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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* HISATOSHI KOBAYASHI, DOHIKO TERADA,  
MASAMI TODOKORO, AKIKO SHIMATANI, and  
YUKINORI KATAOKA<sup>1</sup>

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Appeal 2017-011513  
Application 13/848,738  
Technology Center 1700

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Before JANET A. GONGOLA, *Vice Chief Administrative Patent Judge*,  
ROMULO H. DELMENDO, and JAMES T. MOORE, *Administrative  
Patent Judges*.

GONGOLA, *Vice Chief Administrative Patent Judge*.

DECISION ON APPEAL

Appellant files this appeal under 35 U.S.C. § 134(a) from a final rejection of claims 1–12. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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<sup>1</sup> JNC CORPORATION is listed as the Applicant and the real party in interest. Application Data Sheet filed March 22, 2013 at 5; Appeal Brief filed April 25, 2017 (“App. Br.”) 1.

## BACKGROUND

The claims on appeal are directed to a method of producing a nano-fiber by electrospinning a solution containing a synthetic collagen and a polymer. Specification filed March 22, 2013 (“Spec.”) ¶ 11. The synthetic collagen is a polypeptide having a peptide fragment represented by the formula  $-(\text{Pro-Y-Gly})_n-$  wherein Y represents hydroxyproline or proline. Spec. ¶ 12. The Specification discloses that electrospinning is a known method for producing nanofibers. Spec. ¶ 2. The Specification also discloses the claimed method results in uniform and long fibers. Spec. ¶ 7.

Claim 1 is representative of the subject matter on appeal and is reproduced below:

1. A method of producing a nano-fiber that contains a polypeptide having a peptide fragment represented by Formula (1):



wherein Y represents a hydroxyproline or proline, and n is an integer ranging from 5 to 9000, the producing method comprising:

preparing a spinning solution containing the polypeptide and a polymer, and

spinning with an electrospinning method using the spinning solution, wherein a solvent in the spinning solution comprises an organic solvent.

App. Br. 19 (Claims App’x)(paragraphing added).

Independent claims 7 and 12 differ from claim 1 in that they recite “the polymer comprises one, two or more selected from the group consisting of natural collagen and polyvinyl alcohols,” among other features. App. Br. 19–20.

### REJECTIONS ON APPEAL

1. The Examiner rejected claims 1–6 under 35 U.S.C. § 103(a) as unpatentable over Huang,<sup>2</sup> Shibasaki,<sup>3</sup> and Matthews.<sup>4</sup> Final Office Action entered December 12, 2016 (“Final Act.”) 2–5.

2. The Examiner rejected claims 7–12 under 35 U.S.C. § 103(a) as unpatentable over Huang, Shibasaki, Matthews, and Simpson.<sup>5</sup> Final Act. 5–11.

Appellant states that the independent claims, 1, 7, and 12 may be taken as representative of the claims on appeal. *See* Appeal Br. 5. Accordingly, we select these claims as representative of the dependent claims and decide this appeal based on the rejection of claims 1, 7, and 12. 37 C.F.R. § 41.37(c)(1)(iv). We combine the discussion of the rejections that involve the same references hereinafter.

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<sup>2</sup> Huang, L. et al., *Engineered collagen-PEO nanofibers and fabrics*, 12 J. Biomater. Sci. Polymer Edn. 979–993 (2001) (“Huang”).

<sup>3</sup> Shibasaki, Y. et al., *Collagen-Like Polypeptide Poly(Pro-Hyp-Gly) Conjugated with Gly-Arg-Gly-Asp-Ser and Pro-His-Ser-Arg-Asn Peptides Enhances Cell Adhesion, Migration, and Stratification*, 96 Peptide Science 302–315 (2010) (“Shibasaki”).

<sup>4</sup> Matthews, J. A. et al., *Electrospinning of Collagen Nanofibers*, 3 Biomacromolecules 232–238 (2002) (“Matthews”).

<sup>5</sup> Simpson et al., U.S. Pat. Pub. No. 2004/0037813 A1, published February 26, 2004 (“Simpson”).

## DISCUSSION

### *I. Obviousness of Claims 1–6 over the Combination of Huang, Shibasaki, and Matthews*

The Examiner finds that “Huang teaches a method of preparing nanofibers by (i) preparing a solution of type I collagen and polyethylene oxide (i.e., a polymer); and (ii) electrospinning the solution.” Final Act. 3, citing Huang Abst. The Examiner acknowledges that Huang teaches a spinning solution that is aqueous HCl and not an organic solvent. *Id.* However, the Examiner finds “Matthews teaches that the organic solvent 1,1,1,3,3,3-hexafluoro-2-isopropanol (i.e., HFP) is the solvent of choice for electrospinning collagen because its lower boiling point promotes the evaporation of the solvent under conventional atmospheric conditions.” *Id.*, citing Matthews 234. The Examiner also acknowledges that Huang does not teach the claimed peptide fragment of Formula (1). *Id.* But the Examiner finds that Shibasaki teaches a collagen-like synthetic peptide containing a poly(Pro-Y-Gly)<sub>n</sub>- peptide fragment, wherein Y is hydroxyproline, and n is equal to about 50. *Id.*, citing Shibasaki Abst.; 306. The Examiner determines:

[i]t would have been obvious to a person having ordinary skill in the art at the time of the invention to have replaced the type I collagen of Huang with the collagen-like peptide of Shibasaki, and the motivation to have done so would have been, as Shibasaki suggests, that poly(Pro-Hyp-Gly[ ])-based collagen-like polypeptides enhance cell adhesion, migration, and stratification, and, consequently, may be useful scaffolds for tissue regeneration.

*Id.*

Appellant presents a series of arguments in attempt to overturn the Examiner. First, Appellant contends “Huang merely indicates that **natural** collagen is soluble in acidic water . . . and can be electrospun . . . but mentions nothing about . . . **synthetic** collagen.” App. Br. 7 (emphases in original). Appellant contends that “Shibasaki mentions nothing about fiber spinning using a synthetic collagen . . . .” *Id.* (emphasis omitted). Appellant contends that “Matthews only teaches using an organic solvent . . . as a solvent for electrospinning a **natural collagen** . . . but also fails to disclose i) whether or not a synthetic collagen could be dissolved in an organic solvent . . . or ii) *any other property of the synthetic collagen in an organic solvent . . . .*” *Id.* (emphases in original).

We are not persuaded by Appellant’s arguments. Appellant erroneously argues the prior art references on an individual basis. “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).

Here, the Examiner identified each component of the claims in the combined prior art. Therefore, the question is whether it would have been obvious to one of ordinary skill in the art, working with the Huang, Matthews, and Shibasaki references before them, to apply an electrospinning method to synthetic collagen in an organic solvent to produce nano-fibers. *In re Keller*, 642 F.2d 413, 425 (CCPA 1981) (“the test [for obviousness] is

what the combined teachings of the references would have suggested to those of ordinary skill in the art”). We address this question below.

Second, Appellant contends “that synthetic collagen and natural collagen have **remarkably different properties**” and, therefore, there would be no reasonable expectation of success in combining the references. App. Br. 7–8 (emphasis in original). To support this argument, Appellant submits a Declaration describing two different experiments comparing natural to synthetic collagen.<sup>6</sup> Appellant contends that Experiment 1 proves the viscosity of natural collagen varies significantly at different pHs, but the viscosity of synthetic collagen does not vary at different pHs. App. Br. 8–9. Appellant contends that Experiment 2 proves the triple helix structure of natural collagen is destroyed at high temperatures, but the triple helix structure of synthetic collagen is maintained at high temperatures. App. Br. 10–12.

We are not persuaded by Appellant’s arguments. We agree with Appellant that natural and synthetic collagen have different physical properties. But Appellant has not shown that these different properties would preclude one of ordinary skill in the art from combining the references. “Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

Moreover, because Shibasaki itself acknowledges that natural collagen has several drawbacks such as “low thermal stability,” (Shibasaki

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<sup>6</sup> Declaration of Hideaki Fukushi, filed October 12, 2016 (“Fukushi Decl.”)

302), Shibasaki teaches the chemical synthesis of poly(Pro-Hyp-Gly), which forms a stable triple-helical structure at temperatures up to 80° C and does not present the same drawbacks as natural collagen (*Id.* at 303). Appellant's argument that a skilled artisan would not consider synthetic collagen over natural collagen, App. Br. 9, thus is not supported by the evidence of record. Accordingly, Appellant has not provided persuasive evidence that a person of ordinary skill in the art would not expect Shibasaki's synthetic collagen to be applicable to Huang's electrospinning methods using Matthews' organic solvent.

Third, Appellant contends that modifying the use of natural collagen in Huang with synthetic collagen as taught by Shibasaki draws away from the original purpose of Huang. App. Br. 12.

We are not persuaded by Appellant's argument. Appellant does not identify any teaching in Huang that would have suggested that the electrospinning method would not apply to synthetic collagen. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention"). Rather, substituting synthetic collagen into the known method of electrospinning natural collagen would have been considered by a skilled artisan as the "mere substitution of one element for another known in the field," that yields a predictable result. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Finally, Appellant argues that "Shibasaki teaches that in order to enhance cell adhesion, migration and stratification, the collagen-like

polypeptide Poly(Pro-Hyp-Gly) is conjugated with Gly-Arg-Gly-Asp-Ser and Pro-His-Ser-Arg-Asn peptides.” App. Br. 13. Appellant argues that combining the references without the conjugated peptide fragments is hindsight gleaned from the instant application. *Id.*

We are not persuaded by Appellant’s arguments. In rejecting the claimed invention as obvious, we find that the Examiner has taken into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and has not applied improper hindsight. *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971) (“Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made . . . such a reconstruction is proper”).

Shibasaki teaches that conjugation of peptides with natural collagen enhance cell adhesion and differentiation. *See* Shibasaki 303. Appellant has not identified any teaching in Shibasaki that conjugated peptides are necessary to address the drawbacks of natural collagen, nor any limitation in the claims that would necessarily exclude the conjugated peptides.

Appellant raises similar arguments to distinguish Matthews individually. *See* App. Br. 13–14. In particular, Appellant argues that Matthews only teaches using HFP to dissolve natural collagen (App. Br. 13) and that the Fukushi Declaration establishes that synthetic collagen has “much higher” stability than natural collagen (App. Br. 14). Therefore, Appellant argues there is no reasonable expectation of success in combining the references. App. Br. 14; *see also* Reply Brief filed September 12, 2017

(“Reply Br.”) 1–2. Moreover, Appellant argues the Examiner has not provided a reason for combining Matthews with Huang and Shibasaki. *Id.*

We are not persuaded by Appellant’s arguments. Matthews unambiguously states “[p]reliminary experimentation identified HFP as the solvent of choice for electrospinning collagen.” Matthews 234. Matthews’ teaching establishes a reasonable expectation of success in applying HFP as a solvent for electrospinning various collagens, including synthetic collagen. “A person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR*, 550 U.S. at 421.

Appellant has not identified any teaching in Matthews that suggests HFP is unlikely to work for electrospinning synthetic collagen. Appellant’s evidence that natural and synthetic collagen dissolve differently in aqueous solutions of different pHs does not outweigh the Examiner’s showing that a person of ordinary skill in the art would have had a reasonable expectation of success in using HFP as an electrospinning solvent for synthetic collagen.

Accordingly, the preponderance of evidence supports the Examiner’s determination that claims 1–6 would have been obvious over the combination of Huang, Shibasaki, and Matthews, and we affirm the Examiner’s rejection.

*II. Obviousness of Claims 7–12 over Huang, Shibasaki, Matthews, and Simpson*

The Examiner finds that the combination of Huang, Shibasaki, and Matthews teaches a method of producing a nano-fiber by electrospinning a solution of synthetic collagen and a polymer in an organic solvent. Final Act. 6–7. The Examiner acknowledges that “Huang does not teach that the

spinning solution contains a polymer that is natural collagen or a polyvinyl alcohol.” *Id.* at 7. The Examiner cites Simpson for teaching “both polyethylene oxide and polyvinyl alcohol are suitable synthetic materials that may be combined with collagen in electrospinning collagen fibers.” *Id.*, citing Simpson ¶¶ 92, 96, and 99. The Examiner finds the motivation to substitute polyvinyl alcohol for polyethylene oxide as taught by Huang is that the prior art teaches the two polymers are equivalents for the same purpose. *Id.*

Appellant advances that “no Example of Simpson used polyethylene oxide or polyvinyl alcohol” and that “polyvinyl alcohol is not even a preferred polymer of Simpson.” App. Br. 16.

We do not find Appellant’s argument persuasive. “[A]ll disclosures of the prior art, including unpreferred embodiments, must be considered.” *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976). Here, Simpson teaches that electroprocessed collagen may be combined with other materials, including synthetic materials such as poly(vinyl alcohol) and poly(ethylene oxide). Simpson ¶ 99. That Simpson does not list polyvinyl alcohol as a preferred synthetic material does not demonstrate nonobviousness of the claims.

Appellant also argues that the claimed method provides the unexpected effect of “a uniform and long fibrous nano-fiber.” App. Br. 16, citing Spec. ¶¶ 7, 8, 36, 41, and 42.

We do not find Appellant’s argument persuasive. Both Huang (Abst.) and Simpson (¶ 134) teach electrospun collagen nanofibers having diameters of 100–150 nm, which qualify as “uniform and long.” *See* Spec.

¶ 33. Indeed, Huang states: “Uniform fibers with a diameter range of 100–150 nm were produced.” Huang Abst. Moreover, Appellant does not submit any evidence that the resulting nano-fibers were unexpected. “[I]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice.” *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Moreover, we do not see such a limitation contained within the claims.

Accordingly, the preponderance of evidence supports the Examiner’s determination that claims 7–12 would have been obvious over Huang, Shibasaki, Matthews, and Simpson, and we affirm the Examiner’s rejection.

### **SUMMARY**

In summary, we affirm the Examiner’s rejections of claims 1–6 under 35 U.S.C. § 103(a) as unpatentable over Huang, Shibasaki, and Matthews.

We affirm the Examiner’s rejections of claims 7–12 under 35 U.S.C. § 103(a) as unpatentable over Huang, Shibasaki, Matthews, and Simpson.

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).

### **AFFIRMED**