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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* ROLAND KREUTZER and STEFAN LIMMER<sup>1</sup>

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Appeal 2015-004375  
Application 13/656,548  
Technology Center 1600

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

SMITH, *Administrative Patent Judge*.

#### DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for inhibiting expression of a target gene. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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<sup>1</sup> According to Appellants, the real party in interest is Alnylam Pharmaceuticals, Inc. (Appeal Br. 2.)

STATEMENT OF THE CASE

*Claims on Appeal*

Claims 14–22, 24, 25, and 27–34 are on appeal. (Claims Appendix, Appeal Br. 17–19.) Claim 14 is illustrative and reads as follows:

14. A method for inhibiting expression of a target gene, comprising:
- a) introducing into a mammalian cell an isolated double stranded RNA (dsRNA) comprising two complementary oligoribonucleotide strands, wherein one strand of the dsRNA is complementary to an RNA transcript of at least part of the target gene and the other strand of the dsRNA is complementary to the first strand, and wherein the dsRNA is 15 to 49 base pairs in length; and
  - b) maintaining the cell produced in step a) for a time sufficient to obtain degradation of an RNA transcript of the target gene, thereby inhibiting the expression of the target gene.

*Examiner's Rejections*

1. Claims 14, 15, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 10 and 12–18 of U.S. Patent No. 8,546,143.<sup>2</sup> (Ans. 2–3.)
2. Claims 14, 15, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–14 of U.S. Patent No. 8,119,608.<sup>3</sup> (*Id.* at 3.)
3. Claims 14–20, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–11 of U.S. Patent No. 8,114,851.<sup>4</sup> (*Id.*)

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<sup>2</sup> Kreutzer et al., US 8,546,143 B2, issued Oct. 1, 2013.

<sup>3</sup> Kreutzer et al., US 8,119,608 B2, issued Feb. 21, 2012.

<sup>4</sup> Kreutzer et al., US 8,114,851 B2, issued Feb. 14, 2012.

4. Claims 14, 15, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–10 of U.S. Patent No. 8,101,584.<sup>5</sup> (*Id.* at 3–4.)
5. Claims 14, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–8 of U.S. Patent No. 7,846,907.<sup>6</sup> (*Id.* at 4.)
6. Claims 14, 15, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 4 and 6 of U.S. Patent No. 7,829,693.<sup>7</sup> (*Id.*)
7. Claims 14, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 7,473,525.<sup>8</sup> (*Id.* at 5.)
8. Claims 14, 24, 25, and 30–33 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–3 of U.S. Patent No. 7,348,314.<sup>9</sup> (*Id.*)
9. Claims 14, 15, 20, 24, 25, and 30–33 stand rejected under 35 U.S.C. § 102(e) as anticipated by Fire.<sup>10</sup> (*Id.* at 5–6.)
10. Claims 14–22, 24, 25, and 27–34 stand rejected under 35 U.S.C.

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<sup>5</sup> Kreutzer et al., US 8,101,584 B2, issued Jan. 24, 2012.

<sup>6</sup> Heidenreich et al., US 7,846,907 B2, issued Dec. 7, 2010.

<sup>7</sup> Kreutzer et al., US 7,829,693 B2, issued Nov. 9, 2010.

<sup>8</sup> Kreutzer et al., US 7,473,525 B2, issued Jan. 6, 2009.

<sup>9</sup> John et al., US 7,348,314 B2, issued Mar. 25, 2008.

<sup>10</sup> Fire et al., US 6,506,559 B1, issued Jan. 14, 2003 (“Fire”).

§ 103(a) as unpatentable over Fire, George,<sup>11</sup> Wengel,<sup>12</sup> and Sridhar.<sup>13</sup> (*Id.* at 6–7.) Claims 14–22, 24, 25, and 27–34 were not separately argued, and we therefore limit our discussion to claim 14.

#### FINDINGS OF FACT

FF 1. Fire teaches “a method of inhibiting gene expression using a double stranded RNA.” (Ans. 5.)

FF 2. Fire teaches that “[t]he length of the identical nucleotide sequences may be at least 25, 50, 100, 200, 300, or 400 bases.” (Fire col. 8, ll. 5–6.) The Examiner thus finds that “the dsRNA can be as short as 25 nucleotides.” (Ans. 6.)

FF 3. Fire teaches that “[t]he cell with the target gene may be derived from or contained in any organism . . . [t]he organism may [be an] . . . animal . . . the animal may be a vertebrate . . . [e]xamples of vertebrate animals include . . . mammal.” (Fire col. 8, ll. 12–36; Appeal Br. 11.)

FF 4. The Examiner finds that “use of liposomes as a vehicle for delivering nucleic acids to cells was well known at the time the invention was made” and that “liposomes are useful for intracellular delivery of oligonucleotides for diagnostic purposes.” (Ans. 7, citing Sridhar Abstract; col. 1, l. 53–col. 2, l. 13.)

#### DISCUSSION

We adopt and agree with the Examiner’s findings, analysis, and conclusions as set forth in the Final Action (Final Act. 7–10)<sup>14</sup> and

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<sup>11</sup> George et al., US 5,683,873, issued Nov. 4, 1997 (“George”).

<sup>12</sup> Wengel, US 2003/0134808 A1, published July 17, 2003 (“Wengel”).

<sup>13</sup> Sridhar et al., US 5,739,271, issued Apr. 14, 1998 (“Sridhar”).

<sup>14</sup> Office Action dated May 29, 2014.

Examiner's Answer (Ans. 6–15) relating to obviousness-type double patenting and obviousness. The obviousness-type double patenting and obviousness rejections are affirmed, and Appellants' arguments are addressed below.

*Rejection Nos. 1–8*

Appellants do not contest the rejections for obviousness-type double patenting (Nos. 1–8). Accordingly, those rejections are affirmed. *See* 37 C.F.R. § 41.37(c)(1)(iv); *Hyatt v. Dudas*, 551 F.3d 1307, 1314 (Fed. Cir. 2008).

*Rejection No. 9—Anticipation*

*Issue*

Whether a preponderance of evidence of record supports the Examiner's finding of anticipation under 35 U.S.C. § 102(e).

*Analysis*

The Examiner's anticipation finding is based on the finding that Fire discloses "that the dsRNA can be as short as 25 nucleotides." (Ans. 6; FF 2.) Appellants argue that "even if Fire disclosed a dsRNA construct length of at least 25 bases . . . the disclosure of 'at least 25 bases' in Fire (in other words, a range from 25 to infinity) does not describe the entire claimed range of 15 to 49 base pairs." (Appeal Br. 10.)

We agree with Appellants. While we agree with the Examiner "that the dsRNA [of Fire] can be as short as 25 nucleotides," Fire's disclosure is "at least" 25 bases (25 and above). (FF 2.) And while Appellants claimed 15 to 49 bases overlaps Fire's disclosure, Fire's disclosure does not describe Appellants' claimed invention within the meaning of 35 U.S.C. § 102(e).

*See In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

*Conclusion*

A preponderance of evidence of record fails to support the Examiner's finding of anticipation under 35 U.S.C. § 102(e).

*Rejection No. 10—Obviousness*

*Issue*

Whether a preponderance of evidence of record supports the Examiner's conclusion of obviousness under 35 U.S.C. § 103(a).

*Analysis*

*Length of dsRNA*

Appellants argue that Fire's reference to identical nucleotide sequences of at least 25 bases "means that the dsRNA itself could be hundreds of base pairs long, as long as 25 bases of the dsRNA are identical to a portion of the target gene," and support this argument by reference to certain RNA constructs disclosed in Fire.<sup>15</sup> (Appeal Br. 5–6.) Appellants

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<sup>15</sup> We acknowledge, but are unpersuaded by, Appellants' argument that at least two of Fire's RNA constructs contain introns and that, "since mRNAs do not contain any intron sequences," Fire's constructs are longer than any regions thereof that are identical to a target RNA sequence. (Appeal Br. 6.) As the Examiner explains, "primary mRNAs transcripts do contain intron sequences," whereas "*mature* mRNA" is apparently what Appellants are referring to by "mRNAs" that do not contain introns, and Fire uses the term "target gene" and does not equate that term with the phrase "*mature* mRNA." (Ans. 20.)

also point to the Ngo<sup>16</sup> article and Fire Article<sup>17</sup> to argue that “the state of the art at the time [Fire was filed] indicated that dsRNAs must be [hundreds of base pairs] long to effectively inhibit gene expression.” (*Id.* at 12–13; *see also id.* at 7–8.) Appellants also take issue with the Examiner’s reference to claims 10 and 15 of Fire as support for the position that Fire discloses a dsRNA of 25 base pairs in length, based on the contention that neither claim was present at the time the Fire patent application was filed.<sup>18</sup> (*Id.* at 8–10; Reply Br. 4.)

We are not persuaded. As explained by the Examiner, Fire teaches “that the dsRNAs can be as short as 25 nucleotides” and the teachings of Fire are not limited to its working examples. (Ans. 8.) *See In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012). And while claims 10 and 15 of Fire may not have been present at the time Fire was filed, their presence in Fire *as issued* supports the Examiner’s position that the specification of Fire *as filed* disclosed dsRNAs as short as 25 nucleotides. Moreover, as the Examiner also explains, “there is no basis to conclude that the RNA of Fire would be hundreds of nucleotides long with only a 25 nucleotide portion identical or complementary to the target.” (Ans. 9.) Accordingly, we discern no error in the Examiner’s finding that Fire teaches and suggests a dsRNA as recited in claim 14. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir.

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<sup>16</sup> Ngo et al., *Double-stranded RNA induces mRNA degradation in Trypanosoma brucei*, PROC. NATL. ACAD. SCI. USA 95, 14687–92 (1998) (“Ngo”).

<sup>17</sup> Fire et al., *Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans*, Nature 391, 806–11 (1998) (“Fire Article”).

<sup>18</sup> For example, claim 15 of Fire recites “said double-stranded ribonucleic acid structure is at least 25 bases in length.” (Fire col. 27.)

1994) (“a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests.”) (quoting *In re Burckel*, 592 F.2d 1175, 1179 (CCPA 1979)).<sup>19</sup>

*Mammalian Target Genes*

Appellants argue that “[n]owhere does the Fire patent describe introducing dsRNA into a mammalian cell at all.” (Appeal Br. 11.) Appellants argue further that “the general understanding in the field at the time of the invention . . . was that dsRNAs may not inhibit mammalian gene expression at all.” (*Id.* at 13.) In support of that argument, Appellants cite to (and quote) the Fire Article, an article by Tuschl,<sup>20</sup> and an article by Sen.<sup>21</sup> (*Id.* at 13–14.) Appellants thus contend that one of ordinary skill “would therefore have been led away, based on Fire’s teaching and the general state of the field, from attempting to introduce a dsRNA into a mammalian cell.” (*Id.* at 14.)

We are not persuaded by Appellants’ arguments. Fire teaches the application of its dsRNA to a mammalian gene. (FF 1–3.) Appellants rely on the Fire Article as “strongly suggest[ing] that dsRNAs were not functional in mammals” based on the protein kinase response (PKR).

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<sup>19</sup> We also acknowledge, but are unpersuaded by, Appellants’ argument that the sentence in Fire stating “[t]he length of the identical nucleotide sequences may be. . .” (FF 2) applies only to the immediately preceding sentence regarding an alternative functional definition. (Reply Br. 2–3.) (See Fire col. 7, l. 53–col. 8, l. 6.)

<sup>20</sup> Tuschl et al., *Targeted mRNA degradation by double-stranded RNA in vitro*, GENES & DEVELOPMENT 13, 3191–97 (1999) (“Tuschl”).

<sup>21</sup> Sen et al., *A brief history of RNAi: the silence of the genes*, FASEB J. 20, 1293–99 (2006) (“Sen”).

(Appeal Br. 13.) Appellants rely on the Sen article for the elicitation of an interferon response by the introduction of long dsRNA into mammalian cells. (*Id.*) However, as explained by the Examiner, Fire “recognized the PKR issue” and cites to Proud<sup>22</sup> (which cites to Manche<sup>23</sup>) as informing “one of ordinary skill that introducing dsRNA of less than about 33bp in length would avoid entirely the activation of the PKR protein, thus avoiding entirely the interferon response.”<sup>24</sup> (Ans. 10–12.) Appellants also point to a quote from Tuschl that reads (in pertinent part) “[i]f RNAi exists in mammals . . . it is likely obscured by the rapid induction of dsRNA of nonspecific antiviral responses.” (Appeal Br. 13.) Such an equivocal postulation about what is “likely” does not persuade us that a person of skill in the art would be “led away” from attempting to introduce a dsRNA into a mammalian cell.

### *Secondary Considerations*

Appellants argue that “there was a long-felt but unsolved need in the art for an invention that would allow the dsRNA-mediated gene expression

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<sup>22</sup> Proud, *PKR: a new name and new roles*, TIBS 20, 241–46 (1995) (“Proud”).

<sup>23</sup> Manche et al., *Interactions between Double-Stranded RNA Regulators and the Protein Kinase DAI*, 12 MOL. CELL. BIOL. 11, 5238–48 (1992) (“Manche”).

<sup>24</sup> Appellants attempt to distinguish Proud and Manche from Fire based on their publication dates, and state that “Proud and Manche may not represent the state of the art at the time of the instant application.” (Reply Br. 6.) But Proud (which cites to Manche) was incorporated by reference into Fire and referred to as “indicative of the level of skill in the art.” (Fire col. 22, ll. 5–8, 20.) *See Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (discussing incorporation by reference).

inhibition mechanism to operate in mammals.” (Appeal Br. 14.) In support of this argument, Appellants point to the Tuschl article and an article by Clemens.<sup>25</sup> Appellants also point to the Sen article to argue that “others had been searching for a mechanism via which to use dsRNA-mediated inhibition of gene expression in mammals, yet had failed.” (*Id.* at 15.)

We are not persuaded. Long-felt need is “analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.” *Texas Instruments, Inc. v. Int'l Trade Comm.*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Establishing long-felt need also requires objective evidence that the invention satisfies the long-felt need. *In re Cavanagh*, 436 F.2d 491, 496 (CCPA 1971).

In this case, the selected quotes from Tuschl, Clemens, and Sen relied upon by Appellants do not persuasively establish a long-felt but unsolved need in the art, such as when the art-recognized problem arose, how long the need was felt, and efforts made to solve the problem. Thus, in light of Fire’s teachings, we are not persuaded that these articles establish a long-felt but unsolved need at the time of Appellants’ claimed invention.

Appellants also argue that “the results of the claimed dsRNA were unexpected,” citing the Fire Article and Tuschl. (Appeal Br. 15.) Appellants also refer to a statement from the Specification to argue that “it was a *surprising* result that the shorter dsRNAs would operate via dsRNA-

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<sup>25</sup> Clemens et al., *Use of double-stranded RNA interference in Drosophila cell lines to dissect signal transduction pathways*, Proc. Natl. Acad. Sci. 97(12), 6499–6503 (2000) (“Clemens”).

mediated inhibition of gene expression in mammals.” (Appeal Br. 15, citing Spec. ¶ 11.)

Based on Fire’s teachings, we are not persuaded that a person of ordinary skill in the art would have found “the results of the claimed dsRNA” to be unexpected. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Moreover, “[m]ere lawyer’s arguments and conclusory statements in the specification, unsupported by objective evidence, are insufficient to establish unexpected results.” *In re Wood*, 582 F.2d 638, 642 (CCPA 1978).

We do not find that Appellants’ arguments regarding secondary considerations are persuasive or otherwise sufficient to rebut the prima facie case of obviousness of claim 14.

#### *Conclusion of Law*

A preponderance of evidence of record supports the Examiner’s conclusion that claim 14 is obvious under 35 U.S.C. § 103(a). Claims 15–22, 24, 25, and 27–34 were not argued separately and fall with claim 14.

#### SUMMARY

We affirm the rejections for obviousness-type double patenting.

We reverse the rejection for anticipation under 35 U.S.C. § 102(e).

We affirm the rejection for obviousness under 35 U.S.C. § 103(a).

#### 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).

AFFIRMED