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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KOKI KANEHIRA, SHUJI SONEZAKI,
YUMI OGAMI, and TOMOMI NAKAMURA

Appeal 2018-000555
Application 14/832,167
Technology Center 1600

Before TAWEN CHANG, TIMOTHY G. MAJORS, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant¹ appeals from the Examiner's decision to reject claims 1–9 and 11–15. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM-IN-PART.

¹ We use the word “Appellant” to refer to “applicant” as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as TOTO LTD. Appeal Br. 1.

BACKGROUND

The Specification teaches that application of ultrasonic waves to titanium oxide particles can generate hydroxyl radicals, which decompose organic matter. Spec. ¶ 6. However, the Specification states that “[t]itanium oxide is said to have an isoelectric point at a pH value around 6” and that, thus, “titanium oxide particles disadvantageously cause coagulation in an aqueous solvent around a neutral pH, making it very difficult to dispers[e] the titanium oxide particles homogeneously.” Spec. ¶ 2.

The Specification states:

The present invention provides titanium oxide composite particles comprising titanium oxide particles having surface modified with a hydrophilic polymer, a dispersion liquid thereof, and a method for accumulating the titanium oxide composite particles into a cancer tissue. The titanium oxide composite particles can be rendered cytotoxic upon exposure to ultrasonic waves, ultraviolet light or the like and thus can be utilized as a cell killer for killing cells such as cancer cells, or as an ultrasonic cancer treatment enhancer for enhancing ultrasonic cancer treatment by irradiating an affected part with ultrasonic waves.

Spec. ¶ 1.

In particular, the Specification asserts that binding a nonionic hydrophilic polymer to the surface of titanium oxide particles allows dispersion of the particles “on a high level by hydration without charging, even in an aqueous solvent around a neutral state.” Spec. ¶ 21. Likewise, the Specification asserts use of uncharged hydrophilic polymer ensures “retention in blood . . . on a level high enough to realize arrival at the target site (tumor), since . . . blood protein can be less likely to be electrostatically adsorbed, making it easier to avoid incorporation into a reticuloendothelial system [(RES)], renal excretion, liver incorporation, and the like,” as well as

“contribut[e] to excellent accumulation in the cancer cells” because “the polymer can easily arrive at the surface of cancer cells at high density.” *Id.*

Finally, the Specification states that bonding the polymer through the claimed functional groups “can ensure a large portion of naked parts on the surface of the titanium oxide particles” and that, “[a]s a result, the catalytic activity of the titanium oxide particles can be satisfactorily developed while suppressing the deactivation of the . . . particles caused by the covering of the surface with the polymer.” *Id.* ¶ 20.

CLAIMED SUBJECT MATTER

The claims are directed to a method for accumulating titanium oxide composite particles into a cancer tissue. Claim 1, the sole independent claim, is illustrative:

1. A method for accumulating titanium oxide composite particles into a cancer tissue, which comprises the steps of
 - providing titanium oxide composite particles which comprise: titanium oxide particles; and a nonionic hydrophilic polymer bound to a surface of the titanium oxide particles through at least one functional group selected from carboxyl group, amino group, diol group, salicylic acid group, and phosphoric acid group, wherein the composite particles have a diameter of 20 to 200 nm, and a bonding amount of the hydrophilic polymer per unit weight of the composite particles is 0.3 to 0.5 g/g, and
 - administering the composite particles to a patient thereby the composite particles are accumulated in the cancer tissue.

Appeal Br. 33.

REJECTION(S)

- A. Claims 1–5, 7–9, and 11–14 are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Sonezaki,² Gupta,³ Fan,⁴ Cunningham,⁵ Rajh,⁶ Xu,⁷ and Levy.⁸ Ans. 2.
- B. Claims 6 and 9 are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, and Thünemann.⁹ Ans. 3.
- C. Claims 11, 14, and 15 are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, Kubo, and Gray.¹⁰ Ans. 3.

OPINION

A. *Obviousness rejection over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy (Claims 1–5, 7–9, and 11–14)*

1. Issue

The Examiner finds that Sonezaki teaches all of the limitations of the rejected claims except that it does not expressly teach “the hydrophilic surface polymer includ[ing] polyethylene glycol [(PEG)] bound to the

² Sonezaki et al., US 2006/0264520 A1, published Nov. 23, 2006.

³ Ajay Kumar Gupta & Stephen Wells, *Surface-Modified Superparamagnetic Nanoparticles for Drug Delivery: Preparation, Characterization, and Cytotoxicity Studies*, 3 IEEE TRANSACTIONS ON NANOBIOSCIENCE 66 (2004).

⁴ Xiaowu Fan et al., *Biomimetic Anchor for Surface-Initiated Polymerization from Metal Substrates*, 127 J. AM. CHEMICAL SOC’Y 15843 (2005).

⁵ Joseph Cunningham & Ghassan Al-Sayyed, *Factors Influencing Efficiencies of TiO₂-sensitised Photodegradation*, 86 J. CHEMICAL SOC’Y, FARADAY TRANSACTIONS 3935 (1990).

surface through a diol group such that the titanium dioxide nanoparticles accumulate into a cancer tissue upon administration,” “the use of ultrasonic energy to destroy cancer tissue,” or a “bonding amount of the hydrophilic polymer per unit weight of the titanium oxide composite particles [from] 0.3 to 0.5 g/g.” Final Act. 7–8, 12–13.

The Examiner finds, however, that Gupta teaches PEG-modified superparamagnetic iron oxide nanoparticles for magnetic resonance imaging. Final Act. 8. The Examiner finds Gupta teaches that (1) biomedical applications of superparamagnetic nanoparticles require nontoxic, biocompatible surface modification that allows for targeted localization of particles; (2) PEG “has been widely used as coating material for nanoparticles”; and (3) “PEG-modified nanoparticles can interact with cell membranes resulting in enhanced cellular response.” *Id.*

The Examiner also finds that Fan teaches attaching PEGylated dopamine to a metal substrate such as a titanium dioxide nanoparticle, that Cunningham teaches adsorption of benzoic acid species such as salicylic acid on titanium dioxide nanoparticles, and that Rajh teaches “dopamine and

⁶ T. Rajh et al., *Surface Restructuring of Nanoparticles: An Efficient Route for Ligand-Metal Oxide Crosstalk*, 106 J. PHYSICAL CHEMISTRY B. 10543 (2002).

⁷ Hao Xu et al., *Room-temperature Preparation and Characterization of Poly(Ethylene Glycol)-Coated Silica Nanoparticles for Biomedical Applications*, 66 J. BIOMEDICAL MATERIALS RES. PART A 870 (2003).

⁸ Levy et al., US 2007/0217996 A1, published Sept. 20, 2007.

⁹ Andreas F. Thünemann et al., *Maghemite Nanoparticles Protectively Coated with Poly(ethylene imine and Poly(ethylene oxide))-block-poly(glutamic acid)*, 22 LANGMUIR 2351 (2006).

¹⁰ Gray et al., US Patent No. 6,167,313, published Dec. 26, 2000.

salicylic acid as suitable surface modifying bidentate ligands for titanium dioxide nanoparticles.” Final Act. 9.

The Examiner finds that, because Cunningham and Rajh teach that salicylic acid can bind to titanium dioxide nanoparticles, and Fan teaches attaching PEGylated dopamine to a metal substrate such as titanium dioxide nanoparticle, binding PEGylated salicylic acid or PEGylated 4-aminosalicylic acid to titanium dioxide nanoparticles would be obvious because it would involve only “the simple substitution of one known bidentate ligand (dopamine) for another (salicylic acid).” Final Act. 10. The Examiner further finds that “it is clear that . . . 4-aminosalicylic acid would have allowed for the PEGylation according to the chemical reaction . . . taught by Fan.” *Id.* at 11.

As to the limitation relating to “accumulating titanium oxide composite particles into a cancer tissue,” the Examiner finds that, given that “the polyethylene glycol nanoparticles are suggested by the prior art, the effect upon administration for the treatment of cancer tissue as suggested by the combination of cited references would have been the same.” Final Act. 12.

As to the limitation regarding “a bonding amount of the hydrophilic polymer per unit weight of the composite particles is 0.3 to 0.5 g/g,” the Examiner finds that Sonezaki teaches coating titanium dioxide particles to prevent agglomeration and maintain dispersion while Levy also teaches surface coating inorganic nanoparticles such as titanium dioxide and further teaches that a porous coating layer is important for “preserv[ing] the activity of the inventive particle” by “allow[ing] the passage of water (or O₂) and the radical form thereof after transformation.” Final Act. 12–13. The Examiner

finds that a skilled artisan would thus recognize “the surface coverage (i.e. the amount of hydrophilic polymer per unit weight of the titanium oxide composite)” to be a result effective variable that is routinely optimizable. *Id.* at 13.

Finally, as to the limitation in claim 9 regarding the zeta potential of the titanium dioxide particles, the Examiner asserts that, “[w]hen, as here, the prior art appears to contain the exact same ingredients and applicant’s own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.” Final Act. 12.

Appellant contends that Sonezaki does not teach

the hydrophilic polymer species poly(ethylene glycol) bound to the surface through a diol group such that the titanium particle accumulate into a cancer tissue upon administration, or the use of ultrasonic energy to destroy cancer tissue; the elected species of a salicylic acid functional group; or the bonding amount of hydrophilic polymer per unit weight of the titanium oxide composite particles of 0.3–0.5 [g/g].

Appeal Br. 17. Appellant argues that there is no reason to combine the teachings of any of the cited secondary references with the teachings of Sonezaki to arrive at the claimed invention and that Levy does not show that “the amount of [its] optional biocompatible coating relative to the amount of [its] composite, [activable] particles [as] important or a result-oriented variable to be optimized.” *Id.* at 18–25. Appellant also argues that the claimed subject matter exhibits unexpected results.

Appellant does not separately argue the claims. Accordingly, we focus our analysis on claim 1 as representative. The issue with respect to this rejection is whether a preponderance of evidence supports the

Examiner's finding that a skilled artisan would have had reason to combine the cited references to arrive at the invention of claim 1, with a reasonable expectation of success and, if so, whether Appellant has provided evidence of unexpected results that, when considered together with the evidence of obviousness, shows claim 1 to be non-obvious.

2. Findings of Fact

1. Sonezaki teaches “[s]urface-modified titanium dioxide particles which have a surface chemically modified with a hydrophilic polymer, wherein a carboxyl group of the hydrophilic polymer and titanium dioxide are bound through an ester bonding,” wherein the titanium dioxide particles have particle sizes of 2 to 200 nm and wherein the “surface-modified titanium dioxide fine particles exhibit excellent dispersibility and stability in an aqueous solvent over a wide pH region including a neutral range.” Sonezaki Abstract; *see also id.* ¶¶ 7–9, 13–14.

2. Sonezaki teaches that titanium dioxide having a high level of photoactivation degradation activity is expected to be useful as a drug delivery system for cancer treatment wherein titanium dioxide particles may be incorporated in target cancer cells and application of light such as ultraviolet light kills the cancer cells. Sonezaki ¶¶ 5–6, 9; *see also id.* ¶ 68 (example “indicating that the polyacrylic acid-bonded titanium dioxide fine particles had cytotoxic activity against cancer cells” under UV irradiation), claims 12 and 13.

3. Sonezaki teaches that “not only single titanium dioxide particles but also composite titanium dioxide particles comprising titanium dioxide and a magnetic material can be advantageously used” for purposes of its invention. Sonezaki ¶ 14; *see also id.* ¶ 25.

4. Sonezaki teaches that its “surface-modified titanium dioxide fine particles are contemplated to be used in a dispersion in an aqueous solution, and, thus, a water soluble polymer is preferred as the hydrophilic polymer used in the present invention. Any water soluble polymer may be used so far as it contains a plurality of carboxyl groups.” Sonezaki ¶ 15. Sonezaki teaches that “[e]xamples of water soluble polymers usable herein include carboxymethyl starch, carboxymethyl dextran, carboxymethylcellulose, polycarboxylic acids, and copolymers containing carboxyl units.” *Id.*

5. Sonezaki teaches an example showing the effect of polyacrylic acid concentration on dispersibility of polyacrylic acid-bonded titanium dioxide fine particles, wherein Sonezaki teaches that, under the reaction conditions of the example, the final concentration of polyacrylic acid should be not less than 0.4 mg/ml in order to achieve compositions of well-dispersed polyacrylic acid-bonded titanium dioxide fine particles. Sonezaki ¶ 48; *see also id.* ¶ 20. Sonezaki further teaches that, “[i]n order to maintain good dispersibility, the ratio of amount of carboxyl group/titanium dioxide in the surface modified titanium dioxide fine particles in the dispersion liquid (mol/g) is preferably not less than 2×10^{-3} although the ratio varies depending upon reaction conditions.” *Id.* ¶ 16; *see also id.* ¶ 62.

6. Gupta teaches that “[s]uperamagnetic iron oxide nanoparticles have been used for many years as magnetic resonance imaging (MRI) contrast agents or in drug delivery applications.” Gupta Abstract.

7. Gupta teaches that “these biomedical and bioengineering applications require that these nanoparticles have . . . size smaller than 100 nm.” Gupta 66, left column.

8. Gupta teaches that,

[b]ecause of large surface area to volume ratio, the magnetic nanoparticles tend to agglomerate and adsorb plasma proteins. The body's reticuloendothelial system (RES), mainly the kupffer cells in the liver, usually take up these nanoparticles due to the hydrophobic surface. Surface coverage by amphiphilic polymeric surfactants such as poloxamers, poloxamines and poly(ethylene glycol) (PEG) derivatives over the nanoparticles significantly increases the blood circulation time by minimizing or eliminating the protein adsorption to the nanoparticles. PEG is widely used as a coating material for nanoparticles due to the following properties: 1) easy excretion through the kidney; 2) low interfacial free energy water; 3) excluded volume effect; 4) nonimmunogenic properties; and 5) nonantigenic properties. In addition, it has been demonstrated that PEG-modified nanoparticles can interact with cell membranes resulting in enhanced cellular response.

For biomedical applications, the size, charge, and surface chemistry of the magnetic particles is particularly important and strongly affects both the blood circulation time as well as bioavailability of the particles within the body. In addition, magnetic properties and internalization of particles depend strongly on the size of the magnetic particles. For example, following systemic administration, larger particles with diameters greater than 200 nm are usually sequestered by the spleen as a result of mechanical filtration and are eventually removed by the cells of the phagocyte system, resulting in decreased blood circulation times. On the other hand, smaller particles with diameters of less than 10 nm are rapidly removed through extravasation and renal clearance. Particles ranging from *circa* 10 to 100 nm are optimal for subcutaneous injection and demonstrate the most prolonged blood circulation times. The particles in this size range are small enough both to evade RES of the body as well as penetrate the very small capillaries within the body tissues and, therefore, may offer the most effective distribution in certain tissues.

Gupta 66, right column; *see also id.* at 72, left column (stating that “PEGs at present are the most important material for tissue engineering and other

biomedical applications including RES avoidance and blood residence prolongation of nanoparticles”), *id.* at 67, right column (stating that “PEG is hydrophilic and is widely used in biological research, as it protects surfaces from interacting with cells or proteins” and thus “coated particles may result in increased blood circulation time”).

9. Gupta teaches a method of “prepar[ing] magnetic polymeric nanoparticles with magnetic core and polymeric shell,” including poly(ethyleneglycol) (PEG)-modified superparamagnetic iron oxide nanoparticles. Gupta Abstract; *see also id.* at 69, left column (explaining that “[m]agnetic nanoparticles . . . tend to agglomerate” but that “colloidal suspension of magnetite particles . . . can be stabilized by coating the particle surfaces with . . . polymers such as PEG, polyvinylalcohol (PVA), dextran, etc.”).

10. Gupta teaches an example wherein the magnetic nanoparticles are modified with maleic acid/anhydride ester of PEG as the polymerizable derivative of PEG. Gupta 67.

11. Levy teaches that

[p]hotodynamic therapy . . . is currently used to treat superficial cancers such as those of the skin or oesophagus. . . . Said treatment is based on the production of free radicals by photosensitive molecules, during exposure to strong UV rays or laser. In fact, the activated molecules convert the surrounding oxygen to free radicals which are highly reactive species producing irreversible damage in cells.

The photosensitive molecules are injected by the intravenous route and generally accumulate at higher concentration in tumor tissue. This makes it possible, after a given time, to have a higher concentration in the tissues to be treated than in healthy tissues. When said molecules are exposed to light (having a suitable wavelength), they produce

free radicals from oxygen, which then react with vital components of the cell.

...

Another approach using TiO₂ particles has shown that it was possible to generate free radicals from water and oxygen molecules under excitation by UV[.]

Levy ¶¶ 2–3, 5.

12. Levy teaches that its invention relates to novel particles that are activatable by X rays and/or UV rays to induce a targeted therapeutic or diagnostic response *in vivo*, for instance to “label, alter or destroy cells,” in “any type of tissue, superficial or deep, in any mammalian organism.” Levy ¶¶ 6–7; *see also id.* ¶¶ 8–9, 87–90, Abstract.

13. More particularly, Levy teaches “a biocompatible composite particle” that “can generate free radicals or heat when excited by X rays,” comprising “a nucleus comprising a first inorganic compound absorbing X rays and emitting UV-visible energy, and a second compound . . . absorbing UV-visible energy and producing free radicals on contact with water or oxygen,” and “optionally, a biocompatible coating.” Levy ¶¶ 10–12.

14. Levy teaches that the size of its particles is “typically comprised between approximately 4 and 250 nm,” because, “[f]or *in vivo* applications in humans or animals,” “the size of the objects must ideally be small enough to enable them to diffuse in the body . . . without being captured by macrophages . . . and without causing significant obstruction.” Levy ¶ 18.

15. Levy teaches that the second compound in its composite particle may be TiO₂ (titanium dioxide). Levy ¶¶ 29–30.

16. Levy teaches that the optional coating may “preserve[] the integrity of the particles *in vivo*, ensure[] or improve[] the biocompatibility thereof, and facilitate[] the functionalization thereof (for example with

spacers molecules, biocompatible polymers, targeting agents, proteins, etc.)”

Levy ¶ 48.

17. Levy teaches that,

[i]n order to preserve the activity of the inventive particles, it is desirable that the coating allow the diffusion of small molecules and free radicals. In particular, it is important that the coating allow the passage of water (or O₂) and the radical form thereof after transformation. This can be accomplished by using materials which are porous and/or a coating layer which has low thickness and is porous. Thus for example, typically a coating is employed which has a porosity comprised between 0.2 and 10 nm. In addition, the coating has a thickness generally comprised between approximately 0.1 and 50 nm, for example between 0.2 and 40 nm.

Levy ¶ 49.

18. Levy teaches that the coating for its particles “preferably comprises one or more compounds selected in the group consisting of silica (SiO₂), alumina, polyethylene glycol (PEG) or dextran, optionally in mixture(s)” and that the coating can also contain functional groups or linkers to allow molecules of interest to bind to the surface of the particle, such as molecules that improve biocompatibility or that enable the particle to escape the immune system by, e.g., avoiding interactions with macrophages and SRE. Levy ¶¶ 51–52, 54, 56–57.

19. Levy teaches using its particles to treat cancer. Levy ¶¶ 91–95.

20. The Specification discloses that preferred examples of nonionic hydrophilic polymer for use in its invention include PEG, polyvinyl alcohol, polyethylene oxide, dextran, and copolymers thereof. Spec. ¶ 28.

21. The Specification teaches a preferred embodiment wherein PEG is the hydrophilic polymer and carboxyl group is the functional group through which PEG is bound to the titanium oxide particles. Spec. ¶ 29.

22. The Specification teaches that “a copolymer of a carboxylic acid or amine and a hydrophilic polymer can be used as the functional group-modified nonionic hydrophilic polymer.” Spec. ¶ 30. The Specification teaches that “[p]referred examples of such copolymers include maleic acid-polyethylene glycol [(MA-PEG)] copolymers.” *Id.* The Specification further teaches that in another preferred embodiment the functional group may be provided by a polycarboxylic acid or a polyamine as the linker and that preferred examples of the polycarboxylic acids include polyacrylic acids. *Id.* ¶ 31.

23. The Specification teaches:

In a preferred embodiment of the present invention, the number of moles of the carboxyl or amino group per unit weight of the titanium oxide composite is 1×10^{-9} to 1×10^{-4} mol/g, more preferably 1×10^{-9} to 1×10^{-6} mol/g. Within this range, the retention in blood and accumulation of the titanium oxide composite particles in cancer cells can be improved while satisfactorily developing the catalytic activity of the titanium oxide composite particles.

In a preferred embodiment of the present invention, the bonding amount of the hydrophilic polymer per unit weight of the titanium oxide composite particles is 0.3 to 1.0 g/g, more preferably 0.3 to 0.5 g/g from the viewpoint of dispersibility. Within this range, the retention in blood and accumulation of the titanium oxide composite particles into cancer cells can be improved while satisfactorily developing the catalytic activity of the titanium oxide composite particles.

Spec. ¶¶ 44–45.

3. Analysis

We agree with the Examiner that claim 1 is obvious over the cited prior art. In particular, Sonezaki teaches titanium dioxide (i.e., titanium oxide) composite particles comprising titanium dioxide particles surface-

modified by a hydrophilic polymer bound to the particles through a carboxyl group, wherein the particles have a particle sizes of 2 to 200 nm. FF1, FF3, FF4. Because the range of particle size disclosed in Sonezaki encompasses and substantially overlaps the claimed range of 20 to 200 nm, the particle size limitation of claim 1 is *prima facie* obvious. *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003) (explaining that “[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art” and that “when . . . the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap”).

With respect to use of a “nonionic” hydrophilic polymer, Sonezaki teaches that any water soluble polymer, including copolymers, may be used so far as it contains a plurality of carboxyl groups. FF4. Sonezaki also teaches that examples of water soluble polymers useful for its invention include, e.g., carboxymethyl dextran. *Id.*

As acknowledged in the Specification, dextran is a nonionic hydrophilic polymer. FF20. While the carboxymethyl group in carboxymethyl dextran may be anionic, the Specification teaches that, for purposes of the invention, “a copolymer of a carboxylic acid . . . and a hydrophilic polymer can be used as the functional group-modified nonionic hydrophilic polymer.” FF22. Thus, under the broadest reasonable interpretation of claim 1, modifying the surface of titanium dioxide nanoparticles with carboxymethyl dextran, wherein the carboxyl group of the carboxymethyl dextran is bound to the nanoparticles through an ester bonding, as taught in Sonezaki, meets the limitations in claim 1 regarding binding a nonionic hydrophilic polymer (i.e., dextran) to a surface of

titanium oxide particles through a carboxyl functional group (i.e., the carboxymethyl group).

With respect to the limitation of “administrating the composite particles to a patient,” we find that the limitation is rendered obvious by Sonezaki’s teaching that its particles may be administered to treat cancer. FF2. Finally, we agree with the Examiner that the claim preamble and “thereby” clause, regarding accumulating titanium dioxide particles in cancer tissue, merely state the result of the structural limitations of claim 1 and thus do not patentably distinguish claim 1 over the cited art. *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997) (explaining that, “where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation”); cf. *Minton v. National Ass’n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (explaining that “[a] whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited”).

At the very least, the Examiner has presented factual findings sufficient to indicate that the claimed method and the method suggested by the prior art are identical or substantially identical; thus, we find it appropriate to shift the burden to Appellant to show that the method suggested by the prior art would not necessarily or inherently result in accumulating of titanium oxide particles in cancer tissue. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Appellant has not satisfied this burden.

In short, Sonezaki teaches all of the limitations of claim 1 except it does not explicitly teach “a bonding amount of the hydrophilic polymer per unit weight of the composite particles [of] 0.3 to 0.5 g/g.” We further find

that this limitation is also obvious in light of the combination of Sonezaki and Levy.

In particular, Sonezaki suggests that the amount of polymer used to modify the surface of the composite titanium dioxide nanoparticle and the ratio of the amount of the binding functional group in the polymer to titanium dioxide are relevant to the maintenance of good dispersibility. FF5. Levy suggests that, in order to preserve the photocatalytic activity of its particles, the surface modification of the particles must be sufficiently porous to allow “passage of water (or O₂) and the radical form thereof.” FF17.

Based on the above, we agree with the Examiner that the weight ratio of the hydrophilic polymer and composite particles is a known result effective variable—namely a variable known to affect dispersibility and photocatalytic activity of nanoparticles—that can be routinely optimized by a skilled artisan. As the predecessor to our reviewing court has explained, “discovery of an optimum value of a variable in a known process is normally obvious,” unless the results of optimizing a variable were unexpectedly good or the parameter optimized was not recognized in the prior art as one that would affect the results. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). As discussed further below, Appellant has not persuasively shown that the claimed weight ratio of the bonding amount of hydrophilic polymer per unit weight of composite particles exhibits unexpected results that, when considered with the entirety of the record, outweigh the evidence of obviousness. Accordingly, this limitation also does not render claim 1 patentable.

We next address Appellant’s arguments. Only those arguments timely made by Appellant in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Appeal Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *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.”).

Appellant first contends that

Sonezaki’s disclosure specifically relates to surface-modified titanium dioxide particles which have a surface thereof chemically modified with a hydrophilic polymer *having a carboxyl group*, whereas claim 1 does not encompass such a hydrophilic polymer, but instead is limited to a nonionic hydrophilic polymer bound to a surface of the titanium oxide particles *through at least one functional group selected from the group consisting of a diol group and a salicylic acid group*.

Appeal Br. 17. Appellant similarly contends that Sonezaki does not teach PEG “bound to the surface through a diol group” and does not teach “the elected species of a salicylic acid functional group.” *Id.*

As the Examiner points out, claim 1 “expressly recites ‘ . . . nonionic hydrophilic polymer bound to a surface of the titanium oxide particles through at least one functional group selected from **carboxyl group**, amino group, diol group, salicylic acid group, and phosphoric acid group, [. . .]’”¹¹
Ans. 7. Thus, we are not persuaded by Appellant’s argument that claim 1

¹¹ Although Appellant refers to “the elected species of a salicylic acid functional group,” Appellant does not cite to any record that an election was made, and we have been unable to locate such evidence in the record. Thus, for purposes of this opinion, we treat the scope of claim 1 as coextensive with the language of the claim as recited in the Claims Appendix.

does not encompass a hydrophilic polymer having a carboxyl group or the argument that claim 1 is patentable because Sonezaki does not teach hydrophilic group bound to the surface of titanium oxide particles through a diol group or a salicylic acid group.

As to Appellant's argument that Sonezaki does not teach PEG as the hydrophilic polymer bound to the surface of the titanium oxide particles, we first note that claim 1 is not limited to PEG. Moreover, we agree with the Examiner that the combination of cited prior art would have rendered the use of PEG obvious.

In particular, Gupta, which also relates to biomedical applications of nanoparticles, teaches that PEG is widely used as a coating material for such nanoparticles and that such coating, among other things, can be useful to reduce agglomeration. FF8, FF9. Gupta also teaches modifying the surface of nanoparticles using PEG derivatives such as MA (maleic anhydride)-PEG, which comprises a carboxyl group. FF10. Likewise, Levy, which like Sonezaki teaches composite nanoparticles comprising titanium dioxide that are useful in treating cancer when activated by X-rays and/or UV rays, teaches coating the nanoparticles with PEG polymer. FF12–FF16, FF18, FF19.

Given the above, a skilled artisan would have had reason to modify the surface of Sonezaki's titanium dioxide nanoparticles using a copolymer of PEG containing carboxylic groups, such as a copolymer of PEG and maleic acid, with a reasonable expectation of success at arriving at the claimed nanoparticles: Sonezaki suggests that hydrophilic (co)polymers comprising carboxyl groups would be useful in its compositions; Gupta and Levy suggest PEG may be advantageously used to modify the surface of

nanoparticles for biomedical applications; and Gupta shows that derivatizing PEG with a carboxyl group is known in the art. As already discussed above, based on the Specification, the broadest reasonable interpretation of “a nonionic hydrophilic polymer bound to a surface . . . through . . . carboxyl group” encompasses modifying the surface of titanium oxide particles using copolymers such as MA-PEG. FF22.

Appellant concedes that Gupta “references surface modification of . . . nanoparticles using maleic acid PEG polymer, which is discussed in the present specification.” Appeal Br. 18. However, Appellant contends that Gupta teaches superparamagnetic nanoparticles and not titanium oxide particles as claimed and further contends that the Examiner has not explained why a skilled artisan “would have been motivated to modify Sonezaki’s disclosure based on [Gupta’s] teachings relative to his superparamagnetic nanoparticles or how this would lead to the claimed invention.” *Id.*

We are not persuaded. Gupta does not limit its teaching regarding PEG to superparamagnetic nanoparticles. Rather, it teaches that PEG is widely used as a coating material for nanoparticles generally. FF8. Furthermore, one of the problems that Gupta discusses as being solved by surface coverage by PEG – i.e., agglomeration of the nanoparticles – is a problem recognized in Sonezaki with respect to the titanium dioxide nanoparticles. *See, e.g.*, Sonezaki ¶ 6 and FF2. Sonezaki also teaches that any water soluble polymer may be used for purposes of its invention so long as it contains carboxyl groups, and Gupta teaches a water soluble polymer (i.e., PEG) derivatized with a carboxyl group. FF4, FF10. Thus, a skilled artisan would be motivated to use PEG derivatized with carboxyl groups as

the surface-modifying hydrophilic monomer for Sonezaki's titanium dioxide particles both because Sonezaki teaches that it would be useful for that purpose and because Gupta teaches that PEG in fact accomplishes the goal described in Sonezaki, i.e., dispersion of the nanoparticles.

Neither are we persuaded by Appellant's apparent argument that the Examiner's reliance on Gupta is based on improper hindsight. Appeal Br. 18 (alleging that "[t]he Examiner apparently located [Gupta] only because it references surface modification . . . using maleic acid PEG copolymer, which is discussed in the present specification"). As the predecessor of our reviewing court has explained,

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 and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (CCPA 1971). For the reasons discussed above, we find that the Examiner's case for obviousness does not include knowledge gleaned only from Appellant's disclosure.

Appellant next contends that Sonezaki does not "remotely suggest a method for accumulating titanium oxide composite particles into a cancer tissue [and] irradiating the accumulated particles with ultrasonic or ultraviolet irradiation to render the particles cytotoxic for targeted killing of the cancer cells." Appeal Br. 17–18. First, we note that claim 1 does not require a method step involving the use of ultrasonic or ultraviolet irradiation. As to claim 1 and the requirement that the functionalized titanium particles "are accumulated in the cancer tissue," we note that such accumulation appears to be a result naturally flowing from the positively

recited step of simply administering the functionalized titanium oxide particle. Absent Appellant's presentation of evidence to the contrary, given Sonezaki's teaching of functionalized titanium oxide composite particles such that the particles do not agglomerate at near neutral pH and Sonezaki's teaching that incorporating such titanium dioxide particles into cancer cells may be useful for cancer treatment, FF1 and FF2, we conclude that Sonezaki's particles when administered for such a cancer treatment would accumulate in the cancer tissue to the same extent claimed.

Appellant further contends that Sonezaki does not suggest "the critical . . . amount of hydrophilic polymer per unit weight of the titanium oxide composite particles of 0.3 - 0.5 [g/g]." Appeal Br. 18. Appellant contends that Levy also does not support that this limitation is obvious, because

Levy does not establish that the amount of his optional biocompatible coating relative to the amount of his composite, activatable particles is important or a result-oriented variable to be optimized. Rather, Levy merely indicates that if an optional coating is used, it may be amorphous or crystalline, and should be porous because this useful in relation to the specific reactions being performed by the different materials in the nucleus of his activatable particles. Porosity of a coating does not *per se* limit the amount material being used.

Based on **Levy's** actual disclosure, persons of ordinary skill in that art would not understand that the amount of hydrophilic polymer *having a carboxyl group* in **Sonezaki's** composite titanium oxide particles is a result oriented variable to be optimized, nor would it be possible to arrive at the claimed critical range based on the general and broad teachings of **Levy**.

Id. at 21–22; *see also id.* at 24–25.

We are not persuaded. Both Sonezaki and Levy teach that the amount of coating on titanium dioxide nanoparticles is relevant to important

functional characteristics of the particles. Sonezaki teaches that the ratio of the amount of carboxyl group to titanium dioxide – which is related to the ratio of the amount of surface-modifying hydrophilic polymer to the particles because carboxyl group is the functional group binding the polymer to the particle – is relevant to maintenance of good dispersibility of the particles. Levy teaches that the thickness and porosity of the coating – which is affected by the type and amount of coating polymer used – are important variables for “preserv[ing] the activity of [its] inventive particles,” i.e., its ability to be activated by X rays or UV rays so as to label, alter, or destroy cells. FF12, FF17. Since Sonezaki also suggests using its titanium dioxide particles in conjunction with UV light to destroy cancer cells, FF2, a skilled artisan would understand that the relative amounts of surface-modifying hydrophilic polymer to titanium composite particles is a factor that affects both dispersibility and photocatalytic ability of the particles. While neither Sonezaki nor Levy specifically discusses the “bonding amount of the hydrophilic polymer per unit weight of the composite particles,” the factors taught by Sonezaki and Levy as affecting dispersibility and photocatalytic ability of titanium dioxide particles are sufficiently similar to the metric recited in claim 1 such that we find the Examiner to have established that the limitation at issue is a known result effective variable that would have been routinely optimized by a skilled artisan.

Appellant contends that the other cited references, Rajh, Cunningham, Fan, and Xu do not remedy the deficiencies in the rejection because a skilled artisan would not have had reason to combine the teachings of these references to arrive at the claimed invention. Appeal Br. 19–21. We are not persuaded. The Examiner cites Rajh, Cunningham, and Fan for the

proposition that it would have been obvious to a skilled artisan to use a salicylic acid, such as 4-aminosalicylic acid, as the functional group binding a nonionic hydrophilic polymer such as PEG to titanium oxide nanoparticles. Final Act. 9–11. However, claim 1 is not limited to binding the nonionic hydrophilic polymer to the nanoparticle using a salicylic acid functional group.¹² *See generally In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (the Board may rely on less than all of the references relied upon by Examiner).

Finally, citing to the Examples in the Specification, particularly Example 25, and the Kanehira declarations,¹³ Appellant contends that the claimed subject matter exhibits unexpected results. Appeal Br. 16–17; *see also id.* at 22 (arguing that “the claimed range is critical and is not ma[d]e obvious by the general and broad teachings of **Levy**”), 25–28. Appellant contends that the proffered evidence

show that the titanium oxide composite particles which fall within the scope of claim 1 have not only an unexpectedly good dispersibility, but also an unexpectedly high photocatalytic activity, in comparison to particles which fall just outside the range of claim 1, and whereby the claimed particles *provide an unexpected and synergistic effect* when used as a (cancer) cell killer or as an ultrasonic cancer treatment enhancer, e.g., not only do the composite particles have unexpectedly good dispersibility such that they accumulate near cancer cells, but the claimed composite particles also achieve an unexpectedly very high decomposition rate of the cancer cells.

¹² The Examiner cites Xu only in support of the finding that the claimed subject matter does not exhibit unexpected results, which is further discussed below.

¹³ Declaration of Koki Kanehira under 37 C.F.R. § 1.132 (Apr. 5, 2011) (“First Kanehira Declaration”); Declaration of Koki Kanehira under 37 C.F.R. § 1.132 (Dec. 20, 2011) (“Second Kanehira Declaration”).

Id. at 27.

We are not persuaded. As an initial matter, Example 25 merely describes a method of introducing 4-aminosalicylic acid-bound polyethylene glycol into titanium dioxide particles. Thus, Example 25 by itself does not suggest any unexpected results.¹⁴

We next turn to the declarations. The Second Kanehira Declaration purports to show that dispersions of titanium dioxide particles surface modified by 4-aminosalicylic acid-PEG polymer and having a “[p]olymer bonding amount per unit titanium amount (g/g)” of 0.466 and 0.521, respectively, had a methylene blue decomposition rate of 90% and less than 15%. Second Kanehira Decl. ¶ 3. The First Kanehira Declaration purports to show that dispersions of titanium dioxide particles surface modified by 4-aminosalicylic acid-PEG polymer and having a “[p]olymer bonding amount per unit titanium amount (g/g)” of 0.32 and 0.23, respectively, had a dispersed particle diameter of ~ 50 nm and over 200 nm after about two weeks. First Kanehira Decl. ¶ 3.

We are not persuaded. As an initial matter, the declarations do not state that the results described therein are *unexpected*, nor does the Specification identify a result as being *unexpected*. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (“[B]y definition, any superior

¹⁴ Appellant states that the results of the Kanehira Declarations “go beyond” the various desirable characteristics shown in Examples 4, 9, 11, 24, 27, and 30. Appeal Br. 27. To the extent Appellant is suggesting that examples 4, 9, 11, 24, 17, and 30 also show that the claimed subject matter exhibits unexpected results, we are unpersuaded because Appellant has not provided any evidence (or even any argument) that the characteristics in question are unexpected.

property must be *unexpected* to be considered evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the [fact-finder] should have considered what properties were expected. Here, Pfizer’s evidence must fail because the record is devoid of *any* evidence of what the skilled artisan would have expected.” (citations omitted). *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (explaining that “when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary”).

While Appellant argues in the Appeal Brief that the results shown in the Kanehira declarations are unexpected, attorney arguments are not substitute for evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Moreover, the results described in the declarations are consistent with the teachings of Sonezaki, which suggests that a certain amount of surface-modifying polymer is required to maintain good dispersibility of the titanium dioxide particles, and the teachings of Levy, which suggests that too much surface coating would negatively affect the activity of photocatalytic nanoparticles. FF5, FF17.

We also agree with the Examiner that Appellant has not provided evidence of unexpected results commensurate with the scope of the claim. *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972) (“It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims.”) “[C]ommensurate in scope” means that the evidence provides a reasonable basis for concluding that the untested embodiments encompassed by the claims would behave in the same manner as the tested embodiment(s). *Id.* In this case, the Kanehira declarations contain results

only regarding titanium dioxide nanoparticles surface modified by 4-aminosalicylic acid-bound PEG, while claim 1 encompasses titanium oxide composite particles wherein any nonionic hydrophilic polymer is bound to the surface of the titanium oxide particles through functional groups selected from carboxyl, amino, diol, and phosphoric acid groups as well as salicylic acid group.

Appellant contends that “[t]he present claims are sufficiently commensurate with the [Second Kanehira Declaration]” because the claimed inventions are “consistent with the composite particles discussed in the Declaration” and the “claims are limited in line with the Declaration . . . and Example 25 of the specification.” Appeal Br. 25–26. We are not persuaded because the Appellant has not explained why there is a reasonable and evidence-backed basis for concluding that all of the surface-modified titanium oxide composite particles encompassed in claim 1 would behave in the same way as the 4-aminosalicylic acid-bound PEG-modified particles tested in the Kanehira declarations.

Finally, we note that “when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). We are further unpersuaded by Appellant’s assertion of unexpected results because Appellant has not compared the photocatalytic activity and dispersibility of the claimed titanium oxide particles to the particles taught by Sonezaki.

Accordingly, we affirm the Examiner’s rejection of claim 1 as obvious over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy. Claims 5, 7–9, and 11–14, which are not separately argued, fall with claim 1.

B. Obviousness rejection over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, and Thünemann (Claims 6 and 9)

1. Issue

Claims 6 and 9 depend from claim 1 and further recite, respectively, that “the functional group is provided by a polyamine as a linker” and that “the composite particles have a zeta potential of -20 to +20 mV.” Appeal Br. 34 (Claims App.). We note that the Examiner also rejected claim 9 under Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy discussed in section A above. As noted above, Appellant does not make a proper separate argument of claim 9 in the obviousness rejection over that combination of references. Because we affirm the Examiner’s rejection of claim 9 above over the combination of Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy, we limit our consideration of this rejection to claim 6.¹⁵

¹⁵ Although Appellant does not make a proper separate argument of claim 9 in the obviousness rejection over the combination of Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy, Appellant contends here that “[t]he Examiner does not explain why persons of ordinary skill in the art would have been motivated to modify **Sonezaki’s** disclosure based on . . . **Thunemann’s** teachings . . . or how this would lead . . . to the method of claim 9 which requires the composite particles to have a zeta potential in a range of -20 to +20 mV.” Appeal Br. 30. For the sake of completeness, we note that we are unpersuaded by Appellant’s argument in this regard. As the Examiner points out, “[w]here . . . the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . [The] fairness [of the burden-shifting] is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products.” *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977); Final Act. 12. We find that the Examiner has shown that the combination of prior art suggests a titanium oxide composite particle substantially as recited in claim 1. Accordingly, the burden is properly

The Examiner relies on Thünemann for teaching the additional limitation in claim 6 that the functional group is provided by a polyamine as a linker. The Examiner finds that Thünemann teaches “superparamagnetic nanoparticles of iron oxide surface stabilized with polyethylene imine (PEI) and subsequently with poly(ethylene oxide)-block-poly(glutamic acid) (PEO-PGA) to modify the surface of the inorganic nanoparticles” and discusses “various reasons for modification of the surface of the inorganic nanoparticles including to stabilize the nanoparticles in biological surroundings with a pH of about 7.4.” Final Act. 16.

The Examiner concludes that it would have been prima facie obvious to a skilled artisan to produce a PEI-coated inorganic nanoparticle with a linked POE-PGA layer, as suggested by Thünemann, “in order to stabilize the nanoparticles in biological surroundings with a pH of about 7.4.” Final Act. 17. The Examiner finds that this would require no more than “[t]he selection of a known material base[d] upon its suitability for its intended use” and that a skilled artisan would have a reasonable expectation of success in producing the claimed invention because, based on the prior art,

it would have required no more than an ordinary level of skill in the art pertaining to nanoparticle preparation to produce the PEI/POE-PGA surface-coated titanium dioxide nanoparticles, and no more than an ordinary level of skill in the art pertaining to nanoparticle drug delivery to administer the compositions to a patient in need thereof.

Id.

shifted to Appellant to show that the prior art particle does not have a zeta potential of -20 to +20 mV. Appellant has not attempted to make a persuasive showing to this effect.

Appellant argues that Thünemann “fails to overcome the deficiencies of the combination of references applied against claim 1 as discussed above” and further argues that it “fails to make obvious the additional features required by claim[] 6.” Appeal Br. 29. Appellant contends that

[t]he Examiner does not explain why persons of ordinary skill in the art would have been motivated to modify Sonezaki’s disclosure based on the Th[ü]nemann’s teachings relative to his superparamagnetic nanoparticles, which are indisputably different from Sonezaki’s surface-modified titanium oxide particles, or how this would lead to the invention of claim 1 including its requirements discussed above, or to the method of claim 6 more specifically involving a functional group provided by a polyamine as a linker for bonding a nonionic hydrophilic polymer to the surface of titanium oxide particles

Id. at 30 (bolding omitted).

The issue with respect to this rejection is whether a preponderance of evidence supports the Examiner’s finding that a skilled artisan would have had reason to combine the cited references to arrive at the invention of claim 6, with a reasonable expectation of success.

2. Findings of Fact

24. Thünemann teaches that “[s]tability of . . . nanoparticles during long-term storage is an important factor for potential medical applications” and that

[t]ailored surfaces play a key role in the future development of advanced superparamagnetic nanoparticle systems for biomedical applications. Such surfaces should (i) stabilize the nanoparticles in biological surroundings with a pH of about 7.4, particularly at physiological salt concentration, (ii) provide functional groups at the surface for further derivatization (e.g., with receptor ligands for cell specific uptake), and (iii) suppress the uptake by the reticuloendothelial system.

Thünemann 2351, right column, 2354, left column.

25. Thünemann teaches that “one of the most attractive [methods of stabilization for superparamagnetic iron oxide particles (SPIOs)] is their stabilization in the presence of biocompatible polymers.” Thünemann 2351, right column.

26. Thünemann teaches “[s]uperparamagnetic iron oxide particles (SPIO) . . . stabilized with polymers in two layer-by-layer deposition steps,” wherein the first layer around the core is formed by poly(ethylene imine) (PEI) and the second layer is formed by poly(ethylene oxide)-block-poly(glutamic acid) (PEO-PGA). Thünemann Abstract; *see also id.* at Fig. 1. PEO is also referred to as PEG. *Id.* at 2351, right column (explaining that “coating of particles with poly(ethylene oxide)s to avoid their uptake by the reticuloendothelial system is . . . often referred to as PEGylation”).

27. Thünemann teaches that the cationic PEO adsorbs to the positively charged SPIO surface, while the anionic PEO–PGA adsorbs to the cationic PEI on the surface. Thünemann 2353, right column. Thünemann teaches that, accordingly, “[t]he final particles . . . are stabilized sterically by PEO chains which are covalently [bond] to the PGA, acting like ‘glue.’” *Id.*

28. Thünemann teaches that “[a] crucial point in [its] studies was whether the steric stabilization is strong enough to prevent precipitation of the particles in solutions of high salt concentration such as physiological sodium chloride solution (0.15M)” and teaches that its particles were “stable in water and in physiological salt solution for longer than 6 months.” Thünemann Abstract, 2353, right column, 2354, bridging paragraph.

29. Thünemann teaches that its particles are useful as an MRI contrast agent. Thünemann Abstract, 2353, right column, 2354, bridging paragraph.

30. The Specification discloses preferred examples of polyamines that include polyethyleneimines. Spec. ¶ 31.

31. The Specification discloses that, for purposes of the invention, the form of the bonding “may be on such a level that can ensure dispersibility 24 to 72 hr after administration into the body from the viewpoint of ensuring retention in blood” but is “preferably a covalent bond because of its excellent dispersion stability under physiological conditions and freedom from polymer liberation and so significant damage to normal cells upon ultrasonic irradiation or ultraviolet irradiation.” Spec. ¶ 19.

3. Analysis

On balance, we find that Appellant has the better argument as to claim 6.

As discussed above, the Examiner asserts Thünemann teaches that a PEI coating linked to a POE-PGA layer stabilizes nanoparticles in biological surroundings with a pH of about 7.4. Final Act. 17. The Examiner asserts that “produc[ing] the PEI/POE-PGA surface-coated titanium dioxide nanoparticles” thus requires no more than “selection of a known material base[d] upon its suitability for its intended use” and “an ordinary level of skill in the art.” *Id.*

As Appellant points out, however, Thünemann teaches applying PEI/POE-PGA polymer coatings to superparamagnetic iron oxide particles rather than titanium dioxide particles. FF26, FF27. The Examiner has not sufficiently articulated a reason why a skilled artisan would consider

titanium dioxide particles and iron oxide particles to be sufficiently similar such that a coating suitable for stabilizing iron oxide particles would also be considered suitable for stabilizing titanium dioxide nanoparticles. For instance, it appears that PEI and POE-PGA polymers coat the iron oxide particles through adsorption, whereas Sonezaki teaches surface modification of the titanium oxide particles through formation of an ester bond. FF1, FF27. “[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

In response to Appellant’s argument that a skilled artisan would not have reason to modify Sonezaki’s titanium dioxide particles based on Thünemann’s teaching that superparamagnetic nanoparticles may be stabilized by a first PEI polymer layer and a second POE-PGA polymer layer, the Examiner asserts that the rejection is not based on Sonezaki and Thünemann alone. Ans. 18. The Examiner asserts that Gupta and Levy show that PEG is “a suitable coating species” for photocatalytic nanoparticles and that it would have been obvious to a skilled artisan to produce a PEI-coated inorganic nanoparticle with a linked POE-PGA layer, as suggested by Thünemann, in order to stabilize the nanoparticles in biological surroundings with a pH of about 7.4. *Id.* Once again, the Examiner asserts that this would be no more than “[t]he selection of a known material base[d] upon its suitability for its intended use.” *Id.*

We are not persuaded for the reasons already discussed. As discussed above, we agree that a skilled artisan would have found it obvious to use

PEG as a hydrophilic polymer for modifying the surface of a titanium dioxide nanoparticle. However, claim 6 does not require the use of PEG as the hydrophilic polymer; rather, it requires that the nonionic hydrophilic polymer such as PEG be bound through a functional group wherein the functional group is provided by a polyamine (e.g., PEI) as a linker. The Examiner has not sufficiently articulated a rationale as to why a skilled artisan would find it obvious to use PEI as a linker between the titanium dioxide nanoparticle taught by Sonezaki and PEG based on Thünemann's teaching of an inner PEI coating layer for iron oxide nanoparticles, even in view of Gupta and Levy's teaching that suggest PEG may be useful as a surface coating polymer for titanium dioxide particles.¹⁶ *KSR*, 550 U.S. at 418.

C. Obviousness rejection over Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, Kubo, and Gray (Claims 11, 14, and 15)

Claims 11 and 14 depend directly from claim 1 and further recite, respectively, that “the composite particles are rendered cytotoxic upon ultrasonic or ultraviolet irradiation” and “[a] step of irradiating the cancer tissue in which the composite particles are accumulated with ultrasonic or ultraviolet.” Appeal Br. 34, 35 (Claims App.). Claim 15 depends from

¹⁶ We note that Sonezaki teaches that composite particles comprising both titanium dioxide and a magnetic material may be used for its invention. FF3. However, the Examiner has not suggested that a skilled artisan would consider coatings for superparamagnetic iron oxide particles to be functionally equivalent to coatings for composite titanium dioxide particles comprising both titanium dioxide and a magnetic material such that it would be obvious to use the coatings taught by Thünemann for such composite titanium dioxide particles. Because the Examiner made no findings on this issue, we decline to make such findings in the first instance.

claim 14 and further recites that “a frequency of the ultrasonic is from 400 kHz to 20 MHz.” *Id.* at 35 (Claims App.).

We note that the Examiner also rejected claims 11 and 14 under Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy discussed in section A above. As noted above, Appellant does not make a proper separate argument of claims 11 and 14 in the obviousness rejection over that combination of references. Those claims recite the use of “ultrasonic *or* ultraviolet irradiation” (emphasis added) to render the composite particles cytotoxic (claim 11), or in the irradiation of the cancer tissue in which the particles are accumulated (claim 14). We have already affirmed the Examiner’s rejection of claims 11 and 14 over the combination of Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy, noting in particular Sonezaki’s teaching of using ultraviolet irradiation of the particles in cancer treatment.¹⁷

With respect to claim 15, which is directed to the ultrasonic irradiation alternative of claim 14, we note that Sonezaki teaches activation of surface-

¹⁷ Although Appellant does not make a proper separate argument of claims 11 and 14 in the obviousness rejection over the combination of Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, and Levy, Appellant does contend in passing that Sonezaki does not suggest a method for “irradiating [titanium oxide composite particles] accumulated [in a cancer tissue] with ultrasonic or ultraviolet irradiation to render the particles cytotoxic for targeted killing of the cancer cells.” Appeal Br. 17–18. For the sake of completeness, we note that we are unpersuaded by Appellant’s argument in this regard. In particular, Sonezaki teaches that “titanium dioxide having a high level of photoactivation degradation activity is expected to be useful as a drug delivery system for cancer treatment wherein titanium dioxide particles may be incorporated in target cancer cells and application of light such as ultraviolet light kills the cancer cells.” FF2.

modified titanium dioxide fine particles for destruction of cancer tissues, teaches that photocatalytic activity-derived redox action of activity of surface-modified titanium dioxide fine particles “can realize degradation of various organic matter,” and also teaches that such activity is induced by “application of ultraviolet light, sunlight or the like.” FF2. The Examiner relied on Kubo for teaching that “the application of light energy has been used with titanium dioxide nanoparticles to stimulate hydroxyl radicals which give a disinfection effect, and ultrasonic irradiation i[s] considered to be an alternative energy source for TiO₂ particles to replace the light.” Final Act. 19.

Appellant concedes that Kubo and Gray disclose that ultrasonic irradiation is effective for activating titanium oxide particles, but contends that “these references fail[] to overcome the deficiencies of the combination of references applied against claim 1 as discussed above.” Appeal Br. 31. Because we find that the combination of references cited against claim 1 renders claim 1 obvious, we also affirm the Examiner’s rejection of claim 15 over the combination of Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, Kubo, and Gray.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–5, 7–9, 11–14	103(a)	Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy	1–5, 7–9, 11–14	

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
6, 9	103(a)	Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, Thünemann	9	6
11, 14, 15	103(a)	Sonezaki, Gupta, Fan, Cunningham, Rajh, Xu, Levy, Kubo, Gray	11, 14, 15	
Overall Outcome			1-5, 7-9, 11-15	6

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED-IN-PART