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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* PREETHI H. GUNARATNE, LALITHYA C. JAYARATHNE, and MATTHEW L. ANDERSON

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Appeal 2019-004170
Application 13/136,498
Technology Center 1600

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Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JOHN G. NEW, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1, 5, 9–11, 13–15, 17, 26, and 28–30. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as the University of Houston and Baylor College of Medicine. Appeal Br. 3.

STATEMENT OF THE CASE

The claims stand finally rejected by the Examiner as follows:

1. Claims 1, 5, 9, 10, and 14 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Tomalia et al. (US 2006/0177376 A1, published Aug. 10, 2006) ("Tomalia"), Lee et al. (*Bioconjug. Chem.*, 2003, 14: 1214–1221) ("Lee-BC"), Giljohann et al. (*J. Am. Chem. Soc.*, online January 2009, 131: 2072–2073) ("Giljohann"), Lee et al. (Int. J. Pharm., 2008, 364: 94–101) ("Lee-IJP"), and Lieberman et al. (US 2010/0310583 A1, published Dec. 9, 2010) ("Lieberman"). Final Act. 3.

2. Claims 1, 5, 9, 10, 13, and 14 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Tomalia, Lee-BC, Lee-IJP, and Lieberman, and further view of Beezer et al. (*Tetrahedron*, 2003, 59: 3873–3880) ("Beezer"). Final Act. 6.

3. Claims 1, 5, 9–11, 13, 14, 26, and 28–30 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Tomalia, Lee-BC, Lee-IJP, Lieberman, and Beezer, and further view of Mizuarai et al. (*Molecular Cancer*, June 2009, 8: 1–12). Final Act. 7.

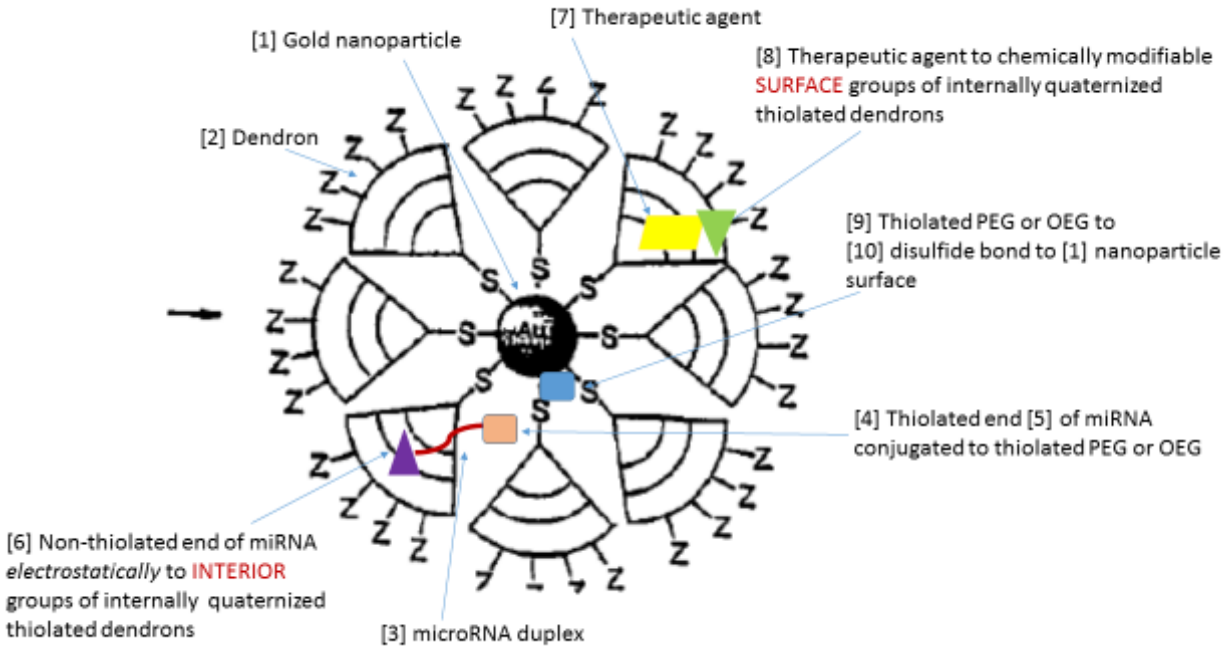
4. Claims 1, 5, 9, 10, 14, 15, and 17 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Tomalia, Lee-BC, Lee-IJP, Lieberman, and Beezer, and further view of Shi et al. (*Small*, 2007, 3: 1245–1252, Abstract). Final Act. 7–8.

## CLAIMED SUBJECT MATTER

Independent claim 1 is representative of the rejected claims. Claim 1 is reproduced below (bracketed numbering added for reference);

> 1. A nanoparticle platform, consisting of:
>
> [1] a gold nanoparticle conjugated to [2] a plurality of internally quaternized thiolated hyperbranched dendrons, said hyperbranched dendrons comprising chemically-modifiable surface groups, interior groups and nano-cavities within the hyperbranched structure;
>
> [3] a microRNA duplex consisting of a non-thiolated sense strand and an antisense strand with one non-thiolated end and [4] one thiolated end that is [5] covalently conjugated via a disulfide bond to a thiolated polyethylene glycol [PEG] or to a thiolated oligoethylene glycol [OEG], said microRNA duplex [6] electrostatically conjugated at the nonthiolated ends directly to the interior groups of the plurality of internally quaternized thiolated hyperbranched dendrons;
>
> [7] one or more therapeutic agents [8] conjugated to the chemically-modifiable surface groups on the plurality of internally quaternized thiolated hyperbranched dendrons; and
>
> [9] one or both of a thiolated oligoethylene glycol or a thiolated polyethylene glycol [10] covalently conjugated via a disulfide bond directly to uncovered surface areas on the nanoparticle surface.

To illustrate the claimed nanoparticle platform, we provide the following drawing. The drawing is for illustrative purposes only. The dendron particle drawing is from Tomalia (Fig. 2).




The drawing shows [1] the "gold nanoparticle" conjugated to [2] the plurality of dendrons. The [3] microRNA, shown as red line, is shown as "[5] covalently conjugated via a disulfide bond to a thiolated polyethylene glycol [PEG] or to a thiolated oligoethylene glycol [OEG]" (orange rectangle) at the [4] thiolated end of the miRNA ("miRNA"). The [7] therapeutic agent (show as a yellow rhombus) of the claim is [8] is conjugated to the [2] dendrons on "chemically-modifiable surface groups." The claims requires a [9] thiolated PEG or OEG [shown as blue rectangle] to be "[10] covalently conjugated via a disulfide bond directly to uncovered surface areas on" the [1] gold nanoparticle." The thiolated PEG or OEG is shown as a blue rectangle.

REJECTION 1

The Examiner found that Tomalia describes [1] gold nanoparticles stabilized by [2] dendrons as required by claim. Final Act. 3.

The Examiner also found that the gold nanoparticle dendrons were used for nucleic acid delivery as they are in claim 1. *Id.*

The Examiner found that Tomalia does not describe "quaternized interior groups" as recited in the claim, but found that Lee-BC does, and provided a reason for making this modification to Tomalia's dendron. *Id.* at 3–4.

The Examiner further found that neither Tomalia nor Lee-BC describe coupling the nucleic acid to PEG or OEG ([4] and [5]). *Id.* at 4.

However, the Examiner that Giljohann and Lee-IJP describe attaching siRNA, a nucleic acid, via OEG and PEG ([4], [5]), respectively, to achieve controlled delivery of the siRNA, meeting the corresponding limitation of the claims. *Id.*

The claim also requires that [9] OEG or PEG is [10] "covalently conjugated via a disulfide bond directly to uncovered surface areas on the nanoparticle surface." The Examiner found that Lee-IJP and Giljohann teach this configuration. *Id.*

With respect to the requirement of the claim that the microRNA duplex is [6] electrostatically conjugated at the non-thiolated ends" (purple triangle in drawing) to the "internally quaternized" dendron, the Examiner found that such configuration would "necessarily" result by electrostatic interactions when the groups on the microRNA are exposed to the internally quaternized groups of the dendron. Ans. 10; Final Act. 5.

The Examiner acknowledged that the Tomalia, Lee-BC, Lee-IJP, and Giljohann publications do not describe a therapeutic agent conjugated to the dendron as required in [7] and [8] of the claim, but found that Lieberman's

teaching of utilizing miRNA and cisplatin in combination would make the claim limitations obvious to make. Final Act. 5.

## DISCUSSION

We address Appellant's arguments below.

### *A. Claim interpretation*

Appellant states that claim 1 comprises "an arrangement in which the microRNA component is exclusively conjugated within the quaternized inner core of the internally quaternized hyperbranched dendron-AuNP [gold nanoparticle]" and "the therapeutic agents are exclusively conjugated on the exterior surface of the internally quaternized hyperbranched dendron-AuNP." Appeal Br. 9–10.

We do not agree with Appellant's interpretation of the claims. Appellant has not identified language in the claim which would require the microRNA and therapeutic agent to be "exclusively conjugated" (Appeal Br. 9) to the respective locations on the dendrons. While the claims require the microRNA and therapeutic agent to be conjugated to these positions on the dendrons, Appellant has not identified language in the claim that would exclude them from being located at other locations on the dendron, as well. *See* Ans. 10. Thus, as discussed in more detail below, the claim recites that the miRNA is "[6] electrostatically conjugated at the nonthiolated ends directly to the interior groups of the plurality of internally quaternized thiolated hyperbranched dendrons"; however, the claim does not exclude the thiolated PEG or thiolated OEG of limitation [5] from also being attached to another and additional position on the nanoparticle.

*B. Attachment of miRNA to gold nanoparticle; thiolated PEG or thiolated OEG attached to the nanoparticle surface.*

To reach the limitation of the thiolated PEG or thiolated OEG attached to the nanoparticle surface as in [9], the Examiner relied on the teachings in Lee-BC and Giljohann in which the miRNA is attached to the gold particle surface by the thiolated PEG or thiolated OEG. Final Act. 4.

Appellant argues that the suggestion from Giljohann to covalently attach OEGylated- or PEGylated- nucleic acids directly to the surface of the Au atom in Tomalia's gold nanoparticle (limitations [9] and [10]) would be "modifying away from Tomalia's nanoparticle (Fig. 2), wherein the core material for the nanoparticle is a gold atom which is dendronized for potential attachment of deliverable biologically active material." Appeal Br. 10.

While it is true that Tomalia describes attaching molecules to the dendron (Tomalia ¶¶ 54–57), Tomalia does not exclude attaching nucleic acids directly to the gold nanoparticle. This configuration is expressly disclosed in Lee-IJP and Giljohann as established by the disclosures reproduced below:

> Gold nanoparticles chemically modified with primary amino groups were developed as intracellular delivery vehicles for therapeutic small interfering RNA (siRNA). The positively charged gold nanoparticles could form stable polyelectrolyte complexes through electrostatic interactions with negatively charged siRNA-polyethylene glycol (PEG) conjugates having a cleavable di-sulfide linkage under reductive cytosol condition.

Lee-IJP 94 (Abstract).

> Duplexes composed of a 27-base RNA strand, and 25-base complement terminated with an ethylene glycol spacer and alkylthiol, were hybridized and added to the RNase-free Au

> NPs, where they were allowed to chemisorb via the thiol-gold bond.

Giljohann 2072 (second column).

Thus, both Lee-IJP and Giljohann disclose ways of attaching a nucleic acid to a gold nanoparticle. It would have been obvious to one of ordinary in the art to have used these techniques to attach the nucleic acid to a gold particle as an alternate and known nucleic acid delivery system. As held in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007):

> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Appellant states that the way in which the nanoparticle platform is manufactured would exclude the nucleic acid from being attached to the gold nanoparticle. Specifically, Appellant explains that the claimed nanoparticle platform is made by conjugating the gold to the internally quaternized hyperbranched dendrons and then "conjugating PEG-microRNA or OEG-microRNA with the pre-formed internally quaternized hyperbranched dendron-AuNP." Appeal Br. 11. Thus, Appellant contends that "the possibility of alternative embodiments of nucleic acids such as direct attachment of the PEG-microRNA or OEG-microRNA to the gold atom as suggested by Giljohann *et al.* does not arise." *Id.*

This argument does not persuade us that the Examiner erred.

The claims are directed to a product, the nanoparticle platform, and not a method of making it. Therefore, even if the way the particles are made in the Specification would preclude the nucleic acid from being conjugated to the particle surface as in [9], the particle is not limited to this method of fabrication.

As discussed by the Examiner, when the microRNA-PEG/OEG conjugate is added to the gold particle dendron, the ends of the microRNA-PEG/OEG conjugate would interact with the gold particle when it is modified as described in Lee-BC and Giljohann. Final Act. 9. We agree with Appellant that the claim does not require nor recite that the PEG/OEG end of the miRNA is conjugated to anything ("[4] one thiolated end [of the miRNA] that is [5] covalently conjugated via a disulfide bond to a thiolated polyethylene glycol [PEG] or to a thiolated oligoethylene glycol [OEG]") (*see* drawing above; orange rectangle); however, we have not been pointed to any language in the claim which excludes the PEG/OEG end from being attached to the nanoparticle gold surface.

In addition, although the claim does not recite that [9] the thiolated oligoethylene glycol or a thiolated polyethylene glycol (*see* drawing above; **blue** rectangle) is bound to anything other than the gold nanoparticle surface ("[9] one or both of a thiolated oligoethylene glycol or a thiolated polyethylene glycol [10] covalently conjugated via a disulfide bond directly to uncovered surface areas on the nanoparticle surface," the claim does not exclude it from being the *same* PEG or OEG attached to the miRNA ([6] **orange** rectangle). While this embodiment is not described in the Specification, limitations from the Specification (in the instant case, the embodiment depicted in Fig. 5J-L) are not read into the claims. *See In re Van Geuns*, 988 F.2d 1181 (Fed. Cir. 1993).

*C. Attachment of therapeutic agent*

Claim 1 recites "[7] one or more therapeutic agents [8] conjugated to the chemically-modifiable surface groups on the plurality of internally

quaternized thiolated hyperbranched dendrons." The Examiner found this limitation to be rendered obvious by Lieberman and Tomalia.

Appellant states that Lee-IJP "provides a suggestion to attach OEGylated- or PEGylated- nucleic acids by electrostatic conjugation to an exterior surface and/or an interior core in Tomalia's nanoparticle with no guidance however, on attachment of therapeutic agents." Appeal Br. 10–11.

This argument is not persuasive because Tomalia teaches that different substances maybe attached to the surface of the dendron:

> The polyvalent surfaces of these quantum dot-core dendritic shell structures are used for the targeted delivery with antibody attachments, receptor directed targeting groups such as folic, biotin/avidin, and the like.

Tomalia ¶ 56. Thus, one of ordinary skill in the art would have had reason to attach a therapeutic agent to the dendron surface.

Appellant also argues that while Lieberman discloses "using microRNA and therapeutic agents together," it does not teach "how they may be arranged in Tomalia's nanoparticle." Appeal Br. 11. Appellant states:

> Consequently, making Applicant's nanoparticle platform based on the combination requires taking recourse from the instant specification which describes a nanoparticle platform with a configuration such that the therapeutic agents are attached ONLY (Applicant's emphasis) to the exterior surface groups and the nucleic acids are attached ONLY to the quaternized groups in the interior core. This is however contrary to 35 U.S.C. § 103.

*Id.*

This argument is not persuasive. The [7] therapeutic agent of Appellant's claimed nanoparticle platform is conjugated to [8] "to the

chemically-modifiable *surface* groups on the plurality of internally quaternized thiolated hyperbranched dendrons." (Emphasis added to claimed langauge.)

Tomalia expressly teaches *surface* functional groups:

> Contemplated within the scope of this invention are functional groups on the surface of the dendrimers/dendrons that are certain hydrophilic, hydrophobic, reactive or passive groups that include, by way of example such groups as: hydroxyl, amino, carboxylic, sulfonic, sulfonato, mercapto, amido, phosphino, –NH–COPh, –COONa, alkyl, aryl, ester, heterocylic, alkynyl, alkenyl, and the like.

Tomalia ¶ 41.

> The ability to functionalize this unique dendritic sheathing with the unlimited examples of dendritic polymeric surfaces functionality allows one to produce very versatile, polyvalent functional surfaces groups on a side variety of metallic quantum dots that includes both metals as well as metal salt or derivatives that may exhibit a wide variety of properties, such as semi-conductivity, paramagnetic, magnetic, fluorescing, electrotumescent, and the like.

Tomalia ¶ 54.

These disclosures, coupled with the disclosure in paragraph 56 which teaches attachment of molecules to the dendron surface for targeted delivery, would have reasonably suggested to one of ordinary skill in the art to attach a therapeutic agent to the dendron surface. It is true that Tomalia does not expressly teach [8] therapeutic agents as required by claim 1. However, one of ordinary skill in that would have recognized that the teaching of antibodies and receptor targeting groups (¶ 56) and the general functionality of the surfaces (¶54), establishes the function of the gold nanoparticle dendron as a carrier for various desired agents. In fact, the purpose of

functionalizing the surface groups in Tomalia is so that they can serve as carriers. Therefore, attaching a therapeutic agent to the gold nanoparticle dendron is using Tomalia's nanoparticle for its known and expected purpose.

For the foregoing reasons, the rejection of claim 1 is affirmed. Claims 5, 9, 10, and 14 fall with claim 1 because separate reason for their patentability were not provided. 37 C.F.R. 41.37(c)(1)(iv).

REJECTIONS 2–4

Rejections 2–4 are based on the same combination of publications cited in Rejection 1 – Tomalia, Lee-BC, Giljohann, Lee-IJP, and Liebermann – and cite additional publications to reach further limitations cited in dependent claims. The Examiner explained how the newly cited publications meet the limitations recited in the dependent claims. Final Act. 6–8. Appellant discusses the newly cited publications, but argues that they did not meet the deficiency in the rejection based on Tomalia, Lee-BC, Giljohann, Lee-IJP, and Liebermann. Br. 13, 18, 20. Consequently, rejections 2–4 are affirmed for the same reasons as rejection 1. None of the claims, in each separately argued rejection, were argued separately.

## DECISION SUMMARY

In summary:

| Claims Rejected | 35 U.S.C. § | Reference(s)/Basis | Affirmed | Reversed |
|---|---|---|---|---|
| 1, 5, 9, 10, 14 | 103 | Tomalia, Lee-BC, Lee-IJP, Lieberman | 1, 5, 9, 10, 14 | |
| 1, 5, 9, 10, 13, 14 | 103 | Tomalia, Lee-BC, Lee-IJP, Lieberman, Beezer | 1, 5, 9, 10, 13, 14 | |
| 1, 5, 9–11, 13, 14, 26, 28–30 | 103 | Tomalia, Lee-BC, Lee-IJP, Lieberman, Beezer, Mizuarai | 1, 5, 9–11, 13, 14, 26, 28–30 | |
| 1, 5, 9, 10, 14, 15, 17 | 103 | Tomalia, Lee-BC, Lee-IJP, Lieberman, Beezer, Shi | 1, 5, 9, 10, 14, 15, 17 | |
| **Overall Outcome** | | | 1, 5, 9–11, 13–15, 17, 26, 28–30 | |

## 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