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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/380,329	03/06/2012	Stefan Miller	DEBE.P0111US	1551

108197 7590 11/29/2018

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
11/29/2018	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEFAN MILLER[1]

Appeal 2017-000833
Application 13/380,329
Technology Center 1600

Before RICHARD M. LEBOVITZ, RICHARD J. SMITH, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision under 35 U.S.C. § 134(a) involving claims directed to a fusion protein. Claims 1, 2, 4, 5, 31, and 43–46 are on appeal as rejected under 35 U.S.C. § 103 and for obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellant identifies the Real Party in Interest as "Lysando AG." Appeal Br. 3. Herein we reference the Specification of Dec. 22, 2011 ("Spec."); Final Office Action of Aug. 12, 2015 ("Final Action"); Appeal Brief of Mar. 11, 2016 ("Appeal Br."); and Examiner's Answer of July 28, 2016 ("Answer"); no Reply Brief was submitted.

STATEMENT OF THE CASE

Independent claim 1 is representative and is reproduced below:

> 1. A fusion protein comprising the amino acid sequence according to SEQ ID NO: 63-65, 67, 70 or 72-81.

Appeal Br. 20 (Claims Appendix). An election of species was made during prosecution where the elected subject matter is SEQ ID NO: 72, which is a fusion of indolicidin (amino acids 1-13 of SEQ ID NO: 72) and Cpl-1 (CPL-1) (amino acids 14-351 of SEQ ID NO: 72). *See* Final Action 3; *see also* Spec. 17 (Table 4).

The following rejections are appealed:

Claims 1, 2, 31, 43, and 46 stand rejected under 35 U.S.C. § 103(a) over Krieger,[2] Borysowski,[3] Briers,[4] Sanz,[5] and Bülow.[6] Final Action 4–5.

Claims 4, 5, 44, and 45 stand rejected under 35 U.S.C. § 103(a) over Krieger, Borysowski, Briers, Sanz, Bülow, and Terpe.[7] *Id.* at 8.

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[2] US 6,503,881 B2 (issued Jan 7, 2003) ("Krieger").
[3] Jan Borysowski et al., *Bacteriophage Endolysins as a Novel Class of Antibacterial Agents*, BACTERIOPHAGE ENDOLYSINS, 366–77 (2006) ("Borysowski").
[4] WO 2010/023207 A2 (published Mar. 4, 2010) ("Briers").
[5] Jesús M. Sanz & José L. Garcia, *Structural studies of the lysozyme coded by the pneumococcal phage Cp-1 Conformational changes induced by choline*, 187 EUR. J. BIOCHEM. 409–16 (1990) ("Sanz").
[6] Lief Bülow & Klaus Mosbach, *Multienzyme systems obtained by gene fusion*, 9 TIBTECH 226–31 (1991) ("Bülow").
[7] K. Terpe, *Overview of tag protein fusions: from molecular and biochemical fundamentals to commercial systems*, 60 *Appl Microbiol Biotechnol* 523–33 (2003) ("Terpe").

Claims 1, 2, 31, 43, and 46 stand rejected under 35 U.S.C. § 103(a) over Krieger, Borysowski, Li,[8] Sanz, and Bülow. *Id.* at 9.

Claims 4, 5, 44, and 45 stand rejected under 35 U.S.C. § 103(a) over Krieger, Borysowski, Li, Sanz, Bülow, and Terpe. *Id.* at 12.

Claims 1, 2, 31, 43, and 46 stand rejected under 35 U.S.C. § 103(a) over Krieger, Borysowski, Sanz, and Bülow. *Id.* at 14.

Claims 4, 5, 44, and 45 stand rejected under 35 U.S.C. § 103(a) over Krieger, Borysowski, Sanz, Bülow, and Terpe. *Id.* at 16–17.

Claims 1, 2, 4, 5, 31, and 43–46 stand rejected for obviousness-type double patenting over claims 1, 5, 6, 12, and 15 of Application No. 13/997,058 in view of Terpe.[9] *Id.* at 23–24.

DISCUSSION

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Arguments made by Appellant in the Appeal Brief have been considered in this Decision; arguments not so-presented are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474

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[8] Qingtian Li et al., *Potential therapeutic efficacy of a bactericidal-immunomodulatory fusion peptide against methicillin-resistant Staphylococcus aureus skin infection*, 86 APPL MICROBIOL BIOTECHNOL 305–09 (2010) ("Li").

[9] Application No. 13/997,058 was abandoned July 26, 2017, for failure to timely file a response to office action. *See* Notice dated February 8, 2018. Therefore, this rejection is dismissed.

(BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

"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). "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *Id.* at 416 (citing *U.S. v. Adams*, 383 U.S. 39, 50–51 (1966)). "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* at 419. "[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)).

> [M]otivation to combine is . . . inextricably linked to the level of ordinary skill. . . . If the level of skill is low, . . . then it may be rational to assume that such an artisan would not think to combine references absent explicit direction in a prior art reference. If, however, . . . the level of skill is . . . [high, as it is here], then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering—without being told to do so.

Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1370 (Fed. Cir. 2006). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the

obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (citation omitted).

We note that the Examiner indicated the following:

> In the interest of clarity it is noted that the rejections that include the reference of Briers or Li are considered to be the most relevant to the claimed invention. The rejections that [do not] include . . . Briers or Li were applied in the interest of compact prosecution in the event that appellant was accorded their foreign priority date and could remove the reference(s) of Briers and/or Li as prior art. However, as of the drafting of this examiner's answer, the references of Briers and Li are still available as prior art. Appellant has collectively addressed the rejections based on Krieger, Borysowski, Sanz, and Bulow and optionally in view of Briers or Li.

Answer 16. The Examiner is correct that Appellant's arguments focus on the obviousness rejections as a unified group and address Briers and/or Li as part of the cited prior art combination(s). *See generally* Appeal Br. 3–18. Therefore, we consider the rejections similarly as a group, addressing the combination of Krieger, Borysowski, Sanz, Bülow, and Briers *or* Li (the rejections not including Briers or Li are subsumed by those that do). For the rejections of claims 4, 5, 44, and 45, we note that Terpe is also included in the prior art combination; however, Appellant argued only that "Terpe cannot possibly address the numerous deficiencies in the combination of Krieger, Borysowski, Sanz and Bulow," thus the rejections including the Terpe reference are considered with the rejections based on the aforementioned prior art combination, as a group. Appeal Br. 18. Appellant

has not argued the claims separately and we find claim 1 representative; therefore, all claims fall with claim 1.

Findings of Fact (FF)

Unless otherwise indicated below, we agree with and adopt the Examiner's findings of fact and rationale. The following findings of fact highlight certain evidence.

FF1. Li disclosed "a bactericidal-bactericidal fusion peptide human β-defensin 3-lysozyme," which "showed the best bactericidal activity in vitro" for controlling MRSA. Li 305 (abstract), 307 (Fig. 1).

FF2. Li further disclosed "[f]usion strategy and immunomodulatory factors should be utilized in novel antimicrobial peptide development." Li 305 (abstract).

FF3. Further to the preceding findings of fact, Li disclosed that β-defensin is an antimicrobial peptide (AMP), where, to date, "[m]ore than 1,000 AMP from various sources are now identified." Li 305.

FF4. Krieger disclosed "treating microorganism-caused infections using cationic peptides or a combination of cationic peptides and antibiotic agents." Krieger 1:18–21.

FF5. Further to the preceding finding of fact, Krieger disclosed "[o]ne cationic peptide found in neutrophils is indolicidin" and "'indolicidin' refers to an antimicrobial cationic peptide." Krieger 2:3–5, 7:11–12.

FF6. Krieger disclosed "enhancing the antibiotic activity of lysozyme or nisin, comprising administering lysozyme or nisin with a

cationic peptide," and also "fusions of cationic peptides," and "[t]he combination of cationic peptides and lysozyme or nisin may improve their antibacterial effectiveness and allow use in situations in which the single agent is inactive or inappropriate." Krieger 4:38–41, 13:40–47, 27:63–66, 101:20–30 (Example 9).

FF7. Krieger disclosed:

> Lysozymes disrupt certain bacteria by cleaving the glycosidic bond between N-acetylglucosamine and N-acetylmuramic acid in the polysaccharide component of bacterial cell walls. However, lysozyme exhibits only weak antibacterial activity with a narrow spectrum of activity. The addition of cationic peptide may improve the effectiveness of this activity and broaden the spectrum of activity.

Krieger 28:1–7; *see also* Appeal Br. 6–7 ("strictly speaking, 'lysozyme' could theoretically refer to any enzyme of any source displaying the activity of cleaving the glycosidic bond between the NAM and NAG sugars of the peptidoglycan backbone"), 8 (lysozymes, whether hen egg white lysozymes or CPL-1, "all cleave the same bond"); and Michiels Declaration[10] ¶ 4 ("strictly speaking, 'lysozyme' could theoretically refer to any enzyme of any source displaying the activity of cleaving the glycosidic bond between the NAM and NAG sugars of the peptidoglycan backbone"), ¶¶ 6, 7 (lysozymes, whether hen egg white lysozymes of CPL-1, "all cleave the same bond."); *see also* Callewaert[11] 127 (cited by Appellant's

[10] Declaration of Prof. Dr. Chris W. Michiels Under 37 C.F.R. § 1.132 dated June 8, 2015 ("Michiels Declaration").
[11] Lien Callewaert & Chris W. Michiels, *Lysozymes in the Animal Kingdom*, 35 (1) J. BIOSCI. 127–60 (2010) ("Callewaert").

submitted Michiels Declaration ¶ 6, but stating "Lysozymes (EC 3.21.17) are hydrolytic enzymes, characterized by their ability to cleave the β-(l,4)-glycosidic bond between *N*-acetylmuramic acid and *N*-acetylglucosamine in peptidoglycan, the major bacterial cell wall polymer. In the animal kingdom, three major distinct lysozyme types have been identified - the c-type (chicken or conventional type), the g-type (goose-type) and the i-type (invertebrate type) lysozyme."); *see also* Nakimbugwe[12] 41 (also cited in the Michiels Declaration ¶ 6, but similarly to Callewaert indicating "Lysozymes (EC 3.2.1.17) are 1,4-β-*N*-acetylmuramidases, cleaving the glycosidic bond between the C-1 of *N*-acetylmuramic acid (NAM) and the C-4 of *N*-acetylglucosamine (NAG) in the bacterial peptidoglycan (PG). They are widespread in nature," and indicating an investigation into six different types of lysozymes, including two commercially available ones (hen egg white lysozyme and *Streptomyces globisporus* / M1L lysozyme)).

FF8. Krieger disclosed a list of "[e]xamples of native cationic peptides" suitable for use in its invention, including "Defensins-beta" and "Indolicidins." Krieger Table 1; *see also supra* FF1–FF3 (Li discloses a fusion of β-defensin and lysosome).

FF9. Briers disclosed "endolysin to which a peptide stretch with membrane or LPS disrupting activity is fused," "for use as a

[12] Dorothy Nakimbugwe et al., *Cell Wall Substrate Specificity of Six Different Lysozymes and Lysozyme Inhibitory Activity of Bacterial Extracts*, 259 FEMS MICROBIOL LETT 41–46 (2008) ("Nakimbugwe").

medicament," and as a "pharmaceutical composition." Briers Abstract.

FF10. Further to the preceding finding of fact, Briers disclosed that fusing an endolysin with a cationic peptide advantageously "enhance[es] the cationicity of said endolysin," "particular[ly] for the treatment or prevention of Gram-negative bacterial contamination." Briers 1:7–10, 1:21–23.

FF11. Further to the preceding findings of fact, Briers confirmed that lysozymes are endolysins. Briers 1:32–35, 8:22–26, 12 (Table).

FF12. Further to the preceding findings of fact, Briers disclosed that the term "fusion protein" refers to an endolysin with, preferably, a cationic and/or polycationic peptide. Briers 6:29–7:3; *see also supra* FF4–FF8 (Krieger teaching and suggesting pairing cationic peptides, such as indolicidin and β-defensin, with lysozyme, e.g., a type of endolysin).

FF13. Borysowski disclosed that endolysins are produced in phage-infected bacterial cells, induce lysis of bacterial cells, are capable of degrading peptidoglycan when applied externally to bacteria cell walls causing rapid lysis, were originally developed with a view to killing bacterial colonies, and hold promise for treatment of systemic infections. Borysowski 366 (abstract).

FF14. Borysowski disclosed that "there is an urgent need for the development of novel antibacterial agents" and "[e]ndolysins seem to be very promising in this regard." Borysowski 374.

FF15. Borysowski also confirmed that lysozymes are a type of endolysin. Borysowski 367.

FF16. Borysowski disclosed that CPL-1 (Cpl-1) is a phage lysozyme that has, advantageously, proven highly efficient for decolonizing bacteria, that CPL-1 exposure does not diminish its therapeutic efficacy in vivo (lack of immuno-resistance/tolerance), that CPL-1 is thermostable, and that CPL-1 has reportedly acted synergistically with antibiotics. Borysowski 371, 373, 374.

FF17. Sanz disclosed that CPL-1 is a lysozyme that can, advantageously, be readily overproduced in *E.coli* to supply amounts needed, and which has a known amino acid sequence. Sanz 409 (abstract), 413 (Fig. 5), 414.

FF18. Bülow disclosed that, advantageously, "[i]f the entire primary sequences of [] native enzymes are maintained in the fusion enzymes, the enzymes usually retain most of their native specific activities despite being fused together." Bülow 230.

FF19. Based on the preceding findings of fact, one of ordinary skill in the art would have combined and fused the cationic peptide indolicidin with the lysozyme CPL-1 as an anti-bacterial composition or pharmaceutical formulation. *See, e.g.*, Answer 7–10, 17–21. Indolicidin was recognized as a suitable, alternative, cationic peptide that could be substituted for the β-defensin of Li's disclosed fusion peptide of human β-defensin 3-lysozyme in view of Krieger's teaching that β-defensin and indolicidin are both cationic peptides suitable for its disclosed invention, particularly because Krieger

discloses the advantages of pairing such cationic peptides with lysozyme. *Id.* One of ordinary skill in the art would also have fused Krieger's disclosed (taught to be combined) cationic peptide, e.g., indolicidin, and a lysozyme in view of Briers's disclosure that fusion of cationic peptides and endolysins, e.g., lysozymes, result in improved anti-bacterial compositions. *Supra* FF1–FF18; *see also* Answer 4–5, 9–10 (*see* quote *infra* discussing combining, modifying prior art, rationale therefor, and expectation of success).

FF20. In view of Li, Borysowski, and Sanz, as well as Krieger, including the lysozyme CPL-1 (FF16) in an anti-bacterial protein fusion with the cationic peptide indolicidin (FF5, FF12) would be an obvious choice because CPL-1 was a well-known lysozyme that could be readily produced and was understood to be effective. *Supra* FF1–FF18; *see also* Answer 4–5, 9–10 (*see* quote *infra* discussing combining, modifying prior art, rationale therefor, and expectation of success).

FF21. In view of Li, Briers, and Bülow, one of ordinary skill in the art would have expected that upon fusing indolicidin and CPL-1, each of these anti-bacterial components would retain most of its native, specific activity and, in view of Krieger, Briers, and Li, one would have expected the combination and fusion of indolicidin and CPL-1 to improve the overall anti-bacterial activity of the pair. *Supra* FF1–FF18; *see also* Answer 4–5, 9–10 (*see* quote *infra* discussing combining, modifying prior art, rationale therefor, and expectation of success).

Analysis

The Examiner determined claims 1, 2, 31, 43, and 46 would have been obvious over the combination of Krieger, Borysowski, Briers *or* Li, Sanz, and Bülow, and that claims 4, 5, 44, and 45 would have been obvious over this same prior art combination also including Terpe. Final Action 4–23 and Answer 2–26 (collectively citing and/or discussing Krieger 2:3–9, 2:36–42, 3:63–65, 4:38–41, 7:5–12, Table 1, 13:40–47, 15:23–24, 27:63–28:7, 39:66–67, 45:29–35, 101:20–30; Borysowski 366, 367, 369, 371, 372; Briers abstract, 1:9–10, 1:21–24, 1:32–2:1, 8:22–32; Li 305, 307, 308; Sanz 409, 413, 414; Bülow 230; Terpe 523–25). Further, the Examiner determined:

> At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the references of Krieger, Borysowski, Sanz, Briers, and Bulow to fuse Krieger's indolicidin analogue with the endolysin lysozyme Cpl-1 into a single fusion protein, which fusion protein would comprise the amino acid sequence of SEQ ID NO:72 herein.
>
> One would have been motivated to use the endolysin lysozyme Cpl-1 as Krieger's antibacterial lysozyme because Cpl-1 is a lysozyme and Borysowski teaches Cpl-1 is an antibacterial lysozyme. One would have been motivated to fuse Krieger's indolicidin analogue with the endolysin lysozyme Cpl-1 into a single fusion protein in order to enhance the antimicrobial activity of Cpl-1 because Krieger teaches indolicidin synergistically enhances the antibacterial activity of lysozyme, Briers teaches fusing a cationic peptide and an endolysin, including an endolysin lysozyme, which has the beneficial effect of enhancing antibacterial activity, [and, alternatively, Li teaches enhancing the activity of an antimicrobial peptide by fusion with lysozyme,] and Borysowski teaches the benefit of the dual antibacterial activity of endolysins comprising sequences similar to those of cationic antimicrobial peptides, i.e., antibacterial activity of the lysozyme, which cleaves peptidoglycan and antibacterial activity of the cationic

> sequence, which enables interactions with the negatively charged bacterial membrane.
>
> One would have had a reasonable expectation of success to fuse Krieger's indolicidin analogue with the endolysin lysozyme Cpl-1 lysozyme into a single fusion protein because Krieger teaches the sequence of indolicidin analogue, Sanz teaches the sequence of the endolysin lysozyme Cpl-1, Briers teaches a method for fusing the sequences of a cationic peptide and a lysozyme, [and, alternatively, Li teaches a method for fusing the sequences of a cationic peptide and a lysozyme,] and Bulow teaches the polypeptides of a fusion usually retain most of their native specific activities.
>
> Therefore, the fusion protein and pharmaceutical composition of claims 1, 2, 31, 43, and 46 would have been obvious to one of ordinary skill in the art at the time of the invention.

Answer 4–5, 9–10 (paragraphing added for readability); *see also* FF1–FF21 (highlighting certain evidence). We find no error in the Examiner's determinations and adopt the Examiner's findings of fact and rationale.

Appellant's primary argument is that the skilled artisan would read Krieger's disclosure of pairing lysozyme with indolicidin to refer specifically to egg white lysozymes in contrast to the elected species which is the phage lysozyme CPL-1. *See* Appeal Br. 6. As support for this argument, Appellant cites the Michiels Declaration (along with Callewaert and Nakimbugwe), which concludes:

> Applicant has submitted considerable evidence that the enzyme Krieger was referring to is egg white lysozyme. I have reviewed that evidence and the supporting arguments (see RCE Submission filed October 17, 2014) and wholeheartedly agree with applicant's conclusion. In particular, would conclude that

> when Krieger is referring to "lysozyme", this has to be interpreted as being hen egg white lysozyme.

Michiels Declaration ¶ 4. The Michiels Declaration goes on to conclude that such an express definition by Krieger excludes other types of endolysins, e.g., amidases and endopeptides (these are other categories of endolysins, along with lysozymes — *see* FF11, FF15, and Spec. 2:13–17), without explaining why an exclusion of unclaimed endolysins is relevant. *Id.* The Michiels Declaration further states that, although *all* lysozymes *function identically* by cleaving the same bond, the different types of lysozymes *function differently* in that they have different amino acid sequences and different ancestral origins and evolutionary paths. *Id.* ¶¶ 6–7. Again, if the known universe of lysozymes functions by cleaving the same bond as stated by Michiels Declaration and, hence, would be understood to kill bacteria similarly, neither Appellant's Brief nor Michiels Declaration offers an explanation as to why these alleged differences matter to the obviousness of utilizing a lysozyme from a different source than Krieger to prepare a fusion protein with indolicidin.

Moreover, we find no persuasive evidence on this appeal record that Krieger's disclosed lysozymes are restricted to just one type of lysozyme, i.e., those derived from hen egg whites. Krieger never indicates this. Moreover, the Michiels Declaration, other than its conclusory statements to the contrary, supports the fact that, even though there are several types of lysozymes, the class of proteins called lysozymes function the same way by cleaving the same bond and, in this way, would be considered functionally interchangeable where the objective is to kill bacteria cells.

Appellant also argues Krieger does not teach fusing cationic peptides, like indolicidin, with entire proteins like lysozymes, but only discloses fusion with short peptides. Appeal Br. 9–10. Appellant further contends that Krieger's disclosure of administering cationic peptides with lysozymes does not refer to a fusion of the two. *Id.* at 11. Appellant further argues that the skilled artisan would not have reasonably expected that the improved effect (improvements in anti-bacterial properties) achieved by combining indolicidin and lysozyme, as disclosed by Krieger (at, e.g., Example 9), would be attainable in a fusion of these components because Krieger reports results for other examples in more detail than it does for Example 9. *Id.* at 11–12. Appellant also argues that there would have been no reason to combine Krieger's and Sanz's teachings because Krieger's lysozymes are not the endolysins mentioned in Sanz. *Id.* at 13.

Appellant's arguments are not persuasive.

"Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The Examiner rejected the claims over a combination of references, not Krieger individually. As explained above, even if Krieger were limited to hen lysozyme (which it is not), it would have been obvious to one of ordinary skill in the art to have substituted it for the CPL-1 lysozyme because they cleave the same bond. Michiels Declaration ¶¶ 6–7. Therefore, Appellant's arguments over Krieger alone are not persuasive.

Appellant's argument that Krieger does not teach fusing cationic indolicidin with entire proteins like lysozymes, but only with short peptides, is not persuasive in view of Li's disclosure of a fusion of a similar cationic peptide (β-defensin) and a lysozyme (CPL-1) and Briers's disclosure of fusing endolysins (e.g., lysozymes) and cationic or polycationic peptides (e.g., indolicidin). *See* FF1–FF3, FF9–FF12. In other words, even if Krieger's disclosure were related to short peptides, both Li and Brier disclose the fusion of longer polypeptides. Appellant's argument that Krieger's disclosure of administering cationic peptides with lysozymes does not refer to a fusion of the two is likewise not persuasive in view of Krieger's suggestion to pair indolicidin and lysozymes and the disclosures of Li and Briers that teach a fusion, rather than mere combination, is effective and was within the skill in the art. *Id.*; *see also* FF5–FF8.

Appellant's argument that the skilled artisan would not have reasonably expected that the improved effect (improvements in anti-bacterial properties) by combining indolicidin and lysozyme, as disclosed by Krieger's Example 9, would be attainable in a fusion of these components because Krieger reports results in more detail for other examples as compared to Example 9 is not persuasive in view of Bülow, which teaches and suggests that the anti-bacterial active properties of indolicidin and CPL-1 lysozyme would be retained upon their fusion and Krieger's indication that combining the two would improve their effectiveness. FF6, FF7, FF18. Moreover, Li provides evidence that such a fusion would effectively kill MRSA. FF1.

Appellant's argument that there would have been no reason to combine Krieger's and Sanz's teachings because Krieger's lysozymes are not the endolysins mentioned in Sanz is not persuasive because the cited prior art combination teaches and suggests that lysozymes are a type of endolysin, that cationic peptides, like indolicidin, can be fused with endolysins, e.g., lysozymes including CPL-1 specifically, and that such fusions are expected to and actually do effectively kill bacteria. *See generally supra* Findings of Fact.

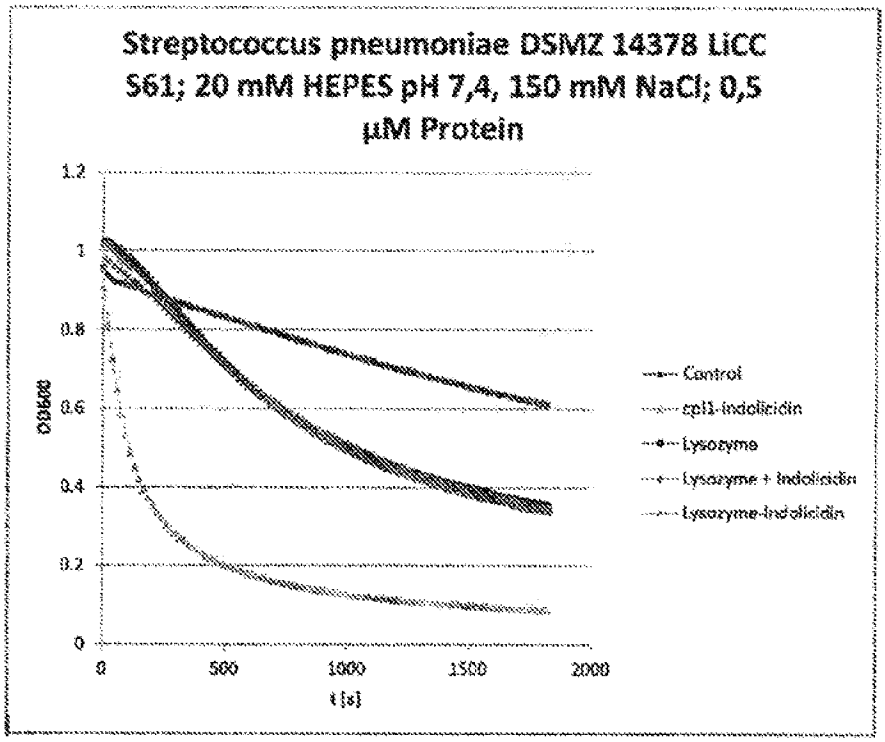
Appellant argues further that there would have been no reasonable expectation of success in combining the prior art to achieve the invention because the art is unpredictable. Appeal Br. 13. As support, Appellant submits and cites the Biebl Declaration.[13] The Biebl Declaration stated, "We have performed an experiment testing the antibacterial activity a fusion protein of cpl1 and indolicin (cpl1-indolicin), and compared it to (i) (egg white) lysozyme, (ii) lysozyme + indolicidin (i.e., as separate compounds) and (iii) a fusion protein of lysozyme and indolicidin."[14] Biebl Declaration ¶ 3. The Biebl Declaration further states that,

> The results, which are shown below, suggest that for the tested *S. pneumoniae* strain, a combination of lysozyme + indolicidin (much as described by Krieger) does not yield any effect going beyond lysozyme on its own. Moreover, a fusion falling within the scope of the present claims would be much more effective

[13] Declaration of Manfred Biebl under 37 C.F.R. § 1.132 dated June 9, 2015 ("Biebl Declaration").
[14] Indolicidin (the cationic peptide of the claims' elected species) is an antimicrobial peptide; we assume the Biebl Declaration's use of the term "indolicin" in paragraph 3 is a typographical error and intends to refer to indolicidin.

> than a fusion of egg white lysozyme with indolicidin, which was again only about as effective as lysozyme + indolicidin[,]

and goes on to produce the following graph, without more, which is also reproduced in the Appeal Brief (at 14):



Biebl Declaration ¶ 5 (first paragraph 5 therein, as there are two).

The supporting graph cannot be interpreted so as to support the Biebl Declaration's or Appellant's conclusions. Based on the quality of the graph that appears in the declaration, there is simply no way to discern which tested sample is represented by which line, how it was superior to others, or why.

Even if Appellant's evidence showed some degree of unpredictability, as contended, the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as

there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364. Moreover, the fact that a fusion of CPL-1 and indolicidin is "more effective" than a fusion of egg white lysozyme and indolicidin on *Streptococcus pneumoniae* is not surprising because Borysowski (at 371) teaches that the CPL-1 is effective against this specific bacteria, making it an obvious choice when targeting *Streptococcus pneumoniae*. Moreover, the CPL-1 fusion worked, as did the lysozyme fusion. Thus, both worked as predicted by the prior art. Appellant has not provided evidence that the CPL-1 fusion would have been unpredictable or not effective. A reasonable expectation of success has been established based on the findings of fact, *supra*. Furthermore, we note that neither the Declarations nor the Appellant's brief indicates that any results achieved by the claimed invention were unexpectedly superior to those of the closest prior art.

Appellant argues the Examiner erred in failing to consider the prior art as a whole, including that Krieger is directed to hen egg white lysozymes to the exclusion of other types and that Krieger does not specify what it means by fusions, e.g., of cationic peptides to other peptides. Appeal Br. 15. We discern no error by the Examiner. The Examiner merely refused to venture down Appellant's offered rabbit-hole on hen egg white lysozymes and simply recognized the fact that, as agreed-to by Appellant's Michiels Declaration, all lysozymes function by cleaving the same bond and, hence, disclosure of lysozymes generally invokes such a protein. Moreover, the Examiner need not have further considered the specific fusions of Krieger because other cited references even more clearly teach fusing cationic peptides and lysozymes (or endolysin). Appellant's arguments that Krieger

is so scientifically different from the other cited and combined prior art, which is also directed to anti-bacterial compositions, many including cationic peptides (e.g., indolicidin) and several including endolysins (e.g., lysozymes and specifically CPL-1), and some combining the two, is not supported by persuasive evidence and is thus not persuasive. Regarding Appellant's argument that extra technical "hoops" must be leapt through to achieve the claimed fused protein based on the prior art and there would have been no motivation to do so, this is likewise not persuasive in view of the active encouragement offered by the prior art. *See* FF1, FF2, FF6, FF7, FF10, FF13, FF14, FF16, FF18.

For the reasons set forth above, we are unpersuaded that the Examiner erred in presenting a case for obviousness or that secondary indicia of non-obviousness has been provided to establish patentability. The balance of evidence on appeal favors the Examiner's position.

SUMMARY

The obviousness rejections under 35 U.S.C. § 103 are each affirmed.

The double patenting rejection is dismissed.

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)(1)(iv).

AFFIRMED