



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/038,924	03/02/2011	SUDHIR AGRAWAL	4204.1025 US4	9791
38473	7590	11/02/2016	EXAMINER	
ELMORE PATENT LAW GROUP, PC 484 Groton Road Westford, MA 01886			SHIN, DANA H	
			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			11/02/2016	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docteting@elmorepatents.com  
pair\_elmore@firsttofile.com

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

*Ex parte* SUDHIR AGRAWAL, EKAMBAR KANDIMALLA,  
MALLIKARJUNA PUTTA, TAO LAN, LAKSHMI BHAGAT,  
DAQING WANG, and DONG YU<sup>1</sup>

---

Appeal 2014-000450  
Application 13/038,924  
Technology Center 1600

---

Before ULRIKE W. JENKS, ROBERT A. POLLOCK, and  
TAWEN CHANG, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants appeal under 35 U.S.C. § 134(a) from the final rejection of claims 1–10 and 14–15. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

Appellants' invention relates to "oligonucleotide-based compounds comprising two or more single stranded antisense oligonucleotides that are

---

<sup>1</sup> Appellants identify the Real Party in Interest as Idera Pharmaceuticals, Inc. App. Br. 1.

linked through their 5'-ends to allow the presence of two or more accessible 3'-ends, which effectively inhibit or decrease gene expression." Spec. ¶ 15.

Independent claim 1 is illustrative and reads as follows (paragraphing added):

1. A synthetic oligonucleotide-based compound comprising two or more oligonucleotides that are complementary to one or more single-stranded RNA sequences,

wherein the oligonucleotides form a sufficient number of hydrogen bonds through Watson-Crick interactions of its nucleobases with nucleobases of the one or more single-stranded RNA sequence to form a double helix with the single-stranded RNA sequence under physiological conditions,

wherein the oligonucleotides are linked at their 5' - ends, such that the oligonucleotide-based compound has two or more accessible 3'-ends and the oligonucleotide-based compound specifically hybridizes to and inhibits the expression of the one or more single-stranded RNA sequences.

- I. Claims 1–10 and 14–15 stand rejected under 35 U.S.C. § 102(e) as anticipated by Lan.<sup>2</sup> See Rejection dated March 16, 2012 (“Rej.”), 3–6; Final Rejection dated Aug 21, 2012 (“Fin. Rej.”), 2–5; Ans. 3–10.

---

<sup>2</sup> Lan et al., US 2010/0215642 A1, published Aug. 26, 2010.

- II. Claims 1–10 and 14–15 stand rejected for obviousness-type double patenting over claims 1 and 2 the Lan '472 Patent<sup>3</sup> in view of Kandimalla.<sup>4</sup> See Rej. 7; Fin. Rej. 5–6; Ans. 10–14.
- III. Claims 1–10 and 14–15 stand rejected for obviousness-type double patenting over claims 1 and 2 over the Agrawal '464 Patent<sup>5</sup> in view of Kandimalla. See Rej. 8; Fin. Rej. 6–7; Ans. 14–16.

## ANALYSIS

### I. 35 U.S.C. § 102(e)

Appellants contend that the Examiner errs in rejecting claims 1–10 and 14–15 as anticipated by Lan. App. Br. 2–9; Reply Br. 4–10. To establish a prima facie case of anticipation under § 102 the Examiner must show, as a matter of fact, that all elements arranged as specified in a claim are disclosed within the four corners of a reference, either expressly or inherently, in a manner enabling one skilled in the art to practice an embodiment of the claimed invention without undue experimentation. *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344 (Fed. Cir. 2012). For the reasons set forth below, we agree with Appellants that, this standard is not satisfied.

---

<sup>3</sup> Lan et al., US 8,202,974 B2, issued June 19, 2012 (originally published as US 2010/0215642 A1).

<sup>4</sup> Kandimalla et al., US 2008/0171712 A1, published July 17, 2008 (now US 8,106,173 B2, issued Jan. 31, 2012).

<sup>5</sup> Agrawal et al., US 6,489,464 B1, issued Dec. 3, 2002.

A. Findings of Fact

FF1. Lan teaches that toll-like receptors (TLRs) “are intimately involved in inducing the innate immune response to microbial infection.” Lan, ¶ 8.

Two members of the TLR family, TLR7 and TLR8, “recognize viral and synthetic single stranded RNAs and small molecules, including a number of nucleosides.” *Id.* ¶ 13. “The lack of any known specific ssRNA motif for TLR7 or TLR8 recognition and the potentially wide range of stimulatory ssRNA molecules suggest that TLR7 and TLR8 can recognize both self and viral RNA.” *Id.* ¶ 14. “However, the instability of these RNA molecules has hindered progress in using and applying these molecules in many areas (e.g., prevention and treatment of human disease).” *Id.*

FF2. Lan discloses stabilized immune modulatory RNA compounds (SIMRAs) “for modulating the immune response through Toll-like receptor 7 (TLR7).” Lan, ¶3, *see* Abstract, ¶ 57. Lan defines SIMRAs as, “stabilized immune modulatory RNA compounds, wherein the compounds may contain single-stranded RNA (ssRNA) and/or double-stranded RNA (dsRNA), *and modifications to protect or stabilize its 3’ ends* (e.g., by blocking 3’ degradation or by capping the 3’ ends or by linking the 3’ ends of two or more oligoribonucleotides)”. *Id.* ¶ 57 (emphasis added); *see also* ¶ 60 (“The instant application shows that modification of an immune modulatory oligoribonucleotide to protect its 3’ end . . . surprisingly affects its immune modulatory capabilities.”). In addition to “modifications to protect or stabilize [its] 3’ ends,” “[t]he SIMRA compound may also contain modifications to protect its 5’ ends

(e.g., by blocking 5' degradation or capping the 5' ends) to further improve the stability of the oligoribonucleotide(s)." *Id.* ¶ 57; *see* ¶ 60  
FF3. Lan discloses SIMRA compounds comprising "at least two RNA-based oligonucleotides linked at their 3' or 5' ends." *Id.* ¶ 69; *see* Table 2. Consistent with the stated "lack of any known specific ssRNA motif for TLR7 . . . recognition," Lan discusses the option of complementarity of the linked RNA-based oligonucleotides to each other, but is silent with respect to complementarity to any particular cellular or microbial transcript or genomic sequence. *See id.* ¶¶ 14, 66, 67. To the contrary, Lan indicates that single-stranded RNAs of the SIMRA compounds comprise agonists that interact with the TLR7 and TLR8 *proteins*. *See id.*, Title, ¶¶ 13, 16.

FF4. Lan Table 4 discloses 62 exemplary SIMRA sequences, each having at least two RNA-based oligonucleotides linked at their 3' ends. *Id.* ¶ 83. As reproduced below, Table 4 includes the following structure for SIMRA 28:

TABLE 4

---

Stabilized RNA-based Immune Modulatory Oligonucleotide (SIMRA) Sequences

---

SEQ SIMRA# ID NO: Sequence and Modification	SIMRA Structure
. . .	
28      28    5'-AACUG <sub>1</sub> AA <sub>2</sub> CUU-X-UUCG <sub>1</sub> AA <sub>2</sub> UCAA-5'	5'-SEQ ID NO: 28-3'-X-3'-SEQ ID NO: 28-5'

FF5. Lan discloses that "in certain embodiments the oligoribonucleotide can independently be . . . 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 ribonucleotides long." *Id.* ¶ 70; *see also id.* ("In the context of immune modulatory oligoribonucleotides, preferred embodiments have from about 1 to about 35 ribonucleotides,

preferably from about 5 to about 26 ribonucleotides, more preferably from about 13 to about 26 ribonucleotides.”).

## B. Analysis

Citing paragraph 69 of Lan, the Examiner finds that “Lan et al. expressly disclosed that any of the two RNA-based oligonucleotides disclosed in their patent application are “linked at their 3' or 5' ends” (emphasis added).” Fin. Rej. 3. The Examiner further finds that Lan’s disclosure of SIMRA 28 exemplifies two RNA-based oligonucleotides, fully complementary to human TLR7 mRNA, and linked at their 3’ ends. *Id.*

Hence, when the explicit instruction for making two RNA-based oligonucleotides as provided in [Lan] paragraph 0069 such that the oligonucleotides are either linked at their 3’ ends or linked at their 5’ ends is taken into consideration, it is clear that one skilled in the art can readily envisage two RNA-based oligonucleotides (SEQ ID N0:28) that are linked at their 5’ ends as arranged and claimed in the instant case since there are “only two alternatives” expressly disclosed for linking two RNA oligonucleotides . . . with “these circumstances in mind,” it is clear that Lan et al. described to those with ordinary skill in this art each of the elements as arranged in the claims “as fully as if he had drawn each structural formula and had written each name.”

*Id.* (quoting *In re Petering*, 301 F.2d 676,133 (CCPA 1962)). The Examiner further finds that since SIMRA 28 “meets all the structural requirements set forth in the instant claims, it necessarily and inherently follows that the product of Lan et al. must possess the ability ‘to inhibit the expression of human TLR7 expression.” Rejection dated March 16, 2012 at 5.

Although Lan discloses that SIMRA oligonucleotides may be linked at their 3’ or 5’ ends, the reference also emphasizes that such constructs must include modifications to protect or stabilize the 3’ ends of the RNA

oligonucleotides. *See* FF2–3. In light of this requirement, the Examiner fails to explain how Lan teaches compounds comprising oligonucleotides “linked at their 5’ -ends, *such that the oligonucleotide-based compound has two or more accessible 3’-ends,*” as set forth in independent claims 1 and 15.<sup>6</sup> Accordingly, we reverse the rejection.

Further, with respect to the requirement of claim 2 that “the oligonucleotides are independently 15 to 40 nucleotides in length,” the Examiner finds that “the human TLR7 nucleotide sequence was in the public’s possession, whereas “Lan taught that ‘the oligoribonucleotides each independently have from about 2 to about 35 ribonucleoside residues.’” *Id.* at 3–4. Accordingly, because “Lan taught making a 5’-5’ linked RNA compound, wherein each RNA is up to 35 ribonucleotides long and comprises SEQ ID N0:28 that is fully complementary to an art recognized human TLR7 nucleotide sequence, it necessarily and logically follows that the Lan reference as a whole taught the subject matter of claim 2.” *Id.* at 4 (internal quotation omitted).

We do not find the Examiner’s argument persuasive. “[A] reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d

---

<sup>6</sup> We also fail to discern where the Examiner has established that Lan (or any of the cited references) expressly or inherently discloses oligonucleotide-based compounds that “form a double helix with the single-stranded RNA sequence under physiological conditions,” as required by the independent claims.

1376, 1381 (Fed. Cir. 2015). In this case however, outside of the 11 nucleotide sequences of SIMRA 28 itself, nothing in Lan indicates that SIMRA sequences should be complementary to the nucleotide sequence of TLR7. To the contrary, Lan teaches a “lack of any known specific ssRNA motif for TLR7 or TLR8 recognition.” FF1. Accordingly, we find reasonable Appellants’ characterization that the complementarity between SIMRA 28 and TLR7 is merely coincidental.<sup>7</sup> *See also*, Reply Br. 11 “[t]he sequence of oligonucleotides of compound 28 of the ’974 patent *just so happen* to be inherently complementary to TLR7”); *id.* fn2 (“Lan does not teach compounds that are complementary to any target.”)

In light of the above, we are not convinced that one of ordinary skill in the art reading Lan, and having knowledge of the publically available TLR7 sequence, would at once envision the claimed constructs having the length recited in claim 2. For this additional reason, we reverse the rejection of claim 2.

## II. Obviousness Type Double Patenting

Appellants contend that the Examiner errs in rejecting claims 1–12 and 14–15 on the ground of nonstatutory obviousness-type double patenting over claims 1-2 of the Lan ’472 Patent in view of Kandimalla. App. Br. 9–11; Reply Br. 10–12. A prima facie case for obviousness “requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). A determination of obviousness must also show that “a skilled artisan would have been motivated to combined the teachings of the prior art references to achieve the claimed invention, and

---

<sup>7</sup> *See* Transcript of Oral Argument, dated Oct. 4, 2016, at 8:8–10, 11:19–21.

that the skilled artisan would have had a reasonable expectation of success in doing so.” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)); *see also In re Keller*, 642 F.2d 413, 425 (CCPA 1981) (stating that, in determining obviousness, “the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art”).

#### A. Findings of Fact

FF6. The Lan ’472 Patent issued from Application No. 12/1703,612, the same application published as Lan. Claim 1, sub-part (p), of the Lan ’472 Patent corresponds to SIMRA 28 in Lan Table 4.

FF7. Largely paralleling Lan’s disclosure (*see* FFs 1–3), Kandimalla teaches that toll-like receptors (TLRs), “are intimately involved in inducing the innate immune response to microbial infection.” Kandimalla, ¶ 8. Two members of the TLR family, TLR7 and TLR8, “recognize viral and synthetic single stranded RNAs and small molecules, including a number of nucleosides.” *Id.* ¶ 8. “The lack of any known specific ssRNA motif for TLR7 or TLR8 recognition and the potentially wide range of stimulatory ssRNA molecules suggest that TLR7 and TLR8 can recognize both self and viral RNA.” *Id.* ¶ 9. “However, the instability of these RNA molecules has hindered progress in using and applying these molecules in many areas (e.g., prevention and treatment of human disease).” *Id.*; *see id.* ¶ 14.

FF8. Kandimalla discloses stabilized immune modulatory RNA compounds (SIMRAs) for modulating an immune response through TLR7 and/or TLR 8. *Id.*, Abstract, ¶¶ 2, 70, 82. Kandimalla defines SIMRAs as:

stabilized immune modulatory RNA compounds which are recognized as ligands by TLR7 and/or TLR8, wherein the compounds may contain single-stranded RNA (ssRNA) and/or double-stranded RNA (dsRNA), *and modifications to protect (stabilize) its 3' ends* (e.g., by blocking 3' degradation or by capping the 3' ends or by linking the 3' ends of two or more oligoribonucleotides).

*Id.* ¶ 70 (emphasis added); *see also* ¶ 73 (“The present inventors have discovered that modifications of an immune modulatory oligoribonucleotide to protect its 3' end . . . surprisingly affects its immune modulatory capabilities.”). In addition to “modifications to protect (stabilize) its 3' ends,” “[t]he SIMRA compound may also contain modifications to protect its 5' ends (e.g., by blocking 5' degradation or capping the 5' ends) to further improve the stability of the oligoribonucleotide(s).” *Id.* ¶ 70; *see id.* ¶ 73.

FF9. Kandimalla discloses SIMRA compounds comprising “at least two RNA-based oligonucleotides linked at their 3' or 5' ends,” *Id.* ¶ 82; *see* ¶ 76, Table 1; Figs 1, 2. Consistent with the stated “lack of any known specific ssRNA motif for TLR7 . . . recognition” (*id.* ¶ 9), Kandimalla discusses the option of complementarity of the linked RNA-based oligonucleotides to each other, but is silent with respect to complementarity to any particular cellular or microbial transcript or genomic sequence. *See id.* ¶ 9, 80, 81. Rather, Kandimalla indicates that single-stranded RNAs of the SIMRA compounds comprise agonists that interact with the TLR7 and TLR8 *proteins*. *See id.*, Fig. 13B, Abstract, ¶¶ 8, 9, 16, 18, 40.

B. Analysis

The Examiner contends that claims 1 and 2 of the Lan '472 Patent are broadly drawn to an oligonucleotide composition having at least two "single-stranded viral RNA" sequences that "are hybridized to the target nucleic acid." Further, making a 5'-5' linked RNA composition was known in the art as taught by Kandimalla et al. (US 2008/0171712 A1). See paragraph 0082 and Figures 1-2. Hence, the invention defined in claims 1-12 and 14-15 of this application is an obvious variation of the invention defined in claims 1-10 and 14-22 of [the Lan '472 Patent] in view of Kandimalla et al.

Rej. 8. The Examiner further states that,

[s]ince making a 5'-5' linked SIMRA compound was known in the art as taught by Kandimalla (see in particular Figures 1 and 2), it would have been obvious to one skilled in the art to modify the "SIMRA" compound "(p)" of the '974 patent claims to have a 5'-5' linkage in place of the 3'-3' linkage, thereby arriving at the compound that is structurally identical to the instantly claimed compound, which is thus presumed to inherently possess the functional characteristics of the instantly claimed compound

Ans. 12. Accordingly,

one skilled in the art would have been motivated to use another approach (5'-5' parallel synthesis) to make SIMRA compounds, thus would have modified, with a reasonable expectation of success, the 3'-3' linked SIMRA compounds of the '974 patent claims (including the "(p)" compound) to 5'-5' linked SIMRA compounds as directed by Kandimalla.

*Id.* at 13.

Considering the record before us, we agree with Appellants that the Examiner fails to provide an adequate reason to combine the cited references to arrive at the claimed invention. *See, e.g.*, Reply Br. 10. Most particularly, although Kandimalla discloses that SIMRA oligonucleotides

may be linked at their 3' or 5' ends, the reference also emphasizes that such constructs must include modifications to protect or stabilize the 3' ends of the RNA oligonucleotides. *See* FF7–8. In light of this requirement, the Examiner fails to explain how claims 1 and 2 of the Lan '472 Patent in combination with Kandimalla teaches or suggest compounds comprising oligonucleotides “linked at their 5'-ends, *such that the oligonucleotide-based compound has two or more accessible 3'-ends,*” as set forth in independent claims 1 and 15. Accordingly, we reverse the rejection.

### III. Obviousness Type Double Patenting

Appellants contend that the Examiner erred in rejecting claims 1–10 and 14–15 for obviousness-type double patenting over claims 1–8 of the Agrawal '464 Patent in view of Kandimalla.

#### A. Findings of Fact

FF10. Claims 1–8 of the Agrawal '464 Patent are generally directed to oligonucleotides having at least two antisense sequences complementary to human HIV gag or tat sequences. *See* Rej. 8.

#### B. Analysis

The Examiner takes the position that because claims 1–8 of the Agrawal '464 Patent “are broadly drawn to an oligonucleotide having at least two antisense sequences complementary to gag or tat of human HIV sequence [and] making a 5'-5' linked RNA composition was known in the art as taught by Kandimalla[, then] the invention defined in claims 1-12 and 14-15 of this application is an obvious variation of the invention defined in claims 1-8 of U.S. Patent No. 6,489,464 B1 in view of Kandimalla.” Rej. 8. Examiner further states that,

in view of the evolved state of the art at the time the instant invention was made such that utilizing a 5'-5' linkage to link two oligonucleotides has been an art-accepted methodology/approach of making a compound comprising two linked oligonucleotides as taught by Kandimalla, it would have been obvious to one skilled in the art that the term "linked together" of the '464 patent claims encompasses a 5'-5' linkage thus would have been motivated to make, with a reasonable expectation of success, two anti-HIV oligonucleotides "linked together" via a 5'-5' linkage, thereby arriving at the instantly claimed subject matter.

Ans. 15.

We do not find the Examiner's reasoning persuasive. As noted above, Kandimalla emphasizes that SIMRA constructs must include modifications to protect or stabilize the 3' ends of the RNA oligonucleotides. *See* FF7-8. The Examiner fails to explain how claims 1-8 of the Agrawal '464 Patent in combination with Kandimalla teaches or suggest compounds comprising oligonucleotides "linked at their 5'-ends, *such that the oligonucleotide-based compound has two or more accessible 3'-ends,*" as set forth in independent claims 1 and 15. Accordingly, we reverse the rejection.

#### SUMMARY

- I. We *reverse* the rejection of claims 1-10 and 14-15 under 35 U.S.C. § 102(e) as anticipated by Lan.
- II. We *reverse* the rejection of claims 1-10 and 14-15 for obviousness-type double patenting over claims 1 and 2 the Lan '472 Patent in view of Kandimalla.
- III. We *reverse* the rejection of claims 1-10 and 14-15 for obviousness-type double patenting over claims 1 and 2 over the Agrawal '464 Patent in view of Kandimalla.

Appeal 2014-000450  
Application 13/038,924

REVERSED