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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROLAND KREUTZER and STEFAN LIMMER¹

Appeal 2015-004586
Application 13/656,540
Technology Center 1600

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 an isolated double stranded RNA (dsRNA). We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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

STATEMENT OF THE CASE

Claims on Appeal

Claims 1–7, 9–13, and 27–35 are on appeal.² (Claims Appendix, Appeal Br. 22–24.) Claim 1 is illustrative and reads as follows (emphasis added):

1. An isolated double stranded RNA (dsRNA) comprising two complementary oligoribonucleotide strands wherein the dsRNA is 15 to 49 base pairs in length, wherein one strand of the dsRNA is complementary to an RNA transcript of at least part of a mammalian target gene and the other strand of the dsRNA is complementary to the first strand, wherein the dsRNA is enclosed by a micellar structure, and *wherein said dsRNA is capable of specifically inhibiting the expression of the mammalian target gene.*

Examiner's Rejections

1. Claims 1–7, 9–13, and 27–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 7,196,184,³ in view of Crooke⁴ and Wengel.⁵ (Ans. 2–3.)

² Claim 35 was not specifically addressed in the Final Action dated May 12, 2014, and the rejection under 35 U.S.C. § 112, 4th paragraph contained a typographical error in that it referred to claim 34 rather than claim 35. (Ans. 10.) The rejection of claim 34 under § 112 is thus withdrawn and a new ground under § 112 entered as to claim 35. (*Id.* at 13–14.) Claim 35 was also inadvertently left out of the double patenting and obviousness rejections, and the Examiner entered new grounds of rejection in the Answer as to claim 35 and those rejections. (*Id.* at 10–14.) Because Appellants filed a Reply Brief responding to the rejections of claim 35, rather than reopening prosecution as to the new grounds of rejection, we treat claim 35 as on appeal, as subject to the new grounds rejection, and as included in the double patenting and obviousness rejections.

³ Heidenreich et al., US 7,196,184 B2, issued Mar. 27, 2007.

⁴ Crooke, US 6,107,094, issued Aug. 22, 2000 (“Crooke”).

⁵ Wengel, US 2003/0134808 A1, published July 17, 2003 (“Wengel”).

2. Claims 1, 7, 9, 11, 12, and 30–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 11 and 26 of U.S. Patent No. 7,745,418.⁶ (*Id.* at 3.)
3. Claims 1, 7, 9, 11, 12, and 30–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 6–8, 13, 22, 29, and 30 of U.S. Patent No. 7,994,309.⁷ (*Id.* at 3–4.)
4. Claims 1–7, 9–13, and 27–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–22 of U.S. Patent No. 8,114,981.⁸ (*Id.* at 4.)
5. Claims 1–7, 9–13, and 27–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–6 and 9–16 of U.S. Patent No. 8,183,362.⁹ (*Id.*)
6. Claims 1, 7, 9–12, and 30–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 6, 7, 14, 19, 30, and 31 of U.S. Patent No. 8,273,870.¹⁰ (*Id.* at 4–5.)
7. Claims 1, 7, 9, 11, 12, and 30–35 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 9 and 22 of U.S. Patent No. 8,273,868.¹¹ (*Id.* at 5.)
8. Claim 30 stands rejected under 35 U.S.C. § 112(d) or 35 U.S.C. § 112 (pre-AIA), 4th paragraph, as being of improper dependent form. (*Id.*)

⁶ John et al., US 7,745,418 B2, issued June 29, 2010.

⁷ Kreutzer et al., US 7,994,309 B2, issued Aug. 9, 2011.

⁸ Kreutzer et al., US 8,114,981 B2, issued Feb. 14, 2012.

⁹ Kreutzer et al., US 8,183,362 B2, issued May 22, 2012.

¹⁰ Kreutzer et al., US 8,273,870 B2, issued Sept. 25, 2012.

¹¹ John et al., US 8,273,868 B2, issued Sept. 25, 2012.

9. Claim 32 stands rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as indefinite. (*Id.* at 6.)

10. Claim 35 stands rejected under 35 U.S.C. § 112(d) or 35 U.S.C. § 112 (pre-AIA), 4th paragraph, as being of improper dependent form. (*Id.* at 13.)

11. Claims 1–7, 9–13, and 27–35 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Crooke, Sridhar,¹² and Wengel. (*Id.* at 6–8.)

12. Claims 1–7, 9–13, and 27–35 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Fire,¹³ George,¹⁴ Wengel, and Sridhar. (*Id.* at 8–10.)

FINDINGS OF FACT

We adopt as our own the Examiner’s findings and analysis concerning the scope and content of the prior art. The following findings are included for emphasis and reference convenience.

FF 1. The Examiner finds that Crooke teaches “oligomeric compounds that bind to a target RNA strand and are substrates for dsRNase enzymes,” and that the “oligomeric compounds include oligoribonucleotides and other oligomeric compounds having a linear sequence of linked ribonucleoside subunits incorporated therein.” (Ans. 6, citing Crooke col. 12.)

FF 2. Crooke teaches oligoribonucleotides used for experiments “to determine if mammalian cells . . . contain double-strand RNase activity.” (Crooke col. 50, ll. 36–40.)

FF 3. Crooke teaches that “[i]t is more preferred that the oligoribonucleotides and oligoribonucleosides of the present invention

¹² Sridhar et al., US 5,739,271, issued Apr. 14, 1998 (“Sridhar”).

¹³ Fire et al., US 6,506,559 B1, issued Jan. 14, 2003 (“Fire”).

¹⁴ George et al., US 5,683,873, issued Nov. 4, 1997 (“George”).

comprise from about 15 to about 25 nucleoside subunits.” (Crooke col. 14, ll. 13–16.)

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. 8, citing Sridhar Abstract; col. 1, l. 53–col. 2, l. 13.)

FF 5. Fire teaches a process for inhibiting expression of a target gene in a cell in which “RNA containing [] nucleotide sequences identical to a portion of the target gene are preferred for inhibition.” (Fire col. 7, ll. 53–54.)

FF 6. 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.)

FF 7. 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; *see also* Appeal Br. 15.)

DISCUSSION

We adopt and agree with the Examiner’s findings, analysis, and conclusions set forth in the Final Action (Final Act. 2–11), as clarified by the Answer, and Examiner’s Answer (Ans. 2–25). The rejections are affirmed, and Appellants’ arguments are addressed below.

Rejection Nos. 1–7

Appellants do not contest the rejections for obviousness-type double patenting (Nos. 1–7). 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 Nos. 8–10: Section 112

Issue

Whether a preponderance of the evidence of record supports the Examiner’s conclusion that claims 30, 32, and 35 fail to comply with 35 U.S.C. § 112.

Analysis

Claim 30

The Examiner rejects claim 30 “as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.” (Ans. 5.) In particular, the Examiner asserts that “claim 1 is directed to a dsRNA and [claim 30] now recites a third strand which does not further define the claimed invention, which is the dsRNA, not the RNA transcript.” (*Id.* at 25.)

Appellants argue that claim 30 does not broaden the scope of claim 1, but rather “narrows the scope of claim 1 by clarifying the nature of the RNA transcript.” (Appeal Br. 18.) Appellants argue further that “claim 30 provides structural limitations to the claim by clarifying that the RNA transcript cannot be a part of the dsRNA, which provides a structural limitation that further limits the dsRNA of claim 1.” (Reply Br. 10.)

We find that the Examiner has the better position. Claim 1 defines the claimed invention as the dsRNA, not the RNA transcript. (Appeal Br. 22.) Thus, the recitation of claim 30 does not further define the claimed invention. Moreover, Appellants argument that claim 30 clarifies that “the RNA transcript cannot be a part of the dsRNA” is not persuasive because, according to claim 1, the RNA transcript is not part of the claimed dsRNA.

Claim 32

The Examiner found that claim 32 was indefinite because “the limitation of this claim[] relate[s] to how the compound will be used for one possible intended use. The amount to be used is a relative quantity . . . which is not related to the claimed dsRNA itself, but is based on the cell in which the dsRNA is to be used.” (Ans. 6.)

Appellants argue that claim 32 “does not recite an intended use of the dsRNA, but an amount of dsRNA” (Appeal Br. 19) and that “an amount of dsRNA relative to an amount of RNA transcript is a structural limitation of the dsRNA” (Reply Br. 10).

We find that the Examiner has the better position. While Appellants argue that “[t]he acceptability of relative terminology in claim language ‘depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification’” (Appeal Br. 20, citing MPEP 2173.05(b)), Appellants do not point us to any part of the Specification or otherwise make of record what they believe one skilled in the art would understand by the terminology in claim 32. Moreover, attorney argument cannot take the place of record evidence. *Estee Lauder Inc. v. L’Oreal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997). The phrase “at an amount” as

determined by “an amount” of RNA transcript (which is not claimed) is thus indefinite.

Appellants’ reliance on *Orthokinetics, Inc. v. Safety Travel Charis, Inc.*, 806 F.2d 1565 (Fed. Cir. 1986), is misplaced. That decision is based on patent validity in a district court, rather than a decision in an ex parte appeal within the USPTO. Our reviewing court has noted “that indefiniteness rejections by the USPTO arise in a different posture from that of indefiniteness challenges to an issued patent.” *In re Packard*, 751 F.3d 1307, 1312 (Fed. Cir. 2014). Furthermore, our reviewing court stated:

during patent prosecution [] claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed. . . . An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.

In re Zletz, 893 F.2d 319, 321–322 (Fed. Cir. 1989). Accordingly, Appellants failed to meet their burden before the USPTO of “precisely defin[ing] the invention.” *See In re Morris*, 127 F.3d 1048, 1056 (Fed. Cir. 1997).

Claim 35

The Examiner rejects claim 35 “as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.” (Ans. 13.) In particular, the Examiner finds that

The statement in claim 1 that the dsRNA is capable of inhibiting expression is a mere recitation of a characteristic of the dsRNA, but does not impart a structural limitation itself; any dsRNA satisfying the structural requirements of claim 1 would be expected to have the recited function. Claim 35 does not limit

claim 1 because it recites a limitation that does not further define the structure, but instead states only how the compound of claim 1 would function if used for one possible intended use.

(Id.)

Appellants argue that claim 35 limits the final *wherein* clause of claim 1 (italicized above) by stating that “the inhibition occurs upon introduction of the dsRNA into a mammalian cell.” (Reply Br. 4–5 and 9–10.)

We find that the Examiner has the better position. Claim 1 is directed to a composition of matter (dsRNA). The “wherein” clause of claim 1 merely recites a *use* of the claimed dsRNA, not a structure of the dsRNA, and thus adds nothing to the patentability of the claim. *See Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Claim 35 also recites a use (not structure) and cannot further limit a wherein clause that is not itself a limitation of claim 1.

Conclusion

A preponderance of evidence of record supports the Examiner’s conclusion that claims 30, 32, and 35 fail to comply with 35 U.S.C. § 112.

Rejection Nos. 11–12: Obviousness

Issue

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

Rejection No. 11

Analysis

Appellants contest the obviousness rejections of claims 1, 9, and 30–35 based on Crooke, Sridhar, and Wengel. (Appeal Br. 3–11; Reply Br. 2–5.) We address the arguments as to those claims below.

Claim 1

Appellants argue that “the RNA duplexes of Crooke are produced to test whether the duplexes would be cleaved in the presence of rat liver extracts *in vitro*.” (Appeal Br. 4.) Thus, according to Appellants, “one of ordinary skill would not put Crooke’s RNA duplexes into micellar structures for intracellular delivery since there was no motivation to deliver Crooke’s RNA duplexes into cells.” (*Id.*) Moreover, according to Appellants, “[a] skilled artisan would have understood from Crooke as a whole that the oligomeric compounds were intended to be introduced to a cell for binding with a target RNA to then form a double-stranded structure *within the cell* that could then be cleaved by dsRNase.” (*Id.* at 5.) Thus, according to Appellants, motivation to combine Crooke and Sridhar “is plainly lacking without impermissible hindsight.” (Reply Br. 3.)

We are not persuaded. As the Examiner explains, Crooke’s disclosure is not limited to single stranded oligonucleotides that act via the antisense mechanism. (Ans. 15.) In this regard, it is well settled that a prior art reference may be read for all that it teaches, including uses beyond its primary purpose. *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012). As further explained by the Examiner, “Crooke also produces and uses double stranded oligonucleotides as ‘artificial substrates’ which satisfy the structural limitations of the claims” and are “used for experiments

‘determin[ing] if mammalian cells . . . contain double-strand RNase activity.’” (Ans. 15; FF 2.) Moreover, as stated by the Examiner, “there is a reason for the person of ordinary skill to perform further experiments within these cells. The person of ordinary skill recognizes that if one wishes to study dsRNAses in cells, then intracellular delivery would be necessary.” (Ans. 15–16.)

Claim 1 recites a double stranded RNA (dsRNA) that is “enclosed by a micellar structure.” (Appeal Br. 22.) According to Appellants, based on Crooke’s teachings “as a whole,” motivation to combine Crooke and Sridhar is lacking because “there was no motivation to deliver Crooke’s RNA duplexes into cells.” (Appeal Br. 4–5; Reply Br. 2–3.) However, “[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls,” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007), and “[o]ne of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings” *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.* 424 F.3d 1293, 1323 (Fed. Cir. 2005). Moreover, evaluating suggestion or motivation in an obviousness analysis “not only permits, but *requires*, consideration of common knowledge.” *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006).

Here, the Examiner makes clear that “[t]he person of ordinary skill recognizes that if one wishes to study dsRNAses in cells, then intracellular delivery would be necessary” (Ans. 16), and that the use of liposomes (a micellar structure) for intracellular delivery of oligonucleotides “was well known at the time the invention was made” (Ans. 8; FF 4). Thus, the

Examiner concluded, and we agree, that the enclosure of Appellants' recited dsRNA in a micellular structure would have been obvious.

We find Appellants' argument regarding "impermissible hindsight" similarly unpersuasive. (*See* Appeal Br. 5 and Reply Br. 3.) Appellants adduce no evidence that the Examiner's findings were beyond the level of ordinary skill in the art at the time of invention, nor do they point to any of the Examiner's findings that could have been taken only from Appellants' Specification. *See In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

Claim 9

Appellants rely on the same arguments set forth above in connection with claim 1 (Appeal Br. 6), and they are unpersuasive as to claim 9 for the reasons set forth above.

Claim 30

Appellants argue that "Crooke does not disclose a third strand at all" and rely on the same arguments advanced above in connection with claim 1. (Appeal Br. 7–8.) However, as discussed above, claim 30 does not further limit claim 1 and is obvious for the reasons set forth in connection with claim 1. (*See* Ans. 16.)

Claim 31

Appellants rely on the same motivation arguments as set forth above in connection with claim 1, and those arguments are unpersuasive as to claim 31 for the reasons set forth above. (*See* Appeal Br. 8; Ans. 16–17.)

Claim 32

Appellants argue that the cited art "does not teach or suggest a dsRNA at an amount, wherein the amount of dsRNA introduced into a mammalian cell is less than an amount of RNA transcript of the mammalian target gene

in the mammalian cell.” (Appeal Br. 8.) However, “the patentability of apparatus or composition claims depends on the claimed structure, not on the use or purpose of that structure.” *Catalina Mktg.*, 289 F.3d at 809. Here, as the Examiner explains, the claims are directed to the dsRNA while the amount recited in claim 32 “is a relative amount that is related to the cell in which the dsRNA is to be used.”¹⁵ (Ans. 17.)

Claim 33

Appellants rely on the same arguments set forth above (Appeal Br. 10), and those arguments are unpersuasive as to claim 33 for the reasons set forth above.

Claim 34

Appellants rely on the same arguments set forth above; namely, that “none of the references alone or in combination teach a dsRNA enclosed by a micellar structure at all.” (Appeal Br. 11.) That argument is unpersuasive as to claim 34 for the reasons set forth above.

Claim 35

Appellants argue that “[c]laim 35 is patentable for at least the same reasons that claim 1 is patentable” and that “claim 35 does limit claim 1, as it recites that ‘the inhibition occurs upon introduction of the dsRNA into a mammalian cell.’” (Reply Br. 4.) We are unpersuaded, for the reasons set

¹⁵ We do not agree with Appellants’ contention, based on *In re Lemin*, 326 F.2d 437 (CCPA 1964), that an amount recited in a composition claim is necessarily a “physical limitation.” (Reply Br. 4.) *See, e.g., Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (construing the term “in a stabilizing amount” in a drug formulation claim as not a limitation).

forth above in connection with claim 1 and because claim 35 is a non-limiting statement of a use of the claimed dsRNA, as also set forth above.

Conclusion of Law

A preponderance of evidence of record supports the Examiner's conclusion that claims 1, 9, and 30–35 are obvious under 35 U.S.C. § 103(a). Claims 2–7, 10–13, and 27–29 were not argued separately and fall with claim 1.

Rejection No. 12

Analysis

Appellants contest the obviousness rejections of claims 1 and 35 by advancing arguments regarding the disclosure of Fire (relating to dsRNAs) and secondary considerations. (Appeal Br. 11–18; Reply Br. 5–10.)

Claim 1

Length of dsRNA

Appellants argue that “one of ordinary skill would not find it obvious to make a dsRNA of 15 to 49 base pairs based on the disclosure of Fire.” (Appeal Br. 12.) In particular, 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. (*Id.* at 12–13.) Appellants also take issue with the Examiner's reference to claim 15 of Fire as support for the position that Fire discloses a dsRNA of 25 base pairs in

length, based on the contention that claim 15 was not present at the time the Fire patent application was filed.¹⁶ (Appeal Br. 15; Reply Br. 7.)

Appellants also point to two articles for the proposition that “[t]he state of the art at the time [Fire was filed] also lends evidence that one of ordinary skill would not find it obvious to make dsRNAs of 15 to 49 base pairs in length based on the teachings of the Fire patent.” (Appeal Br. 13.) Appellants cite to Ngo¹⁷ for the proposition that “it was understood in the field that dsRNAs had to be . . . over 150 base pairs [] to be effective, and really much longer than that for robust inhibition,” and a Fire Article¹⁸ that Appellants argue discloses dsRNAs “between 299-1033 kilobases in length, but no dsRNAs that were 25 base pairs long.” (*Id.* at 14.) Thus, according to Appellants, “[o]ne of ordinary skill would be led away from believing that dsRNAs of 15 to 49 base pairs were effective.” (*Id.* at 14–15.)

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.¹⁹ (Ans. 18.) *See Mouttet*, 686

¹⁶ Claim 15 of Fire recites “said double-stranded ribonucleic acid structure is at least 25 bases in length.” (Fire cols. 27.)

¹⁷ Ngo et al., *Double-stranded RNA induces mRNA degradation in Trypanosoma brucei*, PROC. NATL. ACAD. SCI. USA 95, 14687–92 (1998) (“Ngo”).

¹⁸ Fire et al., *Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans*, Nature 391, 806–11 (1998) (“Fire Article”).

¹⁹ 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. 12–13.) 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

F.3d at 1331. And while Fire claim 15 may not have been present at the time Fire was filed, its 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.” (*Id.* at 19.) Accordingly, we discern no error in the Examiner’s finding that Fire teaches and suggests a dsRNA as recited in claim 1. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 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)).²⁰

We are similarly unpersuaded by Appellants’ arguments regarding the Ngo article and Fire Article, and how those articles purportedly led away from dsRNAs of 15 to 49 base pairs. Fire teaches and suggests the dsRNA as recited in claim 1, and Appellants’ arguments do not persuade us that Ngo or the Fire Article criticize, discredit, or otherwise discourage the claimed invention. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Mammalian Target Genes

Appellants argue that, while Fire discloses that the cell with the target gene may be derived from a mammal, Fire “does not teach that one strand of

term “target gene” and does not equate that term with the term “*mature mRNA*.” (Ans. 20.)

²⁰ 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 6) applies only to the immediately preceding sentence regarding an alternative functional definition. (Reply Br. 6.) (*See* Fire col. 7, l. 53–col. 8, l. 6.)

the dsRNA is complementary to an RNA transcript of at least part of a mammalian target gene.” (Appeal Br. 15.) Appellants also cite to Fire and “the general understanding in the field” for the proposition that one of ordinary skill would not have been motivated to make (and would have been led away from making) “a dsRNA having one strand that is complementary to an RNA transcript of at least part of a mammalian target gene.” (*Id.* at 16.)

We are not persuaded by Appellants’ arguments. Fire teaches the application of its dsRNA to a mammalian gene. (FF 7.) Appellants rely on the Fire Article as “strongly suggest[ing] that dsRNAs were not functional in mammals” based on the protein kinase response (PKR). (Appeal Br. 16.) Appellants rely on the Sen²¹ article for the elicitation of an interferon response by the introduction of long dsRNA into mammalian cells. (*Id.* at 16–17.) However, as explained by the Examiner, Fire “recognized the PKR issue” and cites to Proud²² (which cites to Manche²³) 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.”²⁴ (Ans. 21–23.) Appellants also point to a

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

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

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

²⁴ 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. 8.) But Proud (which cites to Manche) was incorporated by reference into Fire and

quote from Tuschl²⁵ 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. 16.) 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” a dsRNA strand complementary to an RNA transcript of at least part of a mammalian target gene, particularly given the express teachings of Fire.

Secondary Considerations

Appellants argue that “[t]he fact that a dsRNA of 15 to 49 base pairs in length would be capable of specifically inhibiting expression of a mammalian target gene was unexpected,” citing the Fire Article and Tuschl. (Appeal Br. 17.) 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-mediated inhibition of gene expression in mammals.” (Appeal Br. 17, citing Spec. ¶ 11.)

Based on Fire’s teachings, we are not persuaded that a person of ordinary skill in the art would have found “that a dsRNA of 15 to 49 base pairs in length would be capable of specifically inhibiting expression of a mammalian target gene” 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

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).

²⁵ Tuschl et al., *Targeted mRNA degradation by double-stranded RNA in vitro*, GENES & DEVELOPMENT 13, 3191–97 (1999) (“Tuschl”).

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. Moreover, the dsRNA of claim 1 is taught by Fire and that dsRNA “enclosed by a micellar structure” would have been obvious based on the combination of Fire and Sridhar for the reasons set forth above in connection with the combination of Crooke and Sridhar in Rejection No. 11.

Claim 35

Appellants argue that claim 35 is patentable based on their arguments regarding claim 1 and their arguments that claim 35 limits claim 1. (Reply Br. 9.) Appellants also argue that the references do not teach that “the dsRNA is capable of inhibiting expression of the mammalian target gene upon introduction of the dsRNA into a mammalian cell.” (*Id.*) Appellants argue further that there is no motivation to “to encapsulate a dsRNA of 15 to 49 base pairs in length in a micellar structure.” (*Id.* at 9–10.)

We are not persuaded. Claim 1 is unpatentable for the reasons set forth above and claim 35 does not further limit claim 1 for the reasons set forth above. Moreover, we find Appellants’ argument regarding lack of motivation to encapsulate the dsRNA based on Fire alone or in combination with other references similarly unpersuasive for the reasons set forth above.

Conclusion of Law

A preponderance of evidence of record supports the Examiner’s conclusion that claims 1 and 35 are obvious under 35 U.S.C. § 103(a).

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Claims 2–7, 9–13, and 27–34 were not argued separately and fall with claim 1.

SUMMARY

We affirm all rejections of all claims on appeal.

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