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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/229,851	03/29/2014	Andrew Peter Mallon	CAL-CT007	1055

145247 7590 11/25/2019

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EXAMINER	
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ART UNIT	PAPER NUMBER
1658	

NOTIFICATION DATE	DELIVERY MODE
11/25/2019	ELECTRONIC

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANDREW PETER MALLON and ALVIN C. BACH II

Appeal 2018-005324
Application 14/229,851
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims to a cystic fibrosis transmembrane regulator-associated ligand (CAL) inhibitor peptide. Appellant appeals the Examiner's rejection of claims 1, 4, 6, 9, and 13 under 35 U.S.C. § 103.[1] We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] "Appellant" herein refers to the "applicant" as defined by 37 C.F.R. § 1.42. Appellant identifies "Calista Therapeutics, Inc.," as the real party-in-interest. Appeal Brief 1 ("Appeal Brief." herein refers to the brief filed Jan. 6, 2018). The Appeal Brief does not include page numbering; therefore, we cite to the brief by counting its pages sequentially, beginning with its first page as "1."

STATEMENT OF THE CASE

The Specification states that the invention "relates to stable, soluble, cell permeant and targeted PDZ domain inhibitor peptide drugs, and more particularly to inhibitors of the cystic fibrosis transmembrane regulator (CFTR) associated ligand (CAL)." Spec. ¶ 3. Independent claim 1, reproduced below, is representative of the claims on appeal:

> 1. A cystic fibrosis transmembrane regulator-associated ligand (CAL) inhibitor peptide, X_1-YGRKKRRQRRR-X_2-WQVTRV-X_3 (SEQ ID NO: 1), wherein X_1 is an acetyl group; X_2 is a cleavable linker comprising glycoyl; and X_3 is an amide group.

Appeal Brief 9 (Claims Appendix). Stated concisely, the claimed peptide is, for example: [acetyl group]-YGRKKRRQRRR-[HO-CH_2-COOH]-WQVTRV-[amide group]. The Specification's Background section further describes the prior art's, namely Madden's,[2] use of "a Cell Permeability Peptide (CPP) to impart cell uptake" of amino acid sequences for pharmaceutical use. Spec. ¶ 5. The Specification identifies that the claimed sequence portion "YGRKKRRQRRR" is TAT (a regulatory protein called Trans-Activator of Transcription, encoded for by the tat gene in HIV-1), and also identifies that the claimed "glycoyl" is HO-CH_2-COOH (i.e., glycolic acid). *Id.* at ¶ 11. The Specification also describes the claimed sequence portion "WQVTRV" as the "active sequence," which is a CAL inhibitor (iCAL) sequence. *Id.* at ¶¶ 11, 39–40. The Specification describes its invention as both "not predictable" in its advantages and as example of "optimized iCAL drug compounds." *Id.* ¶¶ 15, 41.

[2] US 2012/0071396 Al (published Mar. 22, 2012) ("Madden"). Madden is cited by the Examiner in an obviousness rejection, as discussed *infra*.

The following rejection is on appeal:

Claims 1, 4, 6, 9, and 13 stand rejected under 35 U.S.C. § 103 over Madden, Meyer,[3] Crielaard,[4] Balasubramaniam,[5] and Peers.[6] Answer 3–6.

FINDINGS OF FACT

We agree with and adopt the Examiner's findings of fact as set forth in the Final Action and Answer. Final Action 2–8, 10–19; Answer 3–15. We provide the following findings of fact to highlight certain evidence:

FF1. Madden teaches pairing a peptide (amino acid polymer) CAL inhibitor, WQVTRV (also called kCAL01), with HIV-1 tat (a CPP) to enhance cell penetration. Madden ¶¶ 14 (Table 1), 17, 31 (Table 2). Madden discloses that this CAL inhibitor is useful for preventing or treating cystic fibrosis. *Id.* at Abstract, ¶ 44.

FF2. Madden teaches modifying a peptide derivative, which retains the CAL inhibitor peptide, e.g., WQVTRV, at its N- and C-terminus to have an acetyl group and/or amide group to enhance stability *in vivo*. Madden ¶ 16. Madden teaches that such a peptide derivative would include the penetration enhancer noted in FF1. *Id.* ¶ 17.

FF3. Madden does not discuss incorporating a *cleavable* linker between its active sequence and its CPP; however, Madden teaches a variety of linkages for coupling structural components of the peptide

[3] EP 1884521 A1 (published February 6, 2008) ("Meyer").
[4] Bart J. Crielaard et al., *Liposomes as carriers for colchicine-derived prodrugs: Vascular disrupting nanomedicines with tailorable drug release kinetics*, 45 EURO. J. PHARMA. SCI. 429–35 (2012) ("Crielaard").
[5] US 2008/0221038 A1 (published Sept. 11, 2008) ("Balasubramaniam").
[6] US 5,837,218 (issued Nov. 17, 1998) ("Peers").

other than the natural amide bond linkages, including, for example, amide bonds, coupling means, and linking groups, such as ketomethylene and ester. Madden ¶ 23. Madden also discloses coupling the active peptide with biotin via a linker sequence. *Id.* ¶ 57.

FF4. Meyer is directed to a "fusion peptide" including an inhibiting peptide and a transporter peptide. Meyer, Abstract.

FF5. Meyer teaches that, because "peptide compounds administered *in vivo* targeting intracellular sites, e.g., for treatment of a specific disease, . . . typically comprise poor bioavailability in cells to be treated," they thus, benefit from fusion with a transporter peptide, such as TAT, i.e., YGRKKRRQRRR. Meyer ¶¶ 11–15.

FF6. Meyer teaches that the inhibiting peptide and transporter peptide of the fusion peptide can be linked directly or via a linker, such as a cleavable oligo- or polypeptide sequence or a coupling or conjugating agent. Meyer ¶ 22. Such cleavable linkers would be cleavable under cellular conditions to permit the fused inhibiting peptide and transporter peptide to separate after delivery into the target cell. *Id.* The linker may also provide spacer arms to provide intramolecular flexibility or adjustment of intramolecular distances between the conjugated moieties and, thereby, help preserve biological activity. *Id.*

FF7. Balasubramaniam is directed to peptides for pharmaceutical treatment and discloses that conjugating such peptides with TAT enhances deliverability of the peptides because of TAT's ability to cross the blood brain barrier. Balasubramaniam, Abstract, ¶ 12.

FF8. Balasubramaniam teaches that TAT can be coupled to the active peptide via a linker or spacer and that such a linker is "advantageously" glycolic acid ($HO–CH_2–COOH$). Balasubramaniam ¶¶ 45–48, 140.

FF9. Crielaard discloses that glycolic acid is a hydrolyzing, biodegradable linker, useful for coupling with an active pharmaceutical agent, which confirms that glycolic acid is a cleavable linker. Crielaard 429, 430.

FF10. Peers teaches that N- or C-terminal modification protects the termini of peptides from undesirable enzymatic, chemical, or biochemical attack and that the addition of protecting groups, such as acetyl and amide groups, "is common practice in the art in the preparation of peptides having greater stability, particularly for in vivo use" and preserves the functionality of the peptide. Peers 3:4–36.

FF11. Further to the preceding findings of fact, Madden states that "[t]he peptides, derivatives and peptidomimetics [of its invention] can be produced and isolated using any method known in the art" and "[p]eptides can be synthesized, [in] whole or in part, using chemical methods known in the art." Madden ¶ 33; *see also id.* ¶ 34 ("Techniques for generating peptide and peptidomimetic libraries are well-known . . . ."), ¶ 35 ("the peptide is purified or isolated using methods known in the art."). Similarly, and further to the preceding findings of fact, Meyer states, "methods for production of derivatives of components (I) and (II) of the inventive fusion peptide as disclosed above are well known and can be carried out following standard methods which are well known by a person skilled in the art." Meyer

¶ 28; *see also id.* ¶ 39 ("The inventive pharmaceutical composition as defined herein may also be administered by nasal aerosol or inhalation. Such a composition may be prepared according to techniques well-known in the art"). Further to the preceding findings of fact, Balasubramaniam also states "[t]he formulation and preparation of such compositions is well-known to those skilled in the art of pharmaceutical formulation." Balasubramaniam ¶ 277; *see also id.* ¶¶ 290, 301, 321. And, as noted *supra* at FF10, Peers states "N- and C-terminal modification of peptides is common practice in the art in the preparation of peptides having greater stability, particularly for in vivo use." Peers 3:15–18.

DISCUSSION

I. LEGAL STANDARDS

"[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. [Once] . . . 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 and properly presented in the Reply Brief have been considered; arguments not so-presented are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2017); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (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 [or steps] 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). "One way

for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014); *see also In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

With these standards in mind, we address the Examiner's rejection and Appellant's arguments there-over.

II. ANALYSIS

The Examiner determined that the claims would have been obvious over the prior art combination of Madden, Myer, Crielaard, Balasubramaniam, and Peers. *See* Final Action 10–19 and Answer 3–15 (collectively citing Madden Abstract, 3–4 (Tables 1, 2), ¶¶ 5, 16, 17, 48, 49, 51117; Myer ¶¶ 11, 14, 15, 22, Figs. 1, 2; Crielaard in its entirety; Balasubramaniam ¶¶ 45, 140; and Peers 3:15–25, 3:28–33); *see also supra* FF1–FF11 (highlighting evidence). The Examiner summarizes her position and rationale in the Answer and we reproduce the Examiner's summary below:

Madden et al teach kCAL01 with the amino acid sequence ***WQVTRV*** is the best binding predicted CAL inhibitor peptide. ***Madden*** et al further teach the CAL inhibitor peptide can be modified with one or more post-translational modifications such as ***acetylation***, ***amidation*** and many others. ***Madden*** et al also teach the CAL inhibitor peptide can be conjugated to ***cell-penetrating sequence*** which facilitates the transmembrane transport or intracellular delivery of the peptide into a cell; one of the suitable cell-penetrating sequences is ***HIV-1 tat sequence***; and conjugates comprising cell-penetrating sequence coupled to the N-terminus of the CAL inhibitor peptide.

The Examiner agrees that ***Madden*** et al ***do not teach the use of a cleavage linker*** such as glycoyl between WQVTRV and the tat peptide. However, ***Meyer*** explicitly teaches the advantage of using a ***cleavable linker*** in that the peptide compound can be separate from the CPP after being delivered into the target cell. The use of cleavable linker to remove CPP and its advantage are also well-known in the art, as shown in Wagstaff et al (Current Medicinal Chemistry, 2006, 13, pages 1371-1387, cited and provided in previous office action, for example, pages 1379-1380, Section "4.1.2. Coupling of CPP to Cargo" and Figure 2), Heitz et al (British Journal of Pharmacology, 2009, 157, pages 195-206, cited and provided in previous office action, for example, page 197, left column, Section "Covalent strategy") and many others. Heitz et al explicitly state that "the covalent CPP technology is limited from a chemical point of view and risks altering the biological activity of the cargo", for example, page 197, left column, Section "Covalent strategy". Therefore, in view of the combined teachings of ***Madden*** et al and ***Meyer***, it would have been obvious to one of ordinary skilled in the art to ***use a cleavable linker between the HIV tat sequence and the CAL inhibitor peptide WQVTRV so that the CAL inhibitor peptide WQVTRV can be separated from HIV tat sequence after being delivered into the target cell, thereby eliminating the risk of altering the biological activity of the CAL inhibitor peptide WQVTRV***.

One of ordinary skill[] in the art would have been ***motivated*** to use a cleavable linker between the HIV tat sequence

and the CAL inhibitor peptide WQVTRV so that the CAL inhibitor peptide WQVTRV can be separated from HIV tat sequence after being delivered into the target cell, thereby ***eliminating the risk of altering the biological activity of the CAL inhibitor peptide WQVTRV***.

The Examiner understands that ***Crielaard*** et al describe ***cleavable linker such as glycolic acid (synonym of glycoyl)*** in the context of encapsulation of a PEGylated prodrug encapsulated within a liposome, wherein cleavage of the linker molecule is modulated to affect the rate of release of the drug from the liposome into the cell. However, in the instant case, the Crielaard et al reference is cited to teach glycolic acid (synonym of glycoyl) linker is a cleavable linker that can be used to separate the active compound in cells. Crielaard et al teach prodrug comprising glycolic acid (synonym of glycoyl) linker and the release of the active compound can be controlled by using biodegradable/cleavable linker such as glycolic acid linker.

In addition, ***Balasubramaniam*** teaches coupling ***peptide compound to cell penetrating peptide TAT with the amino acid sequence YGRKKRRQRRR via a linker; and HO-CH2-COOH (glycolic acid, synonym of glycoyl) is one of the preferred linkers*** used to connect the peptide compound and TAT.

Therefore, in view of the combined teachings of Madden et al, Meyer, Crielaard et al and Balasubramaniam, it would have been obvious to one of ordinary skilled in the art to develop a CAL inhibitor peptide YGRKKRRQRRR-glycoyl-WQVTRV; and one of ordinary skilled in the art would have been motivated to develop a CAL inhibitor peptide YGRKKRRQRRR-glycoyl-WQVTRV.

With regards to having an acetyl group at the N-terminus of the peptide compound and an amide group at the C-terminus of the peptide compound, as stated above, ***Madden*** et al explicitly teach the CAL inhibitor peptide can be modified with one or more post-translational modifications such as ***acetylation***, ***amidation*** and many others. Furthermore, ***Peers*** et al teach that N- and C-terminal modification of peptides, such as having an ***acetyl*** group at the N-terminus of the peptide compound and an

amide group at the C-terminus of the peptide compound, is common practice in the art of preparation of peptides having greater stability, particularly for in vivo use. In addition, it is well known in the peptide/protein art that N- and C-terminal modification of peptides, such as having an acetyl group at the N-terminus of the peptide compound and an amide group at the C-terminus of the peptide compound, is important to the biological stability and activity of many peptides and protein, as shown in Adessi et al (Current Medicinal Chemistry, 2002, 9, pages 963-978, filed with IDS, for example, page 967, Section "N- and C-terminal Modifications") and many others. Therefore, ***in view of the combined teachings of Madden et al, Meyer, Crielaard et al, Balasubramaniam and Peers, it would have been obvious to one of ordinary skilled in the art to develop a CAL inhibitor peptide acetyl-YGRKKRRQRRR-glycoyl-WQVTRV-amide***.

One of ordinary skill[] in the art would have been ***motivated*** to ***combine the teachings of Madden et al, Meyer, Crielaard et al, Balasubramaniam and Peers et al to develop a CAL inhibitor peptide acetyl-YGRKKRRQRRR-glycoyl-WQVTRV-amide***; and a pharmaceutical composition comprising such peptide and a pharmaceutically acceptable carrier, because ***Meyer*** teaches the advantages of adding transporter peptide such as TAT with the amino acid sequence YGRKKRRQRRR to peptide compound, such as enhanced cellular uptake and many others. ***Meyer*** further teaches the transporter peptide is connected to the peptide compound through a linker; and the use of a(n) intracellularly/endogenously cleavable oligo- or polypeptide sequence as a linker permits the transporter peptide to separate from the peptide compound after delivery into the target cell. ***Crielaard*** et al teach prodrug comprising glycolic acid (synonym of glycoyl) linker and the release of the active compound can be controlled by using biodegradable/cleavable linker such as glycolic acid linker. ***Balasubramaniam*** teaches coupling peptide compound to cell penetrating peptide TAT with the amino acid sequence YGRKKRRQRRR via a linker; and HO-CH2-COOH (glycolic acid, synonym of glycoyl) is one of the preferred linkers used to connect the peptide compound and TAT. ***Peers*** et al teach that N- and C-terminal modification of

> peptides is common practice in the art of preparation of peptides having greater stability, particularly for in vivo use. Such modifications include adding an acetyl group at the N-terminus of the peptide and an amide group at the C-terminus of the peptide.

Answer 10–12 (formatting and emphasis added); *see also* Final Action 14–17 (providing a similar summary). We find no error in the Examiner's well-summarized determinations and rationale on obviousness. *See* FF1–FF11. We address Appellant's arguments below.[7]

Appellant argues that Madden fails to teach the claimed cleavable linker and, although Meyer teaches use of a linker sequence, it is not the same as the cleavable glycoyl linker claimed. Appeal Brief 4. Appellant adds that Crielaard describes cleavable glycolic acid (glycoyl) linkers in the context of PEGylated prodrugs encapsulated in liposomes for regulating release therefrom, which is different from the claimed subject matter, and that Balasubramaniam teaches a glycolic acid linker, but not for the purpose of allowing it to be cleaved for delivery of a compound to a cell. *Id.* This argument is not persuasive.

As illustrated by both the findings of facts and the Examiner's summary of her position, each above, the combination of Madden, Meyer, Balasubramaniam, Crielaard, and Peers teaches or suggests a peptide conjugate structure where the active peptide WQVTRV is coupled to the cell penetrating peptide TAT (i.e., YGRKKRRQRRR) by a cleavable glycolic acid (aka "glycoyl," i.e., HO-CH_2-COOH) linker and has either an acetyl or

[7] Appellant argues only specifically over the patentability of claim 1, and noted that the patentability of the other claims depends on claim 1's patentability. *See* Appeal. Br. 7. Therefore, all claims stand or fall with claim 1.

amide group at the peptide derivative's terminal ends. *See* FF1–FF10. The cell penetrating peptide would have been added to the active peptide to enhance the active's delivery to cells; it would have been attached thereto via a linker and glycoyl would be preferred because it works to pair peptide sequences and was known to be cleavable, both advantages; and, finally, the acetyl and/or amide groups would have been added to the terminal ends of the peptide derivative because such was commonly done to protect such peptides from undesirable attack and to add stability. *See* FF1–FF10.

"Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The references] must be read, not in isolation, but for what [they] fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Here, the rejection is predicated on a combination of references, which we conclude would have been obvious to combine in the way determined by the Examiner. Appellant's attacks on each individual reference, without regard to the teachings of the combination, are not persuasive.

Appellant cites (generally) the Torchilin Declaration as support for the proposition that the specific combination of conjugated elements of the invention would have been unpredictable to the skilled artisan, and also argues, relatedly, there would have been no motivation to combine the five prior art references cited by the Examiner.[8] Appeal Brief 5. Appellant quotes the Torchilin Declaration as follows: "[i]t would not have been possible to have predicted that CT007[,] [which Appellant's Specification's

[8] Declaration of Vladimir Torchilin Ph.D., D.Sc. under 37 C.F.R. § 1.132, dated March 23, 2017 ("Torchilin Declaration").

Figure 4 identifies as acetyl-YGRKKRRQRRR-glycoyl-WQVTRV-amide, a compound within the scope of Appellant's claimed peptide,] would have been the resultant effective composition after reviewing the prior art . . . I do not believe a skilled pharmaceutical chemist would have been able to design CT007." *Id.* (quoting, but not citing, Torchlin Declaration ¶¶ 28–29). This argument is not persuasive.

The Examiner's reasoning for combining Madden, Meyer, Balasubramaniam, Crielaard, and Peers in the way determined by the Examiner is reasonable, sound, and well-supported by the disclosures of the references themselves. As noted above, each reference provides reasons that incorporating its relevant elements into a peptide structure as disclosed by Madden would be advantageous. *See* FF2, FF5–FF6, FF8, FF10. Moreover, each of the cited prior art references emphasizes that the techniques used for producing and using the molecules and structures of its invention were well-known and common in the art—not unpredictable. *See* FF11. 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. . . . [T]he proper standard [is that] the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Thus, while the ultimate peptide structure of the appealed claims might not have been singularly disclosed in the art, the individual parts thereof, their combination, and reason to reasonably expect successful combination was taught or suggested by the cited prior art. Furthermore, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*,

314 F.3d 1313, 1355 (Fed. Cir. 2003). Thus, we presume the peptides, linkers, protective terminal end groups, and therapeutic use thereof as disclosed in the cited prior art is enabled; there is no evidence to the contrary.

In contrast to the evidence cited by the Examiner, neither Appellant nor Dr. Torchilin directs us to evidence or explanation in support of Dr. Torchilin's testimony about the unpredictability of a peptide within the scope of claim 1. Dr. Torchilin states that a skilled artisan would not have been able to design or predict success for such a peptide, but fails to explain why, given the references the Examiner cites about the design and construction of similar peptides. *See* Torchilin Declaration ¶¶ 28–29. For example, Dr. Torchilin identifies the combination of a TAT CPP peptide with the active CAL inhibitor peptide as one of the unusually complex conjugations of the invention, but it is apparent from, e.g., Madden (FF1, FF2), Meyer (FF4, FF5), and Balasubramaniam (FF8), that such conjugation was known, if not routine (FF11). *See* Torchilin Declaration ¶ 11. Also, Dr. Torchilin stated that adding amide and acetyl groups to a peptide conjugate similarly required an unusual level of complexity; however, again, Madden (FF2) and Peers (FF10) each identifies this as a known, and even a commonly used technique to stabilize peptides (FF11). *See* Torchilin Declaration ¶ 11. Based on the evidence before us, we do not agree with the Torchilin Declaration's conclusion argued by Appellant.

Appellant also argues that an embodiment within the scope of the claimed invention, i.e., "CT007," produced superior results compared to other samples (comparative examples CT003, CT004, CT005, and CT006) because it included a glycoyl linker while the comparative examples did not.

Appeal Brief 5. Appellant argues that this is evidence of some *Graham* secondary considerations showing non-obviousness as it suggests "no obvious likelihood of success," but does not specify which *Graham* secondary consideration specifically applies. *Id.* at 6. This argument is not persuasive.

That the invention is superior to comparative examples does not, in and of itself, establish that the claims are non-obvious. Mere improvement does not qualify as evidence of secondary considerations of non-obviousness. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) ("[O]bjective evidence of nonobviousness includes copying, long felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention." (internal citations omitted)). As discussed above, we conclude that, on the evidence before us, the skilled artisan would have had motivation to combine the elements of the cited prior art in the fashion claimed and, based on the disclosures of that prior art, the skilled artisan would have reasonably expected to successfully do so because it would have required no more than performing well-known techniques. *See supra* Findings of Fact, in particular, FF11.

Appellant also argues there is evidence of "unexpected success" (i.e., unexpected results, a *Graham* secondary consideration) "indicative of non-obviousness." Appeal Brief 6 (citing Mallon Declaration, generally).[9]

[9] Declaration of Andrew Peter Mallon Ph.D., under 37 C.F.R. § 1.132 ("Mallon Declaration").

Appellant quotes, somewhat inaccurately, the Mallon Declaration as follows:

> a further animal study of CT007 was conducted[ ] [wherein:] . . . CT007 was administered with high doses to the lungs of test rats. It was observed that a minimal amount of CT007 was absorbed in the systemic circulation. CT007 was effectively sequestered within the first cell type it encountered, the targeted respiratory epithelium.
>
> [10.] A control peptide [(CT110)] containing the selected TAT sequence conjugated to an off-target PDZ binding sequence, but without a glycoyl bond between the TAT moiety and PDZ binding sequence, was administered in high doses to the lungs of test rats. A significantly higher systemic concentration of the control peptide was observed, evidencing that the control peptide was not sequestered within the target respiratory epithelium as expected in the test animals. . . .

Id. (quoting, but not citing, Mallon Declaration ¶¶ 9–10) (formatting, bracketing, and final ellipsis added for accuracy).

As an initial matter, this portion of the Mallon Declaration quoted by Appellant does not state that the results achieved by the invention were unexpected. Nowhere does the Mallon Declaration make such an assertion. *See generally* Mallon Declaration. We do note that the Torchilin Declaration states "it is actually very surprising that CT007 specifically was able to work." Torchilin Declaration ¶ 18.

Although Appellant has presented evidence that CT007 was effective while other comparative samples were not, we conclude that the evidence does not support that the claimed invention was not obvious over the cited prior art combination. Significantly lacking in Appellant's evidence is a comparison between CT007, which Appellant avers is the claimed invention, with the closest prior art, which would be the subject matter taught or

suggested by Madden. CT007 is identified in the Specification's Figure 4 as being "[a]cetyl-YGRKKRRQRRR-glycoyl-WQVTRV-amide." Spec. Figure 4. Madden teaches or suggests the WQVTRV active peptide, TAT as a CPP (i.e., YGRKKRQRRR), that these two peptide sequences can be joined with some linker/coupler, and that the ends of the ultimate derivative peptide could have acetyl and/or amide groups at their N- and C-terminal ends; thus, Madden teaches or suggests: [acetyl or amide]-YGRKKRRQRRR-[linker/coupler]-WQVTRV-[acetyl or amide]. FF1–FF3 (we note that the CPP and active peptide could be reversed in order). None of the comparative samples reflected in Appellant's evidence is such a structure. Spec. Figure 4. Appellant's CT005 comes the closest, but provides no linker between its active and CPP peptide sequences to compare to glycoyl (and reverses the order of the active and CPP compared to CT007). *Id.* Appellant's argument is not persuasive.

We discern no error in the Examiner's determinations, which we conclude presented a prima facie case for the claims' obviousness over the cited prior art combination. We have considered Appellant's arguments over the rejections in their entirety, but find them unpersuasive on the record on appeal.

CONCLUSION

In summary, the obviousness rejection of claims 1, 4, 6, 9, and 13 is affirmed.

Claims Rejected	35 U.S.C. §	Reference(s)	Affirmed	Reversed
1, 4, 6, 9, 13	103	Madden, Meyer, Crielaard, Balasubramaniam, Peers	1, 4, 6, 9, 13	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED