.S. patent application of 21 February 1996, and was granted with effect in the Federal Republic of Germany. Claims 1, 2, 8, 9, 13, 15 and 16 of the patent, as amended after opposition proceedings, are in the language of the proceedings:

1. An isolated immunogenic polypeptide
   (a) having at least 85 % homology to the amino acid sequence of SEQ ID No. 2, and
   (b) which specifically binds with antibodies raised against a polypeptide having the amino acid sequence of SEQ ID No. 2.
2. An isolated nucleic acid segment comprising
   (a) the nucleic acid sequence of SEQ ID No. 1, or
   (b) the complement of (a).
8. An isolated immunogenic polypeptide encoded by a nucleic acid according to any one of claims 2 to 6.
9. The polypeptide of claim 8, further defined as an isolated polypeptide which specifically binds with antibodies raised against a polypeptide having at least the amino acid sequence of SEQ ID No. 2.
13. A purified antibody that specifically binds to the polypeptide of claim 9.

15. An in-vitro method of diagnosing Lyme disease comprising probing a sample from a subject, for the presence of a nucleic acid segment of any of claims 2 to 6, or an antibody that binds immunologically to a polypeptide of claim 9.

16. An in-vitro method of assaying Borrelia infection comprising

    (a) obtaining an antibody that binds immunologically to a polypeptide of claim 9 or a polypeptide that binds immunologically to such an antibody;

    (b) admixing a sample obtained from a subject and the antibody or the polypeptide; and

    (c) determining, whether immunologic binding occurs between the antibody and a polypeptide or between the polypeptide and an antibody in the sample;

    wherein immunologic binding is indicative of Borrelia infection.

2 By its action for nullity, which the defendant sought to have dismissed, the plaintiff attacked the patent in suit to the extent of its claims 13, 15 and 16, claiming that in this respect its subject matter went beyond the content of the application as originally filed and published as international application WO 97/31123, that the scope of protection of the patent was broadened, that its teaching was not disclosed so completely and clearly that a skilled person could carry it out, and that the invention was not patentable.

3 The Patent Court dismissed the action. In its appeal, which the defendant seeks to have dismissed, the plaintiff continues to pursue its request for a declaration of nullity of the patent in suit to the extent of claims 13, 15 and 16.

Grounds of the decision:

4 The admissible appeal is unsuccessful. The Patent Court correctly assessed the patent in suit and the asserted grounds for nullity.

5 I. The patent in suit relates to antigens and antibodies, which can be used for the diagnosis of a form of Lyme disease which is called Lyme borreliosis after the place where it was first described and whose causative agent is the bacterium Borrelia burgdorferi. It also concerns the (nucleic acid) sequence No. 1 coding for the (amino acid) sequence No. 2 of the patent in suit and segments thereof as well as methods for their use.

6 Lyme borreliosis is, as explained in the description of the patent in suit, a bacterial infection transmitted by pathogenic spirochetes of the genus Borrelia. According to the patent specification, the course of the disease is difficult to diagnose, as it often shows atypical forms and overlaps with other infections. Since the disease can also lead to paralysis, there is an urgent need for effective therapeutic and prophylactic treatment. One possibility for diagnosis was seen in the state of the art in the detection of components of the pathogen.

7 The patent in suit further describes endemic recurrent fever as an epizootic infection caused by other Borrelia species, in particular B. hermsii, and occurring in two or more "relapses", the first wave of which is caused by Borreliae expressing a certain variable major protein (VMP). If a patient develops antibodies against this protein after an infection, the bacteria of this stereotype are destroyed and the disease symptoms subside. However, under the pressure of the immune system, some of the Borrelia pathogens still present in the host undergo an antigenic change toward a different stereotype. These altered pathogens would no longer be recognized by the antibodies formed, so that they could multiply and trigger a renewed attack of fever.

8 Similar mechanisms of antigenic variation would be hypothesized for Borrelia burgdorferi pathogens, as this disease also generally persisted for months and years despite the appearance of host antibodies and cellular immune responses, indicating effective evasion of the immune response. Several genes and proteins from Borrelia burgdorferi have been characterized

to date, including the outer surface proteins (OspA to OspD), he said. However, this has not resulted in satisfactory approaches for a reliable diagnosis of Lyme borreliosis, so that there is still a need for suitable diagnostic kits.

9 2) The Patent Court, following the patent specification (para. 8 [= para. 9 of the German translation 697 33 944 T3]), has described it without legal error as the task underlying the invention to provide means and methods for (the treatment and) the reliable detection of Lyme borreliosis (or more precisely: of an infection with the pathogen thereof).

10 3) To solve the problem, the patent in suit with the challenged claims proposes a purified antibody and method with the following features (in bold the alternatives challenged by the plaintiff in substance alone):

Claim 13

13 A purified antibody which specifically binds to an isolated immunogenic polypeptide

13.1 which encodes a nucleic acid comprising the (nucleic acid) sequence No. 1 or a complementary sequence, and

13.2 which specifically binds to antibodies raised against a polypeptide comprising at least the (amino acid) sequence No. 2.

Claim 15

15 An in vitro method for the diagnosis of Lyme disease comprising assaying a sample from a subject for the presence of

15. of a nucleic acid segment according to claims 2 to 6,

15.2 a polypeptide encoded by a nucleic acid comprising the (nucleic acid) sequence No. 1 or a complementary sequence, or

15.3 of an antibody which binds immunologically to a polypeptide,

15.3.1 which is encoded by a nucleic acid comprising (nucleic acid) sequence No. 1 or a complementary sequence, and

15.3.2 which specifically binds to antibodies raised against a polypeptide comprising at least the

(amino acid) sequence No. 2.

Claim 16

16 An in vitro method for detecting Borrelia infection, comprising:

16.1 obtaining an

16.1.1 antibody which immunologically binds to a polypeptide,

16.1.1.1 encoding a nucleic acid comprising the (nucleic acid) sequence No. 1 or a complementary sequence, and

16.1.1.2 which specifically binds to antibodies raised against a polypeptide comprising at least the (amino acid) sequence No. 2, or

16.1.2 polypeptide which binds immunologically to such an antibody,

16.2 mixing a sample obtained from a subject with the antibody or polypeptide, and

16.3 determining whether immunological binding occurs between the antibody and a polypeptide in the sample or between the polypeptide and an antibody in the sample, wherein the binding is indicative of Borrelia infection.

11 The patent in suit explains that the invention discloses a repetitive DNA sequence of a length of about 500 base pairs, which is present in multiple, non-identical copies in a plasmid of infectious Borrelia burgdorferi, the causative agent of Lyme borreliosis. This encoded a surface-exposed lipoprotein that had sequence similarity to the major variable protein (VMP) in Borrelia hermsii (paras 105, 124 of the description [= paras 123, 142 T3]). It had been identified for the first time in B. burgdorferi; because of the similarity to the main protein in B. hermsii, the patent in suit speaks of VMP-like sequences (Vls) (paras 107, 125 [= paras 125, 143 T3]). Regarding the genetic organization of the Vls site, the patent in suit teaches that it consists of one expressed and 15 dormant Vls cassettes, which in turn have conserved and variable regions. The conserved sequences are thereby essential for recombination between the expressed and

resting Vls sequences, with genetic diversity observed in the variable regions of the Vls expression site (VlsE) (paras. 106, 110, 120 [paras. 124, 128, 138 T3]). Therefore, for the VlsE site, the exact nucleic acid sequence (Sequence No. 1 of the patent in suit) and the 356 amino acid amino acid sequence (Sequence No. 2) are given.

12 5. The Patent Court further explained the teaching according to the invention, as far as it is of interest for the appeal proceedings, as follows:

13 A polypeptide within the meaning of feature 16.1.2 is not to be understood solely as the polypeptide with the sequence number 2 (in full length) because of the singular (a polypeptide). This represents the central polypeptide of the teaching according to the invention. However, the skilled person would not reduce the polypeptide according to feature 16.1.2 to a team consisting of a molecular biologist or biochemist working in the field of immunology and a clinically active physician. This was because he understood from the description (paras. 146-155 [= paras. 166-175 T3]) that polypeptides designated as epitopic core sequences were also to be included as belonging to the invention, of which the patent in suit taught that they were immunologically cross-reactive with one or more anti-Vls antibodies due to their conserved regions (e.g. cross-reactivity between a Borrelia burgdorferi sensustricto VlsE peptide and an antibody directed against a VlsE site of the species B. afzelii) and had primary, secondary, or tertiary structures that resembled an epitope in the Vls protein, and the degree of similarity need only be such that a mono- or polyclonal antibody binds to or otherwise recognizes the polypeptide with an epitope core sequence (para. 146 f. [= para. 166 f. T3]). In the epitope core sequences, the skilled person thus recognizes a pool of polypeptides which, due to their origin from conserved regions of the Vls gene cassette and their resulting cross-reactivity, are suitable for the detection of numerous antibodies directed against the VlsE site. This is also not contradicted by the reference in patent claim 16 to patent claim 9, which, from the point of view of skilled persons, is not understood as a material definition of the polypeptides that can be used as diagnostic detection reagents in the method according to patent claim 16, but merely as an indication of the specificity of the antibodies with which these polypeptides form an immunological bond. Accordingly, the antibodies were

those directed against the polypeptide of sequence no. 2 and thus against the VlsE site. Sequence no. 2 thus determines not only the group of antibodies that can be used for the diagnosis of a Borrelia infection, but also indirectly the polypeptides that are suitable for the detection of these antibodies, since only polypeptides with a certain similarity to sequence no. 2 are able to enter into immunological binding with the anti-VlsE antibodies. The skilled person would also consider variants of sequence no. 2 because several antigens are regularly used for the immunological detection of specific antibodies and it is known to the skilled person that in immunodiagnostics truncated proteins are frequently used as epitopes in addition to full-length proteins. Finally, the use of the full-length protein in Example 11 of the patent in suit did not indicate otherwise.

14 6. The appeal unsuccessfully attacks this carefully substantiated understanding of the teaching of the invention.

15 The wording of patent claim 16 alone does not speak in its favor; a fortiori, there can be no question of the interpretation of the Patent Court going far beyond the literal sense, as the appeal suggests. The patent claim presupposes as the first step of the in vitro method (feature 16.1) the obtaining of an antibody or a polypeptide, which in the second step (feature 16.2) is brought into contact with the sample to be examined for an antigen-antibody reaction. In the third step (feature 16.3), it is then determined whether a borrelia (burgdorferi)-specific immunological reaction has occurred. The antibody is characterized in feature 16.1.1 by the fact that it specifically binds to sequence no. 2; only in this respect is a specific sequence involved. The polypeptide (antigen), on the other hand, is characterized by the fact that it binds to an antibody in the sense of feature 16.1.1. Thus, as the Patent Court correctly pointed out, both antibody and antigen are defined only by their specific binding, but not by their sequence length; the patent specification in dispute explicitly notes that peptides about eight to twenty amino acids long would be preferred for use according to the invention (para. 149 [= para. 169 T3]). Therefore, when the Patent Court - somewhat misleadingly - speaks of the "term 'obtaining a polypeptide'" being "to be interpreted as a synonym for a plurality of polypeptides", it does not replace the singular by the plural, but merely expresses that a plurality of antigens can fill out the polypeptide term. The statements of the Patent Court regarding the

epitope core sequences are therefore only consistent.

16 The specific binding, which is therefore decisive for the definition of the polypeptide in the sense of feature 16.1.2, is expressed in patent claim 16 not only in feature 16.1.1.2, but also in feature 16.3, since the sample associated with the polypeptide according to feature 16. 2 is not analyzed for any immunological binding by means of the protected in vitro method according to its purpose, but whether a binding occurs which is indicative of a Borrelia (burgdorferi-sensu-lato) infection. The method is thus also not defined by two unknowns, as the appeal suggests, because patent claim 16 does not serve to indicate to the skilled person how to select a suitable polypeptide in the sense of feature 16.1.2. Rather, it is understood that in carrying out the method, only a polypeptide can be used of which the skilled person knows, on the basis of the description of the patent in suit or his own orientation experiments, that it is suitable for specific binding in the sense of feature 16.1.1.2 and accordingly, on the basis of this binding, can be used as an indicator of Borrelia infection in the sense of feature 16.3.

17 A different result of interpretation also does not result from the limitation of the patent in suit in the opposition proceedings, as the Patent Court has also correctly stated. The challenged patent claims remained unchanged in the opposition proceedings. The extent to which claims to parts of sequence No. 2 have been deleted is irrelevant, since the sequence in the challenged patent claims serves only as a reference point for the bond specificity. No different understanding can be inferred from the decision of the Technical Board of Appeal, which does not comment further on claims 15 and 16. In particular, it does not follow from the fact that the Board of Appeal speaks of the invention paving the way to a more reliable diagnosis of Lyme borreliosis "with appropriate immunogenic polypeptides (see claims 8 to 9) ... [and] in vitro methods for the use of the same" (T 0502/08 3.3.08 of December 16, 2009 at no. 9 of the reasons). A specific definition of the "suitable" immunogenic polypeptides in the context of claims 15 and 16 is not expressed therein; moreover, it would not be binding for the patent nullity proceedings.

18 II. The appeal unsuccessfully challenges the Patent Court's assumption that the subject matter of the challenged patent claims does not go

beyond the application documents as originally filed. 1.

19 1. The Patent Court essentially reasoned as follows:

20 The claims 13 and 23 formulated in the international patent application corresponding to the original application documents, which dealt with the diagnosis of Lyme borreliosis and the detection of a Borrelia infection, respectively, were, in contrast to patent claims 15 and 16, not directed to the detection of a native antibody but of a native protein. However, the description repeatedly contains information that the teaching of the application also comprises a kit for the diagnosis of Lyme borreliosis and related diseases, which contains proteins for the detection of antibodies in the serum of infected humans or animals (WO 97/31123, p. 4, lines 8/9 in conjunction with lines 12-20 and p. 6, lines 10-12 as well as p. 48 f. to 4.3). Corresponding support for in vitro diagnostics based on the detection of antibodies is also found in claims 14 and 24 of the application, which describe isolated polypeptides as well as an immunodiagnostic kit containing these polypeptides for the detection of anti-VlsE antibodies. Accordingly, the "conversion" of the antigen test mentioned in the original claim 23 into an antibody test as described in claims 15 and 16 did not lead to any meaning deviating from the disclosure content of the original documents.

21 The plaintiff was also wrong in missing examples in which the in vitro methods of claims 15 and 16 were originally disclosed. Example 11 of the patent in suit, as already of its application, described immunoblots in which, among other things, the anti-VlsE antibodies in the serum of a patient infected with a Lyme borrelia strain were detected by their binding to the VlsE protein or VlsE variants derived therefrom (p. 87 f. in connection with Figure 6E). Thus, an in vitro test is disclosed in which the polypeptide of sequence No. 2 and derivatives thereof are used for the detection of anti-VlsE antibodies according to the teaching of patent claims 15 and 16.

22 The plaintiff’s objection that the original application documents do not disclose a diagnostic method in which antibodies are detected with any polypeptide as in patent claims 15 and 16 is also incorrect. From a technical point of view, not arbitrary polypeptides would be used in these methods due to

the specific detection of anti-VlsE antibodies, but only those from the polypeptide pool with epitope core sequences which would be recognized by anti-VlsE antibodies and consequently represent variants of the substance-defined VlsE polypeptide with sequence no. 2. Such a polypeptide pool is also supported in the original documents in chapter 4.4 dealing with the provision of epitope core sequences (p. 49, line 23 to p. 52, line 14). 2.

23 2. These correct statements do not need to be supplemented. Contrary to the opinion of the appeal, it is harmless that the original documents do not explicitly claim a method for antibody detection. It is obvious to the skilled person that the disclosed and claimed kits containing polypeptides binding to such antibodies are intended to serve for the detection of the antibodies. The kit virtually "embodies" the method designated in claims 15 and 16. Process features that go beyond the provision and intended use of such a kit are not to be inferred from the patent claims.

24 Insofar as the Patent Court speaks of the "conversion" of the antigen test mentioned in the original claim 23 into an antibody test, it merely wanted to express that the antibody test is also originally disclosed.

25 It is equally irrelevant that, as the appeal contends, epitope core sequences are not "disclosed by origin in connection with the diagnostic methods of claims 15 and 16." It is sufficient that the core sequences are disclosed as essential for antigen-antibody binding.

26 III. The Patent Court also correctly denied an extension of the scope of protection.

27 1. It assumed that the scope of protection of claims 15 and 16 was not broadened by the fact that they continued to comprise materially undefined polypeptides, although the materially defined peptide fragments of the originally granted claim 1 as well as alternatives c and d of the granted claim 2, which were directed to isolated nucleic acid sequences with a length of 20 base pairs, had been deleted without replacement in the opposition proceedings. The provision of epitope core sequences derived from the Vls gene cassette, which would be recognized by anti-VlsE antibodies and would therefore be suitable for

Borrelia diagnostics, was also disclosed in an unchanged manner with regard to claims 15 and 16 in the limited version of the patent in suit. Therefore, not only the polypeptide of sequence No. 2, but also peptide fragments derived therefrom, which are not further defined in terms of substance and which bind with anti-VlsE antibodies, continue to belong to the technical teaching disclosed in the patent in suit, so that their inclusion in claims 15 and 16 does not lead to an extension of the scope of protection.

28 2. The attacks of the appeal against this are unfounded. In this respect, nothing else applies than to the corresponding objections against the disclosure of origin.

29 IV. The invention is disclosed so clearly and completely that the skilled person can carry it out.

30 1. The Patent Court stated in this respect that the polypeptides, which are not defined in more detail in terms of substance, which are used in the in vitro methods of patent claims 15 and 16 for the detection of the anti-VlsE antibodies contained in the patient sera, do not constitute an inadmissible generalization according to which the teaching of patent claims 15 and 16 cannot be realized. The patent in suit contained an example 11 which described the principle of the in vitro methods described in claims 15 and 16 using immunoblots (para. 259 [= para. 279 T3]). The results shown in Figure 6E for the patient serum tested in Example 11 indicated that the anti-VlsE antibodies in the patient's serum were not only associated with the polypeptide of sequence no. 2 from clone B31-5A3 or the GST-Vls1 fusion protein, respectively (para. 259 f. [= para. 279 f. T3]), but also with the VlsE variants M1e4A and M1e4C (para. 259 f. [= para. 279 and 281 T3]). The fact that the VlsE variants M1e4A and M1e4C shown in Figure 6E thereby showed weaker immunochemical binding to the anti-VlsE antibodies than the VlsE polypeptide of sequence no. 2, does not prove the failure of the test, but rather confirms that anti-VlsE antibodies also bind to the VlsE variants mentioned in claims 15 and 16 and that the in vitro tests according to the patent in suit do not depend on the intensity of the individual signals, but on their basic detectability. With the results of figure 6E obtained from example 11, the patent in suit consequently discloses an executable way to carry out the claimed in vitro methods.

31 On the other hand, the patent in suit provided sufficient information to enable the skilled person to realize the claimed methods in practice with reasonable effort. The patent specification in suit not only contains information that the in vitro methods of claims 15 and 16 can be carried out as antibody-based detection methods (enzyme-linked immunosorbent assays, ELISA), but also which structural and functional properties the epitope core sequences used as antigens therein must have and how they are obtained (paras. 142-145 [= paras. 162-165 T3] and 146-155 [= paras. 166-175 T3]). In addition, as explained, the epitope core sequences according to the patent would have to originate from the conserved regions of sequence no. 2 in order to be able to form cross-reactive bonds with various anti-VlsE antibodies, so that, contrary to the plaintiff's view, the number of polypeptides that could be considered as epitope core sequences was also not infinite and finding suitable epitope core sequences would by no means require the skilled person to carry out an extensive research program. The fact that claims 15 and 16 also include unsuitable variants in addition to suitable ones also does not prevent a clear and complete disclosure, since it is part of the general knowledge and skill of a skilled person working in the field of immunology to determine suitable epitopes for an antibody known to him. The statement in the patent in suit that some sera from patients suffering from Lyme borreliosis did not react with some VlsE variants also gave no reason for a contrary assessment of the factual situation. This would not mean that all epitopes according to the patent would be classified as unsuitable. Rather, it would merely point out that such VlsE variants confirmed the expression and antigenic variation of VlsE in vivo (para. 261 [= para. 282 T3]).

32 For its claim that the skilled person is not taught how to distinguish between Borrelia burgdorferi and Borrelia hermsii with the methods according to the patent in suit, the plaintiff, who is obliged to present evidence in this respect, does not offer any evidence. Mere doubts are not sufficient for this.

33 2. This also stands up to scrutiny in the appeal proceedings.

34 a) Already the first line of reasoning of the appealed judgment supports the conclusion reached by the Patent Court that the protected invention described in the challenged patent claims is disclosed in an

executable manner.

35 Admittedly, the appeal may rightly object that the Patent Court assumed that of the new polypeptides arising in the host organism as a result of recombination, which are designated as M1e4A and M1e4C in the patent in suit, both showed a positive reaction in Example 11, whereas such a reaction is in fact only recognizable for the clone M1e4C. However, this is not the point. The plaintiff does not question that the expected antibody reaction occurred not only with the GST-Vls1 fusion protein comprising the VlsE of the patent in suit, but also with the M1e4C variant. However, the skilled person is thus shown the suitability of the full-length polypeptide for the detection of an immunological binding specific in the sense of features 16.1.1.2 and 16.3 and suitable as an infection indicator, and thus a possible way for carrying out the claimed method. The fact that false-negative results may occur, which can never be completely avoided anyway, is irrelevant. The practicability does not require that the best possible way to realize the teaching according to the invention is shown.

36 The executable disclosure justifies not only the protection of an in vitro method in which precisely this full-length polypeptide is used, but also the protection of methods which make use of a fragment of this peptide. This is because by pointing out sequence No. 2 and its immunological significance, the inventor has made the decisive contribution, which makes it possible to achieve the success according to the invention with the sequence in its entirety or individual segments. This also applies if (clearly) superior results can be achieved with such a segment as with the C6 peptide discussed by the parties, which is derived from the sixth conserved region of sequence No. 2 and is in any case responsible for the main part of the stable immune response, and the discovery of the suitability of this segment should in turn require an inventive step. The patent in suit teaches the skilled person that the polypeptide with sequence no. 2 is not responsible for the anti-gene antibody reaction in its entirety, but with certain epitopes. Even if these epitopes are not specifically designated and the patent in suit does not indicate in which conserved region they are to be found, the person who finds such epitopes and uses them instead of the entire peptide therefore also makes use of the teaching according to the invention. According to the evaluative consideration required in such a case of

what constitutes the invention and in which it finds its most general expression (cf. in this respect Federal Court of Justice, judgment of 25 February 2010 Xa ZR 100/05, BGHZ 184, 300 Thermoplastic Composition), the first inventor is entitled to comprehensive protection, which does not run dry if embodiments of the invention are used which do not correspond to the still inadequate form disclosed in the first instance alone, but which make use of a theoretically and practically superior further development. The only prerequisite for this is that the disclosed embodiment is at all practically useful; however, as explained, this is the case here.

37 b) Accordingly, the further statements of the Patent Court that the determination of suitable antigenic epitopes does not require unreasonable effort for the skilled person, but is rather possible on the basis of the information in the patent specification and the general knowledge of the skilled person, are no longer relevant. However, the plaintiff does not sufficiently demonstrate in the second instance that this assessment of the expert Patent Court is not correct. The fact that the suitability of possible epitopes cannot be predicted theoretically is not sufficient for this.

38 c) Also from the point of view of cross-reactivity between Borrelia burgdorferi and Borrelia hermsii, there is no lack of practicability of the invention. In particular, it does not prove the lack of suitability of the polypeptides according to the invention that patients with relapsing fever may also react with the C6 peptide.

39 Cross-reactivity is addressed not only in the state of the art, but likewise in the patent in suit, and has not been overlooked by the Patent Court. On the one hand, however, for the reasons given above under b, it cannot be established that it is not possible for the skilled person to improve the specificity of the immunological binding of the in vitro method according to the invention with a homology of 30 to 50% between Borrelia burgdorferi and Borrelia hermsii. On the other hand, false-positive results possible in individual cases do not exclude the feasibility and practical usefulness of the method any more than false-negative results. Also, in the publication of Ledue et al. in Clin. Vaccine Immunol. 15 (2008), 1796 (BK7) only mentions "lower specificities". In the expert opinion E. submitted by the defendant, it is also pointed out without

contradiction that relapsing fever illnesses and Lyme borreliosis are illnesses that can be easily distinguished from one another by means of the medical history and the clinical picture (Gks-B3, p. 8).

40 V. Finally, the Patent Court rightly affirmed the patentability of the subject matter of the challenged patent claims. 1.

41 1. It stated in this respect:

42 The subject matter of the challenged claims is new.

43 The paper "Immunochemical analysis of the immune response in late manifestations of Lyme borreliosis" by Wilske et al. in Zbl. Bakt. Hyg. A 267 (1988), 549 (K4) concerned an analysis of the immune response in a late manifestation of Lyme borreliosis with the aim of determining whether these show strain-specific heterogeneous patterns in patients infected with a European strain of Lyme borreliosis or whether certain reaction patterns occur depending on the clinical picture (cf. K4, title in connection with p. 551, 2nd paragraph). To find an answer to this question, the authors examined the sera of seven patients suffering from acrodermatitis chronica atrophicans (ACA for short) and ten patients suffering from Lyme arthritis. The sera of these patients would be examined in the Western blot for their reactivity with the proteins of five different Borrelia isolates. Beforehand, the protein pattern of the Lyme borrelia strains used would be determined (cf. K4, p. 550 "Summary", sentences 1 to 3 and p. 551, section "Lyme borrelia strains" and "Patient sera"). In these, the protein bands at 31/32 kDa would be identified as OspA and OspB proteins; the proteins at 21/22 kDa would be designated as protein C (later OspC) and the protein at 41 kDa would be identified as the flagellin protein known in expert circles. Furthermore, the proteins at 17/18 kDa would be evaluated as essential (cf. K4, p. 552, 1st para. iVm Fig. 1 and p. 554, 1st-3rd para.). Subsequently, various protein bands in the whole cell lysates of the Borrelia strains would be detected in a Western blot using the antibodies contained in the patient sera (cf. K4, p. 554/555, Figs. 3 and 4). This described a detection method carried out in vitro, which exhibited the features 16.1, 16.2 and 16.3 according to the patent. However, there is no information that this method also uses polypeptides which form an immunological bond with an anti-VlsE antibody or an antibody specific

for the polypeptide of sequence No. 2. The decisive factor for the lack of novelty of the citation was that no amino acid sequence with the sequence no. 2 according to the patent was disclosed. Consequently, the skilled person could not directly and unambiguously read into K4 any polypeptides which, according to feature 16.1.2, would be capable of entering into an antigen-antibody reaction with an anti-VlsE antibody. Polypeptides with such properties would like to be an inherent component of the Borrelia lysates tested in K4. Ignorant of the teaching of the invention, however, the work does not provide the skilled person with any information enabling him to recognize or identify such polypeptides. Indeed, only polypeptides with a molecular mass in the range of 17/18, 21/22, 31/32 and 41 kDa are reported, whereas the polypeptide of sequence No. 2 has a molecular weight of about 45 kDa according to the information in the patent in suit confirmed by the plaintiff with the experiments submitted by it (patent in suit para. 250 [= para. 270 T3]). As far as the Western blots evaluated in K4 showed numerous further reactive protein bands in the range of 40 kDa, the document did not provide any further details on these protein bands, so that the skilled person could not recognize a VlsE polypeptide with sequence no. 2 in these additional protein bands either. Furthermore, since nucleic acid or amino acid sequences are not of importance for the technical teaching described in K4, no material data are disclosed that would enable the identification of a VlsE polypeptide, irrespective of the protein bands shown. The same applied to patent claim 15.

44 In the paper "Relapsing Fever and Its Serological Discrimination from Lyme Borreliosis" by Rath et al. in Infection 20 (1992), 283 (K8), a case report dealing with the serological discrimination between relapsing fever caused by Borrelia hermsii and Lyme borreliosis caused by Borrelia burgdorferi pathogens, the protein bands typical for Borrelia hermsii and Borrelia burgdorferi, respectively, were compared with those recognized by antibodies in the serum of a patient with relapsing fever. Borrelia burgdorferi would be compared with those protein bands that would be recognized by antibodies in the serum of a patient with relapsing fever for the respective pathogens (cf. K8, p. 284, r. sp, Figure 2 with text). With the help of the immunoblot technique used in this case, IgG and IgM antibodies would be identified in the serum examined, which showed cross-reactivity to polypeptides with a molecular weight of 41 (the

known flagellin protein of Borrelia burgdorferi) and 60 kDa from Borrelia burgdorferi. Furthermore, in connection with the IgG antibodies, a strong cross-reactivity to Borrelia burgdorferi antigens with a molecular weight of 40, 36, 34, 30 and 20 kDa was observed (cf. K8, p. 285, re. sp, 4th para.) and overall the conclusion was drawn that Borrelia hermsii strains expressed conserved epitopes that were cross-reactive with epitopes of Borrelia burgdorferi (cf. K8, p. 286, cross-column para.). This general statement is not further specified. Accordingly, K8 discloses neither an in vitro method using polypeptides with an affinity for anti-VlsE antibodies according to feature 16.1.2, nor such a method detecting anti-VlsE antibodies in patient sera according to feature 15.3. Also purified antibodies directed against the polypeptide of sequence No. 2 (patent claim 13) are not described in K8. The mere visualization of various protein bands was not sufficient to anticipate the technical teaching based on the detection of the polypeptide of sequence no. 2, as underlying patent claims 13, 15 and 16, in a manner detrimental to novelty, even if the VlsE polypeptide of sequence no. 2 according to the patent in suit, as well as antibodies directed against it, had already been present in the serum examined in K8. Their detection could only be carried out in the knowledge of the polypeptide of sequence no. 2.

45 The subject matter of the patent in suit was also not suggested by the citation.

46 It was known to the skilled person from K4 that the antibodies from the sera of patients with a late manifestation of Lyme borreliosis entered into an immunological bond with the most diverse antigens of different European Lyme borreliosis strains and therefore provided a very heterogeneous antibody spectrum. In the protein bands in the range of 17/18, 21/22, 31/32 and 41 kDa, which are repeatedly referred to in the paper, the skilled person will not recognize antigens suitable for serodiagnosis of Lyme borreliosis. The authors considered the detection of IgG antibodies with a single Borrelia strain to be possible when using the immunofluorescence technique (cf. K4, p. 557, last and penultimate sentence). However, this would only provide the skilled person with a reason to continue searching for antigens that would enable reliable detection of an infection with Borrelia pathogens. K4 does not suggest an in vitro method

in which an anti-VlsE antibody is detected as in the methods of claims 15 and 16, nor artificially generated purified antibodies as described in claim 13. A corresponding teaching is also not conveyed to the skilled person by a synopsis of citations K4 and K8.

47 The conclusion to be drawn from K8 that the Borrelia hermsii pathogens, in addition to an antigenic variability, also expressed conserved antigenic epitopes which were cross-reactive with epitopes of Borrelia burgdorferi (cf. K8, p. 286, left column, last sentence and right column), may have brought conserved epitopes in the proteins of Borrelia pathogens to the attention of the skilled person. However, K8 does not provide the skilled person with information on the protein in which these are located and whether such epitopes are actually suitable as antigens for the serological detection of a Borrelia infection. Even the use of conserved epitopes in the in vitro diagnosis of a Borrelia infection would be viewed with skepticism by the skilled person in the knowledge of this work, since the epitopes mentioned there do not allow differentiation between different species such as Borrelia hermsii and Borrelia burgdorferi due to their cross-reactivity. The skilled person does not receive any indication that epitopes are advantageous for the detection of a Borrelia infection which, like sequence no. 2, trigger a strong immune response in the host in the case of a Borrelia infection and, due to their conserved regions, are also recognized by various anti-VlsE antibodies despite genetic variations (cf. patent in suit, para. 124 f. [= para. 142 f. T3] and 248 [= para. 268 T3] in connection with figure 3B).

48 2. The appeal does not raise any valid objections against this assessment.

49 In particular, it is not true that the Patent Court, when assessing novelty, would have contradicted its assumption that the polypeptide within the meaning of feature 16.1.2 is defined only by its immunological binding. This is because only the disclosure of the full-length sequence No. 2 enables the skilled person to provide this peptide or suitable peptides derived from this sequence for an antigen-antibody test. As the Senate has already ruled, a method for detecting a specific antigen-antibody reaction is not affected by novelty by a prior publication in which a specific immune reaction is described but neither antigen nor antibody are characterized in more detail (Federal Court of Justice,

judgment of 19 April 2016 X ZR 148/11, GRUR 2016, 1027 Zöliakiediagnoseverfahren). This is also the case in the dispute, in which only the patent in suit shows that the epitopes relevant for the specific immunological binding within the meaning of feature 16.3 can be traced back to the conserved regions of the VlsE gene cassette.

50 The appeal does not show that this finding and thus the teaching of claims 13, 15 and 16 derived from it would have suggested.

51 VI. The decision on costs is based on Sec. 121(2) Patent Act, Sec. 97(1) Code of Civil Procedure.

Meier-Beck Gröning Grabinski

Hoffmann Kober-Dehm

Previous instance:
Federal Patent Court, judgment of 30 September 2014 – 3 Ni 6/13 (EP) –