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Patent Manager
Emory University - Office of Tech Transfer
1599 Clifton Road NE, 4th Floor
1599-001-1AZ
Atlanta, GA 30322

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte XIMEI QIAN, DOMINIC ANSARI, and SHUMING NIE¹

Appeal 2014-009736
Application 13/680,524
Technology Center 1600

Before FRANCISCO C. PRATS, RICHARD J. SMITH and
TAWEN CHANG, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to a composite nanostructure which is detectable using surface-enhanced Raman spectroscopy, and which is useful for *in vivo* molecular imaging. The Examiner rejected the claims for obviousness and obviousness-type double patenting.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

¹ Appellants identify Emory University as the real party in interest. App. Br. 3.

STATEMENT OF THE CASE

The following rejections are before us for review:

(1) Claims 1–20, under 35 U.S.C. § 103(a), for obviousness over Nie,² Sokolov,³ and Loo⁴ (Ans. 3–9; Final Action 4; Non-Final Act. 2–8); and

(2) Claims 1–20, on the ground of nonstatutory obviousness-type double patenting over claims 1–5, 10–14, and 21–24 of U.S. Patent No. 7,588,827 B1, in view of Sokolov and Loo (Ans. 9–10; Final Action 9; Non-Final Act. 8–9).

Claims 1 and 11 are the appealed independent claims, and read as follows (App. Br. 29 and 30):

1. A surface-enhanced Raman spectroscopic active composite nanostructure comprising:
a core metallic nanoparticle;
a Raman reporter molecule disposed on the surface of the core; and
an encapsulating protective layer disposed on the surface of the core and the reporter molecule, wherein the encapsulating protective layer is a thiopolyethylene glycol, and wherein the encapsulated reporter molecule has a measurable surface-enhanced Raman spectroscopic signature.

11. A surface-enhanced Raman spectroscopic active composite nanostructure comprising:
a core metallic nanoparticle;
a Raman reporter molecule without an isothiocyanate group disposed on the surface of the core; and
an encapsulating protective layer disposed on the surface of the core and the reporter molecule, wherein the encapsulating

² WO 2005/062741 A2 (published July 14, 2005)

³ US 2004/0023415 A1 (published Feb. 5, 2004).

⁴ Christopher Loo et al., *Gold nanoshell bioconjugates for molecular imaging in living cells*, 30 OPTICS LETTERS 1012–14 (2005).

protective layer is a thiolpolyethylene glycol, and wherein the encapsulated reporter molecule has a measurable surface-enhanced Raman spectroscopic signature.

OBVIOUSNESS

The Examiner's Position

The Examiner cited Nie as describing a surface-enhanced Raman spectroscopic (“SERS”) active composite nanostructure composed of a core, a reporter molecule bound to the core, and an encapsulating material. Ans. 3–4. The Examiner noted Nie’s disclosure of using, as its reporter molecule, a number of dyes encompassed by the rejected claims. *Id.* at 4–5. The Examiner noted Nie’s disclosure of using a variety of different encapsulating agents, including silica, as well as its disclosure of attaching probe molecules, such as polypeptides or nucleic acids, to its composite nanostructures. *Id.* at 5.

The Examiner noted in particular Nie’s example of preparing a SERS composite nanostructure by first attaching a Raman reporter dye to gold nanoparticles, and then attaching a coupling agent (3-mercaptopropyl trimethoxy silane, also termed MPTMS) to the particles, after which the particles were encapsulated in silica. *Id.* at 5–6 (citing Nie 13).

The Examiner found that Nie differs from the rejected claims in that Nie does not “teach a surface-enhanced Raman spectroscopic active composite nanostructure wherein the encapsulating protective layer is thiolpolyethylene glycol.” *Id.* at 6.

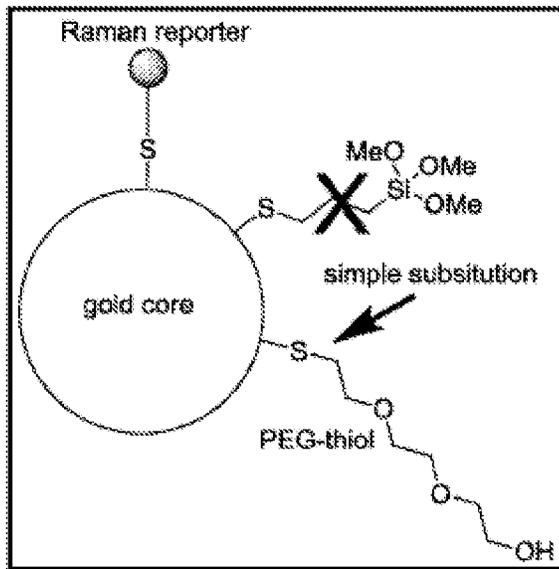
To address that deficiency, the Examiner cited Sokolov as disclosing the attachment of thiolpolyethylene glycol (thiol-PEG) to antibody-conjugated gold nanoparticles. *Id.* at 6–7. In particular, the Examiner

found, Sokolov discloses that, after attaching the antibody to the particles, the thiol-PEG was used to cover the portions of the surface of the gold particles to which the antibody was not attached, thereby avoiding non-specific binding of undesired non-target substances to the particles. *See id.*

The Examiner cited Loo as disclosing, similar to Sokolov, the attachment of thiol-PEG to antibody-conjugated metal-surfaced nanoparticles, also for the purpose of avoiding non-specific binding of undesired non-target substances to the particles' metal surface. *Id.* at 7–8.

Based on the references' combined teachings, the Examiner concluded that an ordinary artisan would have considered it obvious to modify Nie's SERS-active composite nanostructure

by simply substituting in PEG-thiol and optionally a target specific probe as represented by



taught by Nie et al., Loo

et al., and Sokolov et al. because the resulting surface-enhanced Raman spectroscopic active composite nanostructure would advantageously exhibit low non-specific binding and would not be accumulated by the endoreculoendothelial [sic] system (RES).

Id. at 8.

The Examiner reasoned that an ordinary artisan would have had a reasonable expectation of success in view of Nie’s teaching that “in comparison with other biological labels, SERS active composite nanostructures provide high sensitivity and spectroscopic information, two features that enable multiplex analysis of molecular biomarkers and multiparameter flow cytometry.” Ans. 8. As to reasonable expectation of success, the Examiner also identified Sokolov’s teachings that “PEG-thiol may be incorporated onto the surface without bound molecule” and that “PEG-thiol and thiol terminated peptide may be co-absorbed onto the surface of gold nanoparticle by applying them at the same time.” *Id.* at 8–9.

Analysis

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

[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Based on the record before us, we agree with Appellants that a preponderance of the evidence does not support the Examiner’s *prima facie* case of obviousness. In particular, we agree with Appellants that “we do not have a case of simple substitution.” Reply Br. 1; *see also* App. Br. 17 (“Claim 1 is not obvious because using thiol-polyethylene glycol as an encapsulating agent to provide thiol-polyethylene glycol encapsulated particles is not a substitution of 3-mercaptopropyl trimethoxysilane (MPTMS) as an encapsulating agent.”).

Claim 1 recites a SERS-active composite nanostructure composed of a core metallic nanoparticle, a Raman reporter molecule disposed on the core's surface, and an encapsulating protective layer composed of a thiopolyethylene glycol (thiol-PEG). App. Br. 29. Claim 11 recites a similar composite nanostructure, but limits the Raman reporter to molecules lacking an isothiocyanate group. *Id.* at 30

Like claims 1 and 11, Nie describes a SERS-active composite nanostructure composed of a core, a Raman reporter molecule disposed on the core's surface, and an encapsulating protective layer. Nie, Abstract. As the Examiner found, rather than the thiol-PEG recited in claims 1 and 11, Nie exemplifies the use of silica as the encapsulating material. *Id.* at 12.

Before coating its particles with silica, however, Nie first applies “a coupling agent (3-mercaptopropyl trimethoxysilane or MPTMS)” to the surface of the gold particles, to aid in the subsequent deposition of the silica onto the gold particles. *Id.* at 12. Nie explains that the coupling agent is applied “to assist in the bonding between the core . . . and the encapsulant material.” *Id.* at 5; *see also id.* at 13 (“A coupling agent such as aminopropyl trimethoxysilane (APTMS) is often used to make the particle surface vitreophilic, followed by deposition of a more condensed silica layer.”).

As noted above, in concluding that the composite nanostructures of claims 1 and 11 would have been obvious, the Examiner reasoned that an ordinary artisan would have “simply substitute[ed]” thiol-PEG for Nie's MPTMS coupling agent. Ans. 8. The Examiner, however, does not identify, nor do we discern, any clear or specific teaching in any of the cited references, or any evidence of the general knowledge in the art, suggesting

that thiol-PEG would equivalently perform the function for which Nie uses MPTMS—as an agent that enhances deposition of silica onto the Raman dye-conjugated gold particle. Accordingly, we agree with Appellants that the instant situation does not present a case of simple substitution of one prior art equivalent element for another. We conclude, therefore, that a preponderance of the evidence of record does not support the Examiner’s prima facie case of obviousness as to claims 1 and 11.

The Examiner’s contentions do not persuade us to the contrary. We acknowledge, as the Examiner contends (*see, e.g.*, Ans. 15), that both Sokolov and Loo teach that coating antibody-conjugated gold particles with thiol-PEG avoids the problem of non-specific binding of undesired non-target substances to the particles’ metal surface. *See* Sokolov ¶ 241; Loo 1013. As noted above, however, the Examiner’s posited rejection is based on a simple substitution of thiol-PEG for Nie’s MPTMS coupling agent. The Examiner does not explain persuasively why thiol-PEG’s capacity to avoid non-specific binding to the metal particle demonstrates that thiol-PEG would function equivalently to Nie’s MPTMS coupling agent, which enhances deposition of silica onto the Raman dye-conjugated gold particle.

To the extent the Examiner contends (*see* Ans. 17) that thiol-PEG’s capacity to avoid non-specific binding provides motivation for coating the metal core of Nie’s particles with thiol-PEG instead of silica, we first note that the Examiner’s stated rationale is substituting thiol-PEG for MPTMS, not substituting thiol-PEG for silica. *See* Ans. 8. Moreover, Nie discloses attaching its probe molecules, which may be antibodies (Nie 8–9), to the fully assembled particle, rather than the metal core. *See id.* at 8 (describing probe as “linked to the SERS active composite nanostructure”). Because

Nie does not describe attaching its probes to its metal core, and because the core is ultimately encapsulated in silica, and therefore would not be subject to non-specific binding, we are not persuaded that thiol-PEG's capacity to avoid non-specific binding would have provided motivation for coating the metal core of Nie's particles with thiol-PEG.

To that end, the Examiner contends that "Nie motivates one of ordinary skill to find alternative encapsulation material because Nie suggests that silica encapsulation may interfere with reporter absorbance." Ans. 15. The Examiner, however, does not direct us to the specific disclosure in Nie on which this assertion is based.

We note Nie's disclosure that "the low SERS intensities *reported previously* for silica-encapsulated gold particles are likely caused by the interference of a silica shell with reporter adsorption." Nie 13 (emphasis added). As is evident, this disclosure relates to shortcomings in silica-encapsulate particles prepared prior to Nie's disclosure. Indeed, Nie expressly describes the advantages of its disclosed silica-encapsulated particles, including "remarkable stability" (*id.* at 13) as well as the "intense SERS spectra" obtained using the particular dyes disclosed therein. *Id.* at 15.

In sum, for the reasons discussed, we agree with Appellants that a preponderance of the evidence does not support the Examiner's prima facie case of obviousness as to claims 1 and 11 in view of Nie, Sokolov, and Loo. We, therefore, reverse the Examiner's rejection of those claims, and their dependents, over those references.

OBVIOUSNESS-TYPE DOUBLE PATENTING

In rejecting claims 1–20 on the ground of nonstatutory obviousness-type double patenting over claims 1–5, 10–14, and 21–24 of U.S. Patent No. 7,588,827 B1 (“the ’827 patent”), in view of Sokolov and Loo, the Examiner relied on the teachings of Sokolov and Loo, discussed above, and cited the claims of the ’827 patent for disclosures similar to those discussed above, for which Nie was cited. Ans. 9.

The Examiner reasoned that an ordinary artisan would have considered it obvious to modify the SERS active composite nanostructures recited in the claims of the ’827 patent “by simply substituting in PEG-thiol as taught by Sokolov et al. because the resulting surface-enhanced Raman spectroscopic active composite nanostructure would advantageously exhibit low non-specific binding and would not be accumulated by the reticuloendothelial [sic] system (RES).” *Id.* at 9–10.

In traversing this rejection, Appellants rely on the arguments advanced against the rejection discussed above. App. Br. 27.

We reverse this rejection as well. We acknowledge that, like Nie, and like appealed claims 1 and 11, the claims of the ’827 patent recite an SERS-active composite nanostructure composed of a core, a Raman reporter molecule disposed on the core’s surface, and an encapsulating protective layer which may be silica, among other things. *See* the ’827 patent, 12:20–45 (claims 1–5). Like Nie, claims 13 and 14 of the ’827 patent recite that the particles may include a coupling agent. *Id.* at 13:13–16 (claims 13 and 14).

Similar to the discussion above, while Sokolov and Loo teach that thiol-PEG will avoid non-specific binding to an antibody-conjugated metal

nanoparticle, the Examiner fails to direct us to any recitation in any of the cited claims of the '827 patent of an antibody that is conjugated to the metal core particle. We are not persuaded, therefore, that thiol-PEG's capacity to avoid non-specific binding would have provided motivation for coating the metal core of the particles of the '827 patent claims with thiol-PEG.

As to the Examiner's alternative rationale regarding accumulation by RES, the Examiner does not identify any clear or specific evidence in the record suggesting that the specific encapsulated particles recited in the claims of the '827 patent would accumulate in the RES, such that coating with thiol-PEG would be useful, or otherwise desirable. Nor has the Examiner identified any clear or specific teaching in either the cited claims of the '827 patent, or in Sokolov or Loo, suggesting that the particles of the '827 patent claims would be used in an application where accumulation in the RES would be a concern.

Accordingly, because we are not persuaded, for the reasons discussed, that the Examiner has explained persuasively why an ordinary artisan would have modified the particles recited in the cited claims of the '827 patent in a manner that would result in the thiol-PEG coated composite nanostructures recited in appealed claims 1 and 11, we reverse the Examiner's rejection of claims 1 and 11, and their dependent claims, for obviousness-type double patenting.

SUMMARY

We reverse the Examiner's rejection of claims 1–20, under 35 U.S.C. § 103(a), for obviousness over Nie, Sokolov, and Loo.

Appeal 2014-009736
Application 13/680,524

We also reverse the Examiner's rejection of claims 1–20, on the ground of nonstatutory obviousness-type double patenting over claims 1–5, 10–14, and 21–24 of U.S. Patent No. 7,588,827 B1, in view of Sokolov and Loo.

REVERSED