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KILPATRICK TOWNSEND & STOCKTON LLP
Mailstop: IP Docketing - 22
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Suite 2800
Atlanta, GA 30309

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MICHAEL I. WATKINS, GREGORY A. MARR, XIAOYUN YANG, RICHARD BRUEHL, DAMING SHAN, and PATRICK F. COLEMAN[1]

Appeal 2015-005377
Application 12/425,605
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to an antigen for detecting celiac disease and a process for making the antigen. The Examiner rejected the claims as failing to comply with the written description requirement and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as Bio-Rad Laboratories, Inc. Br. 4.

STATEMENT OF THE CASE

Background

The Specification discloses:

> [T]he present invention provides an antigen for detecting celiac disease prepared by the process of contacting a solid support with a gliadin fusion protein, wherein the gliadin fusion protein includes a recombinant deamidated gliadin covalently linked to a tag, such that the gliadin fusion protein is immobilized on the solid support via the tag. In this manner, the antigen for detecting celiac disease is prepared.

Spec. ¶ 11.

The Claims

Claims 1–9, 11–15, 20, and 15–28 are on appeal. Claim 1 illustrates the appealed subject matter and reads as follows:

> 1. An antigen for detecting celiac disease comprising a recombinant deamidated gliadin comprising a trimer of SEQ ID NO: 1, wherein the recombinant deamidated gliadin is covalently linked to a tag to form a gliadin fusion protein, wherein the tag is covalently linked to a solid support via an amino group of the tag and a carboxy group of the solid support, and wherein the recombinant deamidated gliadin is capable of binding to anti-deamidated gliadin IgA or IgG antibodies.

Br. 24, Claims App'x.

The Issues

The following rejections are before us to review:

A. Claims 1–9, 11–15, 20, and 25–28 are rejected under pre-AIA 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Ans. 2)

B. Claims 1, 12, 14, 15, 20, 25, 27, and 28 are rejected under 35 U.S.C. § 103(a) as obvious over Khosla,[2] Aleanzi,[3] Wienhues,[4] and Little.[5] (Ans. 7)

C. Claims 1–2, 4, 12–15, 20, 25, 27, and 28 are rejected under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, and Wear.[6] (Ans. 17)

D. Claims 3 and 5–9 are rejected under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, Wear, Little, and Boehm.[7] (Ans. 24)

E. Claims 11 and 26 are rejected under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, Little, and Jin;[8] or, in the alternative, as obvious over Khosla, Aleanzi, Wienhues, Wear, and Jin (Ans. 27).

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[2] Chaitan Khosla and Lu Shan, US2006/0240475 A1, published Oct. 26, 2006 ("Khosla")
[3] Mabel Aleanzi, et al., *Celiac Disease: Antibody Recognition against Native and Selectively Deamidated Gliadin Peptides*, 47:11 CLINICAL CHEMISTRY, 2023–2028(2001) ("Aleanzi")
[4] U-H Wienhues, et al., US 6,613,530 B1, issued Sept. 2, 2003 ("Wienhues"). We note the Examiner refers to this reference as "Weinhaus"
[5] Daniel Little, et al., US 6,322,970 B1, issued Nov. 27, 2001 ("Little")
[6] M.A. Wear, et al., *A surface plasmon resonance-based assay for small molecule inhibitors of human cyclophilin A*, 345 ANAL. BIOCHEM. 214–226 (2005) ("Wear")
[7] Thomas Boehm, US2004/0023848 Al, published Feb. 5, 2004 ("Boehm")
[8] Pei Jin, et al., US2007/0161081 A1, published July 12, 2007 ("Jin")

WRITTEN DESCRIPTION

The Examiner finds:

> Claim 1 was amended . . . to recite the limitation that "the tag is covalently linked to a solid support via an amino group of the tag and a carboxy group of the solid support." Similarly, claim 12 now recites that the gliadin fusion protein is "covalently linked to the solid support via an amino group of the tag and a carboxy group of the solid support." There is no explicit support for the added limitation. Although there is possible implicit support for one specific embodiment, this would not support/apply to all claims and so implicit/inherent support is also not found.

Ans. 3.

Appellants argue that support for this limitation can be found in paragraphs 88 and 89 of the Specification and that "at the time the instant application was filed, coupling protocols for conjugating molecules to a solid support were well-known and the mechanisms behind coupling reactions were well-understood." Br. 8–9. Appellants further argue "the specification as filed provides a working example [Example 2, ¶¶ 99–104] of immobilizing a gliadin fusion protein to a solid support via an amino group of the tag and a carboxy group of the solid support," that "coupling protocols for conjugating molecules to a solid support were well-known and the mechanisms behind coupling reactions were well-understood," and that paragraphs 33 and 50 provide "support for using either His or GST tags in a gliadin fusion protein that is immobilized to a solid support." *Id*. at 9–10.

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the limitations "the tag is covalently linked to a solid support via an amino group of the tag and a carboxy group

of the solid support" in claim 1 and "covalently linked to a solid support via an amino group of the tag and a carboxy group of the solid support" in claim 12 lack descriptive support in the Specification?

After considering the evidence and the arguments, we conclude the weight of the evidence favors the Examiner's conclusion that the Specification lacks descriptive support for the limitations. Accordingly, we adopt the Examiner's reasoning (*see* Ans. 3–6), and agree that the Examiner properly found Appellants' arguments unpersuasive (*see* Response to Argument, Ans. 30–33). We provide the following points for emphasis.

Findings of Fact (FF)

FF 1. The Specification discloses:

> Additional methods for linking the gliadin fusion protein to the solid support include . . . reagents that induce the condensation of carboxy and primary amino groups to form an amide bond, such as carbodiimides, ethylchloroformate, Woodward's reagent K1, carbonyldiimidazole, etc. . . .
>
> Carboxylic acid groups residing on the surface of paramagnetic latex beads, internally dyed with Luminex dyes, can be converted to N-hydroxysuccinimide esters through the action of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (CMC) and N-hydroxysuccinimide (NHS).

Spec., ¶¶ 88–89.

FF 2. The Specification describes "a method for preparing the antigen of the present invention in the absence of tTG that generally involves immobilization of a gliadin fusion protein (GST-D2 trimer) on a solid support":

> Immobilization of Gliadin Fusion Protein
>
> Into a microfuge tube is placed 8 mg of carboxyl modified magnetic beads. To the tube is added 800 µL of 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) pH 6.1 in 70% EtOH (ethanol). Mix and magnetically separate. Pipet off and discard the supernatant. Repeat one more time.
>
> Add 400µL of 120 mM N-hydroxysuccinimide (NHS) in 50mM MES pH 6.1 in 70% EtOH into the tube and mix. Add 400µL of 100mM N-Cyclohexyl-N'-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (CMC) in 50mM MES pH 6.1 in 70% EtOH into the tube and mix. Mix for 30 minutes at room temperature.
>
> Separate the beads from the supernatant and add 800µL of 5mM MES pH 6.1. Mix, magnetically separate, pipette off and discard the supernatant. Repeat one more time.
>
> Suspend the washed particles by adding 200µL of 5mM MES to the tube and mix. Add a mixture of the gliadin fusion protein prepared in Example 1 (GST-D2 trimer) in 600µL of buffered saline containing a detergent. Mix for 60 minutes at room temperature. After the incubation is complete, magnetically separate, pipet off and discard the supernatant.
>
> Add 800µL Post-Coating Wash Buffer (buffered saline containing detergents, preservatives and calcium chloride) to the tube, mix and magnetically separate. Pipet off and discard the supernatant. Repeat 3 more times.

Id. at ¶¶ 99–104.

FF 3. The Specification states "[a]s used herein, the term "gliadin fusion protein" refers to a gliadin protein linked to a tag such as Glutathione S-transferase (GST) . . . Tags useful in the present invention include, but are not limited to . . . His-tag . . . ." *Id.* at ¶ 33.

FF 4. The Specification states "[t]he gliadin fusion protein also includes a tag . . . Tags suitable in the antigen of the present invention include, but are not limited to, a Glutathione S-transferase (GST), His-tag . . . ." *Id.* at ¶ 50.

Principles of Law

A description adequate to satisfy 35 U.S.C. § 112, first paragraph, "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.' In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citation omitted, alteration in original). "[W]hile the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Id. at* 1352.

Analysis

As in *Ariad*, the Examiner finds that the Specification does not provide descriptive support for the claim limitation "covalently linked to the solid support via an amino group of the tag and a carboxy group of the solid support" because although there is "possible implicit support for one specific embodiment" there is "no explicit support" that would apply to all claims. Ans. 3. The Examiner further finds the paragraphs cited by Appellants as providing support (*see* FF 1–4) fail to specify a chemical reaction "between any amino group <u>of the tag</u> and a carboxy group <u>of the solid support</u>." *Id.* at 3–6. Specific to Appellants' "working example," the Examiner finds "there

is no[] disclosure that immobilization occurs through an amino group of the tag and a carboxy group of the solid support." *Id*. at 4. Rather, the Examiner finds "the specification lacks guidance as to how antigens comprising both a deamidated gliadin and a tag may be selectively immobilized through amino groups present on the tag, given that the deamidated gliadin peptides would also be expected to contain free amino acid groups." *Id*. at 4–5.

Ariad places the burden on Appellants to provide the mechanism for the "covalent binding between any amino group of the tag and a carboxy group of the solid support" in order to "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad,* 598 F.3d at 1336. We find the Examiner has the better position, as none of the portions of the Specification cited by Appellants specify that a covalent reaction between an amino group of the tag and a carboxy group of the solid support would be formed (FF 1–4). "[W]hile the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Ariad*, 598 F.3d at 1352.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the limitations "the tag is covalently linked to a solid support via an amino group of the tag and a carboxy group of the solid support" in claim 1 and "covalently linked to a solid support via an amino group of the tag and a

carboxy group of the solid support" in claim 12 lack descriptive support in the Specification.

Claims 2–9, 11, 13–15, 20, and 15–28 have not been argued separately and therefore fall with claims 1 and 12. 37 C.F.R. § 41.37(c)(1)(iv).

OBVIOUSNESS

Appellants address the four obviousness rejections together on appeal. (*See* Br. 10–23). We agree the same issues are relevant to all rejections and consider the rejections together.

The Examiner finds Khosla teaches a recombinant, deamidated gliadin peptide used to diagnose celiac sprue by binding to patient antibodies (Ans. 10). The Examiner concludes Khosla "fails to specifically teach a deamidated gliadin peptide that comprises a trimer of SEQ ID NO: 1" and "does not explicitly teach *covalently* linking the peptides to the solid support, or in particular covalently linking to the solid support via an amino group of the tag and a carboxy group of the solid support . . . ." *Id.* at 8.

The Examiner finds that, in light of the teachings of Winehues regarding use of multivalent and multimeric antigens "for the purpose of detecting antibodies in body fluids" (*Id.* at 11), it would have been obvious to "employ[] a multimer of the D-2 peptide of Aleanzi et al. (SEQ ID NO:1) as the recombinant, deamidated gliadin peptide in the antigen of Khosla" (Ans. 18) and to "employ the D-2 peptide [] as the epitope in[a] trimeric structure in order to create a multivalent gluten oligopeptide useful for diagnosis of celiac sprue" *Id.* at 11.

The Examiner also finds that the teachings of Aleanzi regarding "recombinant deamidated gliadin peptide SEQ ID NO: 1 teach aspects of the invention but "do not specifically teach providing this peptide in trimeric form covalently linked to a tag that is immobilized on a solid support." *Id.* at 12. The Examiner applies similar rationale to find it obvious to "prepare an antigen comprising a trimer of SEQ ID NO: 1 as claimed [] in view of the teachings of Weinhaus et al. regarding the benefits of using multimeric antigens" and that Khosla teaches covalent linkage by "introducing amino groups for forming amides; or histidines for linking to metal ion complexes." *Id.* at 19. The Examiner finds motivation to combine the teachings in Khosla, who "specifically contemplate multivalent gluten oligopeptides of the trimeric structure E1-X1-E2-X2-E3, where E1, E2 and E3 are epitopes (which may the same or different) and X1-X2 are spacers (which may bet the same and which may comprise one or more amino acids)." *Id.* at 18–19. The Examiner finds Aleanzi "does not specify a covalent linkage using an amino group of the tag and a carboxy group of the solid support," but that Little teaches peptide immobilization techniques such that "one of ordinary skill in the art would have found it obvious to [utilize them to] carry out the goals articulated in Khosla." *Id.* at 12–13.

The Examiner finds Wear's teachings on "an immobilization technique in which a recombinant tag (hexahistidine or Histag) was recombinantly introduced at the N-terminus of the polypeptide cyclophilin A, followed by covalent immobilization using standard chemistries to activate the surface and couple via primary amines" supply the element of "covalent linkage using an amino group of the tag and a carboxy group of

the solid support," because Wear teaches that the "covalent immobilization involved the primary amine at the N-terminus, which was present as part of the N-terminal histidine tag" and Little's teachings explain that the reactants used in Wear would "activate carboxy groups on the surface." *Id.* at 19–20. The Examiner concludes it would have been "obvious to arrive at the claimed invention by using the known immobilization technique of Wear et al. to immobilize the peptides of Khosla et al., Aleanzi et al., and Weinhaus et al. [] because Wear taught that [the] dual non-covalent/ covalent strategy for immobilization overcomes known problems associated with direct covalent immobilization and with affinity His-tag immobilization, which are both strategies suggested by Khosla et al." *Id.* at 21.

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusions that Khosla, Aleanzi, Wienhues, Little and Wear suggest the invention of claim 1?

Findings of Fact

FF 5. Khosla teaches "[g]luten oligopeptides are highly resistant to cleavage by gastric and pancreatic peptidases such as pepsin, trypsin, chymotrypsin, and the like." (Khosla ¶ 19).

FF 6. Khosla teaches:

> The oligopeptides and proteins useful in the methods of the present invention may be prepared in accordance with conventional techniques, such as synthesis, recombinant techniques, isolation from natural sources, or the like. . . . Production of a peptide or protein by recombinant DNA technology can also be performed. Thus, the oligopeptides may be prepared by in vitro synthesis, using conventional methods as known in the art.

Id. at ¶ 45.

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007).

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

We select claim 1 as representative of the claims subject to the obviousness rejections. 37 C.F.R. § 41.37(c)(iv). Initially, we note that, for the foregoing reasons discussed by the Examiner, we find the subject matter of Appellants' claimed invention prima facie obvious in view of Khosla, Aleanzi, Wienhues, Little and Wear alone.[9] The Board may rely upon less than all the references cited by the Examiner. *See In re May,* 574 F.2d 1082, 1090 (CCPA 1978). We adopt and incorporate by reference the Examiner's findings and conclusions with respect to these references as presented in the

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[9] We recognize that the Examiner relied on Boehm and Jin to address elements pertaining to Appellants' dependent claims; however, as Appellants have not separately argued those claims, we do not address them here. 37 C.F.R. § 41.37(c)(1)(iv).

Non-Final Action mailed September 10, 2013, and Answer. We address the arguments raised by Appellants on appeal below.

The Examiner provides sound fact-based reasoning for combining Khosla, Aleanzi, Wienhues, Little and Wear. We adopt and incorporate by reference the Examiner's findings and conclusions as presented in the Answer (pp. 7–20; *see also* FF5–6). Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case as to claim 1. We address Appellants' arguments below.

> Appellants argue "Khosla describes methods of diagnosing celiac sprue by detecting ***digestion-refractory multivalent gluten oligopeptides,*** which are highly resistant to cleavage by gastric and pancreatic peptidases such as pepsin, trypsin, and chymotrypsin . . . To the extent that Khosla describes the use of oligopeptides other than the 33-mer, such as oligopeptides from y-gliadin, for diagnosing celiac sprue, Khosla still emphasizes that ***these other oligopeptides should be resistant to endo- and exo-proteolysis by gastric, pancreatic, and small intestinal enzymes*** . . . Thus [] Khosla specifically teaches that ***gluten oligopeptides that are resistant to proteolytic digestion*** should be used.

Br. 15–16. Appellants argue that the other cited references do not explain that the D-2 gliadin peptide is resistant to endo- and exo-proteoloysis; thus, the skilled artisan would not have been motivated to substitute it for the known proteolytic-resistant Khosla gluten oligopeptides. *Id.* at 16.

The Examiner responds that "Khosla does not create a distinction between some gluten oligopeptides that are digestion-refractory and others that are not; but rather indicates that gluten oligopeptides, generally, are digestion-refractory" (Ans. 34, FF 5). Indeed, Appellants do not cite to any

evidence in Aleanzi or elsewhere that the D-2 peptide is not resistant to endo- and exo-proteoloysis. Accordingly, this argument is unpersuasive.

Appellants next argue that statements made during the prosecution of the Khosla application teach away from use of oligopeptides such as the trimer of D-2 gliadin. Br. 16. We agree with the Examiner (Ans. 36–37) that the Khosla prosecution history is not part of the record on appeal and that Khosla teaches that "synthetically-produced peptides can be used in their invention (*see* FF 6).

Appellants further argue the remaining references "do not provide any motivation to modify the Khosla multivalent gluten oligopeptide with a trimer of D-2 peptide. None of Wienhues, Little, Wear, Boehm, or Jin describe gluten or gliadin antigens or peptide sequences." Br. 16. This argument is unpersuasive as the Examiner's rejection is based on the *combined* teachings of Khosla, Aleanzi, Wienhues, and Little. (*See* Ans. 7). We agree with the Examiner because nonobviousness cannot be established by attacking the references individually when the rejection is predicated upon a combination of prior art disclosures. *In re Merck & Co. Inc.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986); *see also In re Keller,* 642 F.2d 413, 426 (CCPA 1981) (finding "one cannot show nonobviousness by attacking references individually where, as here, the rejections are based on combinations of references" (citations omitted)). Thus, whether Wienhues, Little, Wear, Boehm, or Jin individually fails to teach gluten or gliadin antigens or peptide sequences is not dispositive to the sufficiency of the rationale underlying the rejection. As stated by the Examiner, Khosla teaches a recombinant, deamidated gliadin peptide and methods of covalent

linkage by introducing amino groups to form amides, Aleanzi teaches the D-2 peptide, and Winehues teaches the advantages of using multivalent and multimeric antigens to detect antibodies in body fluids (Ans. 8–13). The Examiner sufficiently establishes that an ordinary artisan reading Khosla, Aleanzi, Wienhues, and Little would have reasonably expected that a multimer of the D-2 peptide of Aleanzi could be used as the recombinant, deamidated gliadin peptide in the antigen of Khosla and employed in a trimeric structure to create a multivalent gluten oligopeptide that could be covalently linked to a tag that is immobilized on a solid support by introducing amino groups for forming amides. *Id.*

Appellants next argue the "cited references do not provide a reasonable expectation of success that covalently linking a recombinant gliadin trimer-tag fusion protein to a solid support via an amino group of the tag and a carboxy group of the solid support would yield a configuration that would be recognized by deamidated gliadin-binding antibodies." Br. 17. Appellants cite the Declaration of Michael Watkins[10] for the proposition that

> at the time the instant application was filed, there were multiple difficulties associated with covalently linking the recombinant gliadin trimer to a tag and covalently linking the tagged gliadin trimer to a solid support to yield a construct having the proper conformation for presenting epitopes for antibody binding, such that a person of ordinary skill in the art would not have had a reasonable expectation of success of arriving at the claimed invention.

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[10] Rule 132 Declaration of Michael L. Watkins, filed February 2, 2012.

Id. at 17–18. The "possible" difficulties cited by Dr. Watkins include "not a reasonable expectation of success that a construct comprising multiple epitopes of the peptide (such as the D-2 peptide trimer of the pending claims) would present its immunologic sites to the solution phrase," the possibility that "the coupling of the trimer to an affinity tag such as a GST tag would result in the tag enveloping the trimer, thus masking the immunologic sites from antibodies," the possibility that "the multiple epitopes *(e.g.,* the epitopes of the D-2 peptide trimer) would become folded onto themselves or folded onto the solid support, instead of being oriented to the solution phase," and the possibility that the "distinct orientation of the constituent peptides [that is] essential for achieving optimal immunogenicity" would not be achieved. *Id*. at 18.

These statements are not evidence that any of the "possible" difficulties would have been encountered by one of skill in the art at the time of the invention. Accordingly, we ascribe these statements little persuasive value in proportion to the Examiner's strong prima facie case. *See In re Beattie*, 974 F.2d 1309, 1313 (Fed. Cir. 1992) (opinion evidence in declarations has little value without factual support). As stated above, we agree with the Examiner that the referenced combination would have provided the ordinary artisan a reasonable expectation of success in making the invention of claim 1.

Appellants once again advance statements from the Khosla applicants' prosecution history regarding the unsuitability of synthetic peptides for use in the invention. Br. 18–19. As discussed above, we find this argument unpersuasive.

Appellants next argue that "any *prima facie* case of obviousness is rebutted by the unexpectedly superior properties exhibited by the claimed antigen comprising a tagged gliadin trimer covalently linked to a solid support." Br. 19. Appellants claim "the use of a D-2 gliadin peptide trimer in combination with a solid support results in an antigen in which the solid support has ***significantly improved peptide coating characteristics*** relative to a solid support coated with D-2 gliadin peptide monomer" (*Id.*). Appellants cite evidence in the Watkins Declaration representing a "***more than twenty-fold improvement for the D-2 peptide trimer*** relative to the D-2 peptide monomer" and that relative fluorescence intensity for the D-2 peptide trimer at its titration plateau was about double that of the D-2 monomer. *Id.* Appellants also cite "significantly improved cutoff signals [] for an antigen comprising D-2 peptide trimer versus an antigen comprising D-2 peptide monomer in IgA and IgG assays . . . representing an almost three-fold improvement" and that "for the non-celiac samples, ***significantly fewer false positives were detected using the antigen comprising D-2 peptide trimer*** relative to the antigen comprising D-2 peptide monomer (specifically, a 50% reduction in the number of false positives). *Id.* at 20–21.

The Examiner responds that "the experiments reported in the Watkins Declaration cannot be clearly equated with the claimed invention. The Watkins Declaration does not state that the gliadin trimer was covalently immobilized via an amino group of the tag and a carboxy group of the solid support, as now claimed." Ans. 42. The Examiner further notes the Watkins Declaration cites to use of a biotinylated peptide, which would suggest "non-

covalent immobilization," which is also disclosed in the Specification, rather than the claimed covalent binding of an amino group of the tag and a carboxy group of the solid support as recited in claim 1. *Id.* at 42–43. We agree with the Examiner that the failure of the Watkins Declaration to establish that the results achieved occurred exclusively in an embodiment of the invention as recited in claim 1 (e.g., covalently bound antigen) renders the observations not commensurate in scope to claim 1, indeed, not drawn to the invention as claimed at all. The results are, therefore, of limited value in overcoming the Examiner's strong prima facie case. Ans. 42–43. Even if the results were exclusive to an embodiment of the invention of claim 1, as Appellants argue, we agree with the Examiner that Appellants' failure to show that the results were unexpected in the face of the teachings of Winehues regarding "improved sensitivity during use of multimeric antigens as compared to the corresponding monomeric antigen" (Ans. 43; Winehues, Examples 4-7) and Khosla regarding improved antibody binding through use of multivalent gluten oligopeptides containing multiple epitopes (Ans. 44; Khosla ¶¶ 21–23, 31) defeats Appellants' claim of unexpected results. Rather, "[e]xpected beneficial results are evidence of obviousness of a claimed invention. Just as unexpected beneficial results are evidence of unobviousness." *In re Skoner*, 517 F.2d 947, 950 (CCPA 1975). Accordingly, we affirm the rejection.

Claims 2–9, 11–15, 20, and 25–28 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claims 1–9, 11–15, 20, and 25–28 under

35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

We affirm the rejection of claims 1, 12, 14, 15, 20, 25, 27, and 28 under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, and Little.

We affirm the rejection of claims 1–2, 4, 12–15, 20, 25, 27, and 28 under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, and Wear.

We affirm the rejection of claims 3 and 5–9 under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, Wear, Little, and Boehm.

We affirm the rejection of claims 11 and 26 under 35 U.S.C. § 103(a) as obvious over Khosla, Aleanzi, Wienhues, Little, and Jin; or, in the alternative, as obvious over Khosla, Aleanzi, Wienhues, Wear, and Jin.

TIME PERIOD FOR RESPONSE

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

AFFIRMED