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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANDREAS BERGMANN and JOACHIM STRUCK

Appeal 2017-003439[1]
Application 10/551,298[2]
Technology Center 1600

Before RICHARD M. LEBOVITZ, DEBORAH KATZ, and RICHARD J. SMITH, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to methods of detecting mid-regional partial peptide of adrenomedullin. The Examiner rejected the claims under 35 U.S.C. §§ 101, 112, 102, 103, and under obviousness-type double-patenting. We have jurisdiction under 35 U.S.C. § 6(b). The § 101 and obviousness-type double-patenting rejections are affirmed. The §§ 112, 102, and 103 rejections are reversed. All claims are rejected.

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[1] The Appeal Brief at page 1 ("Appeal Br.") lists B.R.A.H.M.S. AG, as the real-party-in-interest.
[2] The "'298 Application."

STATEMENT OF THE CASE

There are 16 rejections pending in this appeal. Appellants have listed the grounds of rejection in their Appeal Brief (at pages 3–6). Accordingly, we have not reproduced them here. Appellants listed 17 rejections numbered 1–17, but the rejection 3 under § 112 for lack of enablement was withdrawn by the Examiner (Answer ("Ans.") 41). The grounds of rejection include rejections under 35 U.S.C. § 101, § 112 (written description and indefiniteness), § 102, § 103, and obviousness-type double-patenting.

The Examiner denied the '298 Application the benefit of its earliest priority date of a German patent application (Final Office Action ("Final Act.") 2). The § 102 rejection and a set of the § 103 rejections turn on the priority issue.

REJECTED CLAIMS

Claims 1 and 86 are representative of the claimed subject matter. The claims are reproduced below:

> 1. A method for detecting and quantitating in a biological fluid sample from a human the mid-regional partial peptide of proadrenomedullin (mid-proAM) which consists of the sequence of SEQ ID NO: 3, comprising
>
> (a) contacting the sample with a labeled monoclonal or polyclonal antibody which specifically binds to said mid-proAM partial peptide, and
>
> (b) detecting and quantitating the resulting peptide: antibody complex using an immunoassay, wherein said immunoassay
>
> (i) is not a radioimmunoassay, and
>
> (ii) has a limit of detection of about 50 pmol/l.

> 86. The immunoassay of claim 75, further comprising comparing the level of mid-proAM in the sample to a threshold level of mid-proAM in a population of patients having a pathological state associated with increased physiological production of adrenomedullin, which is substantially distinct from and higher than the level of mid-proAM in a healthy control population,
>
> wherein said pathological state is selected from congestive heart failure, myocardial infarction, kidney diseases, hypertensive disorders, diabetes mellitus, the acute phase of shock, sepsis and septic shock,
>
> whereby if the level of mid-proAM in the patient sample is equal to or higher than the threshold level in patients having a pathological state, the presence of a pathological state associated with increased physiological production of adrenomedullin in the human is indicated.

ADRENOMEDULLIN

Adrenomedullin ("AM" or "ADM") is a hypotensive peptide comprising 52 amino acids (Spec. 2:9–10) which is derived from a precursor protein of 185 amino acids known as preproadrenomedullin ("pre-proAM" or "pre-proADM") (*id.* at 2:14–20). Adrenomedullin comprises amino acids 95 to 146 of pre-proAM and is formed by proteolytic cleavage (*id.* at 2:24–27). Another peptide formed by proteolytic cleavage is mid-regional partial peptide ("mid-proAM" or "mid-proADM") which consists of amino acids 42–95 of pre-proAM (SEQ ID NO: 3) (*id.* at 9:13; Qi 1141). Mid-proAM is the subject of the rejected claims in this appeal.

THE PERSON OF ORDINARY SKILL IN THE ART

When making a patentability determination under 35 U.S.C., we consider the claims to be directed to one of ordinary skill in the art. Thus, a determination as to whether the claims conform to the patentability

requirements of 35 U.S.C. is made from the perspective of one of ordinary skill in the art. In this case, the claimed subject matter involves immunoassays for the detection of a peptide in a biological sample. The claims also involve diagnosing disease based on detection of the peptide in the sample. The cited prior art includes patents, published patent applications, and scientific journal articles in the fields of immunoassays, physiology, and disease detection. Persons who publish in scientific journals typically are scientists who have advanced degrees in the pertinent field (e.g., biology, physiology, medicine), such as masters, Ph.D., and M.D. degrees. Accordingly, the person of ordinary skill in the art pertinent to the claimed subject matter is a scientist, familiar with the patent and scientific literature, who has at least an advanced degree in biology, physiology, medicine, and/or substantial experience in these fields, particularly in the development of immunoassays and using such information to determine the presence of a pathological state or disease.

WRITTEN DESCRIPTION REJECTION

The '298 Application is a National Stage of a PCT application which claims the benefit of German Application 103 16 583.5, filed April 10, 2003 ("the German Application"). The PCT application was filed January 29, 2004. The Examiner denied the pending claims the benefit of the German Application based on the finding that specific limitations recited in the rejected claims are not described in the German Application. Final Act. 2–3. The '298 Application has the same specification as the German Application, albeit translated from German into the English language. *Id.* The Examiner also rejected the claims under 35 U.S.C. § 112 as lacking a written

description of the claimed invention in the instant Specification. Final Act. 8-9. Because the German Application and instant Specification are the same, a determination regarding the written description in the specification of the '298 Application has the same effect with respect to the German Application.

To satisfy the written description requirement of 35 U.S.C. § 112, the inventor must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991). "One shows that one is 'in possession' *of the invention* by describing *the invention*, with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (internal citation omitted). In describing the claimed invention, there is no requirement that the wording be identical to that used in the specification as long as there is sufficient disclosure to show one of skill in the art that the inventor "'invented what is claimed.'" *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000) (internal citation omitted). The written description "need not recite the claimed invention in haec verba but [it] must do more than merely disclose that which would render the claimed invention obvious." *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1377 (Fed. Cir. 2009). Thus, as long as a person "of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

Claims 1 and 75

Claims 1 and 75 are directed to an immunoassay comprising detecting mid-proAM of SEQ ID NO:3 using an antibody that specifically binds to the peptide. The assay is recited in the claims to have "a limit of detection of about 50 pmol/l." The Examiner found that the recited limitation was not described in the Specification because it appears in the Specification only in the context of detecting another peptide having the amino acid sequence of SEQ ID NO:4. Final Act. 8.

Mid-proAM has the sequence of amino acids 45–92 which corresponds to SEQ ID NO:3. Spec. Amdts. (dated July 9, 2009, Oct. 7, 2009, Dec. 7, 2010). Peptide SPCD19 has the sequence of amino acids 69–86 which corresponds to SEQ ID NO:4. Spec. 11:15–17. Peptide SPCD19, therefore, is a smaller peptide that falls within the peptide sequence of mid-proAM.

The Specification describes an immunoassay (SPALT assay or solid-phase antigen luminescence tracer assay) to detect SPCD19 using an anti-SPCD19 antibody. Spec. 11:31–12:32. The assay is described in the Specification as having a limit of detection of about 50 pmol/l. *Id.* at 12:25–26. The Specification discloses that the measurements made by the "SPALT assay were extended." *Id.* at 13:11–12. The Specification discloses that the "results of the extended study are summarized graphically in Figure 1, express reference being made to the above explanation of Figure 1." *Id.* at 13:12–14. Figure 1 shows "results of the measurement of mid-proAM in sera of . . . healthy normal persons, . . . sepsis patients[,] and . . . patients with polytrauma." *Id.* at 9:32–10:7. The assay summarized in Figure 1 was

accomplished using the anti-SPCD antibody, the same antibody used to detect the smaller SPCD19 peptide. *Id.* at 25:4–25.

Based on the description in the Specification of "extend[ing]" the SPALT assay of SPCD19 peptide to the larger mid-proAM peptide and the use of the same anti-SPCD19 antibody to do so, we conclude that the Specification would have conveyed to one of ordinary skill in the art that the SPALT immunoassay for mid-proAM had the same level of detection of the SPALT immunoassay for the SPCD19 peptide. Consequently, we reverse the Examiner's determination that the disputed limitation is not described in the Specification of the '268 Application.

Claims 86 and 89

Claim 86 is directed to the immunoassay of claim 75, and further recites:

> comparing the level of mid-proAM in the sample to a threshold level of mid-proAM in a population of patients having a pathological state associated with increased physiological production of adrenomedullin, which is substantially distinct from and higher than the level of mid-proAM in a healthy control population.

Claim 89 is directed to the immunoassay of claim 75. Claim 89 has the same limitation as claim 86, but does not characterize the "level" as a "threshold level."

The Examiner found the Specification does not describe 1) comparing levels of mid-proAM in healthy and pathological populations, 2) threshold levels; and 3) the genus of pathological states associated with increased production of adrenomedullin. Final Act. 8–9.

As discussed by Appellants, Figures 1 and 2 of the Specification show the measurement of mid-proAM in healthy normal persons in comparison to patients having a pathological state, namely sepsis, polytrauma, cardiac disease, and cancer. Spec. 9:32–10:21. The figures clearly depict levels of mid-proAM in healthy persons and the higher levels associated with a pathological state.

In addition to these specific examples, the Specification describes the concept of comparing levels of mid-proAM in healthy persons and those having a pathological state. First, the Specification discloses that it had been found in the prior art that "the concentrations of AM which can be measured in the circulation and other biological fluids are, in a number of pathological states, significantly above the concentrations to be found in healthy control persons." *Id.* at 4:5–9. The Specification discloses a number of different examples of pathological states, including "congestive heart failure, myocardial infarction, kidney diseases, hypertensive disorders, Diabetes mellitus, in the acute phase of shock and in sepsis and septic shock" in which AM levels were increased as compared to normal individuals. *Id.* at 4:10–16. The Specification describes its own contribution as the finding that mid-proAM is a more sensitive and reliable marker for the pathological disease states. *Id.* at 8:22–9:6, 14:10–25. The same specific pathological states associated with increased AM levels are recited in claims 86 and 89. The Specification expressly discloses that "measurement of mid-proAM can have advantages generally for all clinical pictures for which AM concentration increases are described, a determination in sepsis, cardiac and cancer diagnosis appearing particularly advantageous at present." *Id.* at 29:11–16. Consequently, there is explicit support for the recited limitation

in claims 86 and 89 of "said pathological state is selected from congestive heart failure, myocardial infarction, kidney diseases, hypertensive disorders, diabetes mellitus, the acute phase of shock, sepsis and septic shock."

The Examiner appeared to believe that the recited pathological states are not described by the Specification because the states are not described in sufficient detail to envision what pathological states are encompassed by the claims. Final Act. 9. We do not agree with the Examiner's analysis.

First, the claims recite specific pathological states and, thus, are not purely functional as asserted by the Examiner. *Id.* Second, while it may be correct that "kidney diseases," "hypertensive disorders," etc. may be directed to a genus of disorders generally characterized as being related to the "kidney" or having a "hypertensive" component, one of ordinary skill in the art would have reasonably understood that the inventors had possession of each genus because such diseases and disorders are known in the art and the inventors have not asserted to have discovered their existence, but rather assert to have discovered utilizing the mid-proAM peptide to diagnose a human such diseases and disorders.

The claims require comparing levels of the mid-proAM peptide to levels in a patient population having one of the enumerated pathological states of claims 86 and 89. Claim 86 recites that "if the level of mid-proAM in the patient sample is equal to or higher than the threshold level in patients having a pathological state, the presence of a pathological state associated with increased physiological production of adrenomedullin in the human is indicated." Claim 89 has the substantially same requirement, but does not recite the term "threshold." The Examiner found that these limitations are

not described in the Specification because threshold levels in a population are not described. Final Act. 9.

It is axiomatic that the Specification does not have to utilize the same wording recited in a claim to provide a written description of it. *ICU Med.,* 558 F.3d at 1377; *Alton,* 76 F.3d at 1175. In this case, the Specification expressly describes *comparing* peptide levels in samples from subjects experiencing healthy and pathological states. Spec. 6:19–22; 10:1–14. The Specification does not expressly disclose a specific level of mid-proAM that would constitute a pathological state for the purpose of determining "the presence of a pathological state associated with increased physiological production of adrenomedullin in the human" recited in claims 86 and 89. However, the Specification states that mid-proAM peptide levels can be used to diagnose pathological states. *Id.* at 1:6–15; 29:3–16. Figures 1 and 2 show specific levels of mid-proAM peptide associated with various pathological states. The Specification also discloses a specific concentration of mid-proAM associated with sepsis. *Id.* at 10:10–14. The levels of mid-proAM for the different pathological states are different from each other consistent with the statement in the Specification that "the AM level in patients with congestive heart failure, myocardial infarction, kidney diseases, hypertensive disorders, Diabetes mellitus, in the acute phase of shock and in sepsis and septic shock are significantly increased, although to *different extents*." *Id.* at 4: 10–14 (emphasis added). Consequently, the Specification provides support for "comparing the level of mid-proAM in the sample to a threshold level of mid-proAM in a population of patients having a pathological state" because the Specification shows pathological states having different extents of peptide levels depending on the disease

state (*id.* at 6:19–22; 10: 1–14; Figs. 1 and 2) and discloses diagnosis based on peptide levels (*id.* at 1:6–15; 29:3–16).

Summary

Because the Specification describes the disputed limitations, the written description rejection is reversed. Furthermore, the '298 Application is accorded the benefit of the German priority application having a filing date of April 10, 2003, because it has the same disclosure as the Specification.

REJECTIONS BASED ON BOUGUELERET

Rejections 5–9 are based on Bougueleret. Bougueleret's earliest filing date is of a provisional application filed April 25, 2003 which is after the priority date of April 10, 2003 accorded the '298 Application. Because Bougueleret is not prior art, rejections 5–9 (Appeal Br. 3–4) upon which it is based are reversed.

OBVIOUSNESS REJECTIONS BASED ON HARLOW

The Examiner rejected claims 1, 3–7, 9, 73, 75–81, 83, and 88 as obvious based on a description of an immunoassay in Harlow, the teaching of mid-proAM peptide in Qi, and the teaching in Kennedy of defining the role of AM and its peptides in normal and pathological states. Final Act. 26. The Examiner found that it would have been obvious to one of ordinary skill in the art "to apply the immunoassay methods of Harlow & Lane to detect and quantitate mid-proAM as the antigen in order to carry out studies to define the specific role of this known peptide, as is explicitly suggested by

Kennedy." *Id.* at 27. With regard to the detection limit of about 50 pmol/l, the Examiner cited Leyland-Jones as providing a reason that would have prompted one of ordinary in the art to design an immunoassay with a low detection limit. *Id.* at 28.

With respect to claims 86 and 89, the Examiner cited additional publications for their teaching of detecting peptides of larger proteins as markers for disease. *Id.* at 33–34. As accomplished in the cited publications for a different peptide, the Examiner found it would have been obvious to one of ordinary skill in the art to "indirectly determine AM, a known marker of a pathological state, by instead measuring mid-proAM. In particular, AM was recognized in the prior art at the time of the invention to be a disease marker" as described in Kennedy. *Id.* at 34–35.

Appellants contend that "possible correlations between AM in general and certain disease states would not have provided a reasonable expectation that the specific fragment mid-proAM of the specific SEQ ID No: 3 would be correlated to any particular use . . . being indicative of general pathological conditions or any particular disease state." Appeal Br. 21–22. Appellants also contend that the Kennedy and Qi do not provide "any actual motivation" to detect mid-proAM because there is no "practical value" or correlation of it with a disease. *Id.* at 22.

Qi, as found by the Examiner, describes mid-proAM of amino acids 45–92. Qi 1141. Qi discloses that "studies suggest that these peptides modify and regulate each other physiologically . . . . However, their complicated interactions are not yet clearly elucidated." *Id.* Qi describes the effect of mid-proAM and other peptides on production of adrenomedullin ("ADM") by vascular smooth muscle cells ("VSMC"). *Id.* at 1143. Qi also

discloses that mid-proAM "is a weak vasodilator, but it considerably enhances the hypotensive activity of ADM." *Id.* at 1145. Based on these disclosures, including a biological activity of mid-proAM, one of ordinary skill in the art would have had reason to develop an immunoassay of mid-proAM to determine its presence in normal biological tissues and to quantitate its amount in assays. Kennedy provides further reason to have designed a mid-proAM assay by its teaching that "[t]here clearly exists a need for defining the specific role of AM and its related peptides in normal and pathological states, and a potential therapeutic value in developing pharmacological agonists or antagonists of AM action." Kennedy 832. Thus, even absent a specific correlation with a disease, the skilled worker would have been prompted to detect mid-proAM activity to study its role in biological and physiological processes. Furthermore, mid-proAM has biological activity as described in Qi, and, thus, Appellants' statements that it has no practical value is not supported by the evidence in this record.

Evidence of nonobviousness

Appellants provided evidence of the nonobviousness of the claimed immunoassays. Specifically, Appellants provided declarations under 37 C.F.R. § 1.132 by Joachim Struck, a co-inventor of the '298 Application (Struck 1 Decl. of Dec. 7, 2010; Struck 2 Decl. of Dec. 5, 2014). Mr. Struck, citing published evidence, described problems existing with ADM assays as a result of decrease during storage, absorption to surfaces, and ADM binding proteins. Struck 1 Decl. ¶ 3. Mr. Struck reported that mid-proAM has "unexpected stability" providing a significant advantage over the instability of AM. *Id.* ¶ 4. In response to the Examiner's statements that the

evidence was not adequate to establish high stability of mid-proAM as compared to AM, Mr. Struck prepared a second declaration in which he compared the stability of human ADM (hADM) and mid-proAM. Struck 2 Decl. ¶ 3. Mr. Struck provided data on the stability of ADM and mid-proAM which showed that mid-proAM was more stable as compared to ADM providing an "unexpected, significant advantage" of the claimed immunoassay. *Id.* ¶¶ 3–4.

The Examiner "agreed that Exhibit B (second Declaration of Inventor Struck) shows that mid-proAM was more stable than AM when the peptides are stored at room temperature for 12 hours or more." Ans. 57. However, the Examiner found that "such evidence is not considered sufficient to outweigh the evidence of obviousness." *Id.* The Examiner reasoned that it is not unexpected that differences in stability would be observed and that other peptides obtained from larger proteins had been found to be more stable. *Id.* at 57–58. The Examiner found that the assay of mid-proAM had been "suggested" and that there was "strong motivation" to assay it. *Id.* at 58. The Examiner also stated the "fact that Appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Id.* The Examiner also stated that the results were not commensurate in scope with the claims because the claims do not do require mid-proAM instead of AM, and the assays involve measuring mid-proAM for any purpose. *Id.* at 58–59.

It is true that evidence of secondary considerations "does not always overcome a strong prima facie showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008). However, this is not

a case as in *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483–84 (Fed. Cir. 1997), where two drug components have been combined in a single tablet, where each drug individually was known to treat the same disease state. Instead, in this case, as explained in the Specification (Spec. 7:15–8:9) and in the Declaration by Mr. Struck, there were difficulties in measuring AM due to its instability, absorption, and binding to a circulating binding protein (Struck 2 Decl. ¶¶ 3, 4). The inventors recognized this problem and sought to solve it by finding a surrogate marker for AM and found that mid-proAM solved this problem because of its unexpected stability (Spec. 14:10–25), a showing that is not disputed by the Examiner.

The Examiner did not provide adequate scientific reasoning as to why the stability of an unrelated peptide would predict the stability of mid-proAM having an entirely different sequence. Ans. 57–58. Thus, the Examiner has not shown that it would have been predictable that mid-proAM would be more stable than AM.

The Examiner's finding that the results are not commensurate in scope with the showing in Mr. Struck's Declaration is not persuasive. All the claims are directed to an immunoassay of mid-proAM. Appellants demonstrated that the assay was superior to an assay of AM because of the unexpected stability of mid-proAM, making it useful in any context, whether measuring it in serum to diagnose a disease or to simply detect the peptide. Nonetheless, the unexpected result only has to be shown in one context. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

The Examiner's statement that the stability cannot be a basis for patentability because "Appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art" (Ans. 58) is, in our opinion, a misunderstanding of the law.[3]

In *In re Baxter Travenol Labs.*, 952 F.2d 388 (Fed. Cir. 1991), the applicant had argued that the claimed plasticized blood donor bag comprised of DEHP had unexpected properties in suppressing hemolysis of red blood cells stored inside it. *Baxter*, 952 F.2d at 389. The court found that such evidence did not rebut *prima facie* obviousness because the prior art disclosed a DEHP-plasticized donor bag, and therefore, Baxter's blood bag had the same hemolytic-suppressing function as the prior art — albeit unappreciated at the time of the invention. *Baxter*, 952 F.2d at 391. The court concluded that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Baxter*, 952 F.2d at 392.

Here, mid-proAM was not a subject of an immunoassay in the cited prior art publications so it cannot be said that the inventors merely recognized a property of a known immunoassay. The stability property was not "latent" in the cited prior art because mid-proAM had not been used in an immunoassay before. To say that the newly discovered property in an immunoassay "flow[s] naturally from following the suggestion of the prior art" ignores the role of secondary considerations in an obviousness rejection where an otherwise obvious invention arrived at by "following the suggestion of the prior art" is found to be patentable in view of such

[3] The Examiner's statement appears to be based on MPEP § 2145 citing a non-precedential 1985 Board case.

secondary considerations. As articulated in *Baxter*, a key checkpoint in such circumstances is whether the property relied upon to establish non-obviousness is "latent" in the prior art, i.e., a property that *operated* in the prior art but had not been recognized before. Here, this is not the case.

Summary

Based on the totality of the evidence, the obviousness rejection 10 (Appeal Br. 4, 20) of claims 1 and 75, and claims 3–7, 9, 58, 73, 76–81, 83. and 88, which depend from them, is reversed.

Obviousness rejections 11–13 of claims 10, 11, 84, 85, 86, 87, 89, and 90 (*id.* at 5) are reversed for the same reasons because the claims in the rejections depend on independent claims 1 and 75.

SECTION 101 REJECTION

The Examiner determined that claims 86, 87, 89, and 90 are directed to a law of nature or a natural phenomenon,[4] judicial exceptions to eligibility for a patent under 35 U.S.C. § 101. Final Act. 3. The Examiner found that the claims are directed "to a law of nature/natural phenomenon, specifically the naturally occurring correlation between levels of mid-proAM and a pathological state." *Id.*

[4] The Examiner also found that the claims were directed to an "abstract idea." Final Act. 3. However, we did not reach this determination because the claims were found to be ineligible for a patent under 35 U.S.C. § 101 on other grounds.

To determine whether a claim is eligible for a patent under 35 U.S.C. § 101, a two-step analysis is necessary. As set forth in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014):

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts[, e.g., a law of nature, natural phenomenon, or abstract idea]. If so, we then ask, what else is there in the claims before us? . . . We have described step two of this analysis as a search for an inventive concept—*i.e.*, an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself.

Id. (alterations, internal citations, and quotation marks omitted).

We begin with a discussion of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 77–79 (2012) ("*Mayo*"). In *Mayo*, the claim comprised steps of administering a drug to a subject and determining the levels of the metabolite of drug in the subject. The metabolite levels were recited in a "wherein" clause to determine the need to increase or decrease the amount of drug subsequently administered to the subject. *Mayo*, 566 U.S. at 73–74. The Supreme Court held that the wherein clauses "simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient." *Id.* at 78. Further, the Court wrote:

> Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm. Claim 1, for example, states that *if* the levels of 6–TG in the blood (of a patient who has taken a dose of a thiopurine drug) exceed about 400 pmol per $8x10^{[]}$ red blood cells, *then* the administered dose is likely to produce toxic side effects. While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in

> principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law.

Id. at 77.

Both claims 86 and 89 have a "comparing" step in which the level of mid-proAM in a sample is compared to a "level of mid-proAM in a population of patients having a pathological state associated with increased physiological production of adrenomedullin." The performance of this step indicates the presence of a pathological state "if the level of mid-proAM in the patient sample is equal to or higher than the threshold level in patients having a pathological state." The claims are similar to those in *Mayo* because they involve a "relation itself [which] exists in principle apart from any human action" (*id.*), namely the relationship between the naturally-occurring levels of mid-proAM and one of the enumerated pathological states. Accordingly, the Examiner's determination that the claims describe a "relation [that] sets forth a natural law" (*id.*) is proper.

Because claims 86 and 89 are directed to patent ineligible subject matter, we proceed to step two of the *Alice* test to decide whether the claims contains an "inventive concept" sufficient to transform the claimed law of nature into patent-eligible subject matter. *Alice*, 134 S. Ct. at 2355:

> "The question . . . is whether the claims do significantly more than simply describe [a] natural relation[ ].", *Mayo* 132 S.Ct. at 1297. . . . That is, under *the Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere "well-understood, routine, conventional activity." *Mayo*, 132 S.Ct. at 1294; *see also Myriad*, 133 S.Ct. at

> 2117; *Ariosa*, 788 F.3d at 1379. "[S]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Mayo*, 132 S.Ct. at 1300. Claims directed to laws of nature are ineligible for patent protection when, "(apart from the natural laws themselves) [they] involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 132 S.Ct. at 1294.

Genetic Tech. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1376 (Fed. Cir. 2016).

In this case, as indicated by the analysis under the § 103 rejection, the steps of the claimed method "involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 566 U.S. at 72–73. Specifically, the recited steps of the claimed immunoassay were found by the Examiner to have been described in Harlow & Lane. While Appellants "disagree" that the steps are "merely conventional," they have not identified a nonobvious difference between the claimed steps and those described in Harlow & Lane. Appeal Br. 7. Appellants contend that it was not conventional to measure mid-proAM. *Id.* at 8. However, the measurement of peptides by immunoassay was known in the art as established by the Examiner. In our view, the claim is based on the concept of an immunoassay for a peptide and then performing the conventional immunoassay on a known peptide which, when considered in combination, does not add "significantly more" to the ineligible concept, itself, because it still is a correlation between the levels of naturally-occurring peptide and a pathological state.

Appellants also argued that the claims do not preempt the detection of mid–proAM and, thus, do invoke the preemption concerns discussed in

Mayo. However, as discussed in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (2015): "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Id.* at 1379. Moreover, *Ariosa* held: "Where a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, as they are in this case, preemption concerns are fully addressed and made moot." *Id.* Consequently, since the claimed subject matter is ineligible under *Mayo*, we need not address the preemption concern.

Claims 1 and 75 were not rejected by the Examiner under 35 U.S.C. § 101. Appellants argue that they "fail to see how it is possible that the dependent claims 86-87 and 89-90 could be directed to patent ineligible subject matter when the independent claims they depend from have been found and admitted in the Office actions to be directed to patent eligible subject matter." Appeal Br. 7. Claims 1 and 75 are drawn to methods for detecting and quantitating mid-proAM in a biological fluid sample from a human. The claims are method claims and statutory classes of subject matter. The method involves detecting a naturally-occurring peptide involving steps of contacting a sample with an antibody which specifically binds to the mid-proAM peptide and then detecting the complex of antibody and peptide. The method does not invoke a natural law because, while it involves detection of a natural product, the product, itself, is not claimed. The method involves detecting a *complex* of antibody and peptide and, thus, does detect the natural product, alone. Claims 85 and 89, however, invoke the judicial exception to patent eligibility because they link the detection step to natural-occurring levels of mid-proAM in a patient and then correlate

with a pathological disease state, thus reflecting the same relationship found to be patent ineligible in *Mayo*.

Summary

The rejection under § 101 of claims 86, 87, 89, and 90 is affirmed.

112, SECOND PARAGRAPH, REJECTION

The Examiner found that the recitation in claims 86 and 89 of a "level" of mid-proAM rendered the claim indefinite because the claims also reference a population of individuals who would have different levels. Final Act. 13. Furthermore, the Examiner stated:

> [A] single level in such a population could mean various different things such as mean level, median level, etc. What is the threshold level and how is it derived? In addition to the fact that a level in a population could also be derived by various different statistical techniques, such a level would vary depending on the particular population being examined and the particular assay, for example.

Id.

We shall reverse the rejection. The claims recited "comparing the level of mid-proAM in the sample to a . . . level of mid-proAM in a population of patients having a pathological state." Claims are interpreted in light of the Specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). The Specification provides individual levels for patients having a pathological state (Figs. 1 and 2), but specifically refers to only one concentration as indicative of the population. Spec. 10:10–13. The ordinary skilled worker, a scientist who publishes and reads journal articles on immunoassays, would have understood that the levels in the sample are

compared to a "level" which is indicative of the population because this is most logical understanding of the words in the claim and, scientifically, the way in which such comparisons are typically made. The Examiner did not offer a scientific reason as to why levels in a sample would be compared to each individual patient in the population when the purpose of the method is to establish whether the sample levels are indicative of a disease state. The Examiner's interpretation of the claim is unreasonable based on both the plain wording of the claim and in the context of the Specification as it would have understood by one of ordinary skill in the art.

The claims are also not indefinite because of a lack of description about how the recited levels are "derived." Final Act. 13. The Specification teaches that it was known to detect AM levels and determine whether the AM levels are significantly different from healthy controls. Spec. 4:5–10. Thus, the detection of peptide levels to determine pathological status was known in the art. The same language used in the claim to embody this known method would, therefore, be clear and definite to one of ordinary skill in the art.

OBVIOUSNESS-TYPE DOUBLE-PATENTING REJECTIONS

Obvious-type double patenting rejections were made over the claims of 6 different issued U.S. Patents (collectively, "patented claims") and 11 patent applications.[5] Final Act. 38–46. Two of the applications are abandoned. A terminal disclaimer was filed in one of the patents. The patents and applications are listed below:

[5] The rejections over the claims of the patent applications are provisional since they have not been patented.

Patents

1. U.S. Patent No. 7,547,553 (withdrawn in view of filing of a terminal disclaimer (Ans. 42)).
2. U.S. Patent No. 8,507,210.
3. U.S. Patent No. 8,916,388.
4. U.S. Patent No. 9,012,151.
5. U.S. Patent No. 9,116,153.
6. U.S. Patent No. 9,128,107.

Applications

1. U.S. Serial No. 12/514,194 (Abandoned Apr. 27, 2016) (continuation application 15/055,406 filed).
2. U.S. Serial No. 12/613,891 (Appealed).
3. U.S. Serial No. 12/865,492 (Abandoned Apr. 20, 2017).
4. U.S. Serial No. 13/122,822 (Pending).
5. U.S. Serial No. 13/392,109 (Appealed).
6. U.S. Serial No. 13/704,648 (Pending).
7. U.S. Serial No. 13/868,351 (Pending).
8. U.S. Serial No. 13/882,895 (Pending).
9. U.S. Serial No. 14/383,744 (Pending).
10. U.S. Serial No. 14/396,793 (Pending).
11. U.S. Serial No. 14/664,243 (Pending).

PRINCIPLES OF LAW

"The doctrine of double patenting is intended to prevent a patentee from obtaining a time-wise extension of patent for the same invention or an obvious modification thereof." *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997). "It requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent." *In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir. 1998). "Obviousness-type double patenting . . . is judicially created and prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." *Lonardo*, at 965. The

"one-way" test is the test usually applied in obvious-type double patenting rejections. The "one-way" test asks whether the application claims under examination are obvious in view of the claims of the patent or of a copending patent application. *See Berg*, 140 F.3d at 1432.

OBVIOUSNESS-TYPE DOUBLE PATENTING OVER PATENTED CLAIMS

Claims 1 and 75 of the '298 Application are directed to immunoassays for detecting mid-regional partial peptide of proadrenomedullin (mid-proAM), where the assay has "a limit of detection of 50 pmol/l" and excludes radioimmunoassays. The patented claims involve detecting mid-proAM for the purpose of detecting a disease state (Alzheimer's disease in U.S. Pat. 8,916,388; bacterial infection in U.S. Pat. 8,507,210; post-myocardial infarction in U.S. Pat. 9,012,151; diabetes mellitus in U.S. Pat. 9,116,153; chronic kidney disease in U.S. Pat. 9,128,107) (recited in either independent or dependent claims). The patented claims are, therefore, narrower than the '298 Application claims, except for the detection limit and exclusion of radioimmunoassays in the '298 Application claims.

The immunoassay claims would have been obvious in view of the patented claims because the patented claims expressly disclose an assay for mid-proAM. To the extent that not all the patented claims recite that the assay is an immunoassay (e.g., U.S. Pat. Nos. 8,507,210; 9,116,153; 9,128,107), as found by the Examiner, it would have been obvious to carry out the detection steps using a conventional immunoassay as described in Harlow & Lane because immunoassays are routinely carried out to detect peptides in a sample of interest.

With respect to the detection limit of 50 pmol/l recited in the claims of the '298 Application, Appellants have the burden of establishing that the recited value is "critical" in some way to the claimed process, rather than simply being a range routinely arrived at by following the teachings in Harlow & Lane and Leyland-Jones (Final Act. 41 (explaining the obviousness of optimizing the immunoassay methods "so as to have a detection limit of about 50 pmol/l by applying the known technique of Leyland-Jones et al. of designing immunoassays with a low detection limit in order to ensure that mid-proADM could be successfully detected")).

> The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims . . . . These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.

In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (internal citations omitted.)

Appellants contend that the immunoassays in the cited patented claims are "unrelated" and that no reason has been provided as to why the level of detection could "be applied to the immunoassays . . . in the patent claims." Appeal Br. 31. However, the immunoassay are not "unrelated" as asserted because they each involve detection of the same peptide fragment. Furthermore, the issue is not whether the detection limit would be applied to the patented claims, but whether the recited detection limit in the claims of the '298 Application would have been obvious in view of the patented claims. Appellants did not meet the burden of showing that detection limit of 50 pmol/l is anything more than a routinely determinable value based on

the teachings in Harlow, Leyland-Jones, and the other cited publications (Final Act. 41).

Appellants also attempt to distinguish the patented claims from the claims of the '298 Application based on differences in immunoassay steps and the narrower purposes of the patented claims. Appeal Br. 32. These arguments are unavailing primarily because the issue in the obviousness-doubling patent rejection is whether the limitations of the '298 Application claims would have been obvious in view of the patented claims, not whether the limitations recited in the patented claims would have been obvious in view of the '298 Application claims. Appellants' arguments on pages 32–35 of the Appeal Brief identify differences between the patented claims of the U.S. Patent without addressing the obviousness of the immunoassay of claims 1 and 75 which covers a basic and general immunoassay for any purpose.

With respect to the narrower immunoassays claims involving specific detection technology, the Examiner found that such limitations would have been obvious based on Mathis (Final Act. 42–43). Appellants contend that it would not have been obvious to have utilized Mathis's technology for detecting mid-proAM because "[w]hile Mathis teaches the use of its technology for binding to antibodies, it is taught only for use in assessing molecular interactions, not assessing biomarker levels." Appeal Br. 29. Appellants also contend there would have been no reasonable expectation of success in applying the Mathis technology to the detection of mid-proAM (Appeal Br. 36).

These arguments are not persuasive. Mathis expressly extended its results to detection of other biomolecules, including in existing immunoassays.

> Evaluation of the homogeneous assays yielded results compatible with those from comparison assays and demonstrates the versatility and wide range of applicability of this methodology.

Mathis, Abstract

> The demonstrated ease in labeling different types of molecules, peptides, and oligonucleotides with TBP Eu^{3+} and APC, as well as the straightforward mixing and measuring processes that are available only in homogeneous methods, allows the development of assays that involve only a minimal perturbation of equilibrium or steric environment.

Id. at 1395–96.

> Beside the development of immunoassays already in progress, further clinical applications may be envisaged for this technology in molecular biology, flow cytometry for cell-surface mapping, and fluorescence microscopy . . . .

Id. at 1396.

Appellants have not provided adequate reasoning or scientific explanation as to why Mathis's technology would not have been expected to succeed in the detection of mid-proAM, particularly in view of Mathis's express teachings about extending its technology to immunoassays.

For the foregoing reasons, the obviousness-type double patent rejections over the claims of U.S. Patent Nos. 7,547,553, 8,507,210, 8,916,388, 9,012,151, 9,116,153, and 9,128,107 are affirmed. The dependent claims not separately argued fall with claims 1 and 75. 37 C.F.R. § 41.37(c)(1)(iv).

OBVIOUSNESS-TYPE DOUBLE PATENTING OVER APPLICATION CLAIMS

As with the patented claims, the application claims involve detecting mid-proAM for the purpose of detecting a disease state. The pending claims are attached. Appellants make the same unpersuasive arguments as they did for the patented claims (Appeal Br. 36–38). We, therefore, affirm the rejections for the same reasons discussed above as to the patented claims.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED