Trials@uspto.gov
Tel: 571-272-7822

Paper 7
Entered: April 6, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BENITEC BIOPHARMA LIMITED,
Petitioner,

v.

COLD SPRING HARBOR LABORATORY
Patent Owner.

Case IPR2016-00017
Patent 8,829,264 B2

Before TONI R. SCHEINER, SHERIDAN K. SNEDDEN, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

SCHEINER, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Benitec Biopharma Limited ("Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1–10 of US 8,829,264 B2 (Ex. 1001; "the '264 patent"). Cold Spring Harbor Laboratory ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 6 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '264 patent. *See* 35 U.S.C. § 314(a). We, therefore, deny the Petition for an *inter partes* review.

a. *Related Proceedings*

In addition to the case before us, Petitioner has requested *inter partes* review of claims 1–10 of US 8,202,846 ("the '846 patent") in IPR2016-00014; claims 1–20 of US 8,383,599 B2 ("the '599 patent") in IPR2016-00015; and claims 1–10 of US 8,153,776 B2 ("the '776 patent") in IPR2016-00016.

The '599 patent issued from a continuation of application No. 10/055,797, filed Jan. 22, 2002. The '846, '776, and '264 patents derive from a continuation-in-part of Application No. 10/055,797 (Application No. 10/997,086, filed Nov. 23, 2004) and share substantially the same specification. Ex. 1001 [63].

b. *Technical Background*

The '264 patent, titled METHODS AND COMPOSITIONS FOR RNA INTERFERENCE, relates to methods for silencing the expression of target genes by RNA interference ("RNAi"). RNAi is part of an endogenous

cellular system in plants and animals that recognizes double stranded RNA ("dsRNA") associated with viral infection, and subsequently targets viral mRNA for degradation or translational silencing. *See, e.g.*, Ex. 1001, 1:43–2:41; Ex. 2001, 363;[1] Ex. 2007, 188.[2] At a high level of generality, a nuclease known as "Dicer" processes long dsRNAs into double-stranded fragments of approximately 21–25 nucleotides in length. *See generally*, Ex. 2018,[3] 442–443; Ex. 1001, 20:14–28, 47–60. The resulting fragments, known as short interfering RNAs ("siRNAs"), are themselves incorporated into an RNA-induced silencing complex ("RISC"). *See* Ex. 2018, 443. One strand of an siRNA incorporated into RISC acts as a guide to direct the RISC/siRNA nuclease complex to a complementary sequence in a target mRNA, where it mediates sequence-specific gene silencing. *Id*.

In addition to the Dicer/RISC pathway, mammalian cells have an additional innate anti-viral response, involving a double-stranded RNA activated protein kinase ("PK"). *See generally* Ex. 1001, 20:67–21:9. As Petitioner points out, however, "PK binds dsRNA and initiates a type of post-transcriptional gene silencing different from RNAi." Pet. 6–7. "PK triggers interferon synthesis, initiates interferon-related cellular immune responses and causes cellular death through apoptotic pathways." *Id*. at 7.

---

[1] Emily Bernstein et al., Role for a bidentate ribonuclease in the initiation step of RNA interference, 409 NATURE 363–364 (2001). Ex. 2001.

[2] Sayda M. Elbashir et al., *RNA interference is mediated by 21- and 22-nucleotide RNAs*, 15 GENES & DEVELOPMENT 188–200 (2001). Ex. 2007.

[3] Prosecution History of U.S. Patent No. 8,202,846. Ex. 2018.

c. *The '264 Patent and Illustrative Claim*

The '264 patent discloses methods for attenuating gene expression in a transgenic mouse using short hairpin RNA ("shRNA") molecules that are processed by Dicer, but do not trigger the PK response ("PKR"). *See* Ex. 1001, 19:39–20:13. Claim 1, the sole independent claim of the patent, is illustrative:

> 1. A transgenic mouse comprising a germline or somatic cell, wherein the germline or somatic cell comprises a transgene, wherein the transgene comprises a sequence encoding a short hairpin RNA (shRNA) molecule,
>
> wherein the shRNA molecule comprises a double-stranded region, wherein the double-stranded region consists of at least 20 nucleotides but not more than 29 nucleotides,
>
> wherein the shRNA molecule is a substrate for Dicer-dependent cleavage and dose not trigger a protein kinase RNA-activated (PK) response in the mammalian cell,
>
> wherein the double-stranded region of the shRNA molecule comprises a sequence that is complementary to a portion of a target gene, and
>
> wherein the shRNA molecule is stably expressed in said germline or somatic cell without use of a PK inhibitor and in an amount sufficient to attenuate expression of the target gene in a sequence specific manner.

d. *Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability.

Claims challenged	Basis	Reference(s)
1–10	§ 102(e)	Zamore[4]

[4] Zamore et al., US 7,691,995 B2, issued Apr. 6, 2010 ("Zamore" or the "Zamore patent"). Ex. 1003.

Claims challenged	Basis	Reference(s)
1–10	§ 102(b)	Graham[5]
1–10	§ 103	Graham and/or Zamore, Tuschl,[6] Fire,[7] Harborth,[8] Parrish,[9] Sijen,[10] Green,[11] Tian,[12] Svoboda,[13] Zernicka-Goetz,[14] and/or Wianny,[15] in view of the knowledge of one skilled in the art

[5] Graham et al., US 6,573,099 B2, issued June 3, 2003. Ex. 1005.

[6] Tuschl et al., US 2002/0085356 A1, published July 4, 2002. Ex. 1007.

[7] Fire et al., US 6,506,559 B1, issued January 14, 2003. Ex. 1006.

[8] Jens Harborth et al., Identification of essential genes in cultured mammalian cells using small interfering RNAs, 114 J. CELL SCI. 4557–4565 (2001). Ex. 1012.

[9] Susan Parrish et al., Functional Anatomy of a dsRNA Trigger: Differential Requirement for the Two Trigger Strands in RNA Interference, 6 MOLECULAR CELL 1077–1087 (2000). Ex. 1010.

[10] Titia Sijen et al., On the Role of RNA Amplification in dsRNA-Triggered Gene Silencing, 107 CELL 465–476 (2001). Ex. 1011.

[11] Simon R. Green & Michael B. Mathews, *Two RNA-binding motifs in the double-stranded RNA-activated protein kinase, DAI*, 6 GENES & DEVELOPMENT 2478–2490 (1992). Ex. 1008.

[12] Bin Tian et al., Expanded CUG repeat RNAs form hairpins that activate the double-stranded RNA-dependent protein kinase PKR, 6 RNA 79–87 (2000). Ex. 1009.

[13] Petr Svoboda et al., *RNAi in Mouse Oocytes and Preimplantation Embryos: Effectiveness of Hairpin dsRNA*, 287 BIOCHEM & BIOPHYS. RES. COMM. 1009–1104 (2001). Ex. 1018.

[14] Zernicka-Goetz et al., US 2003/0027783 A1, published Feb. 6, 2003. Ex. 1019.

[15] Florence Wianny & Magdalena Zernicka-Goetz, *Specific interference with gene function by double-stranded RNA in early mouse development*, 2 NATURE CELL BIO. 70–75 (2000). Ex. 1020.

ANALYSIS

a. *Claim Construction*

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275–79 (Fed. Cir. 2015), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention,[16] in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed, however, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

In the present matter, the parties do not dispute the meaning of any claim term nor, for the purposes of our decision, do we find that any term requires express construction. *See* Pet. 5; Prelim. Resp. 9.

b. *Anticipation by Zamore (Ex. 1003)*

Petitioner asserts that claims 1–10 of the '264 patent are anticipated by the Zamore patent under 35 U.S.C. § 102(e). Pet. 25–41. Patent Owner

[16] Patent Owner adopts, as do we, Petitioner's definition of a person of ordinary skill in the art as "'a graduate or post-graduate student in the life sciences field, or have a Master's degree or Ph.D. in molecular biology, microbiology, biochemistry, chemistry or a related discipline.'" Prelim. Resp. 9 (quoting Pet. 4).

contends that Zamore does not qualify as prior art under § 102(e) because none of the issued claims of the Zamore patent is supported by US Provisional Application No. 60/305,185 ("the '185 provisional application" (Ex. 1004)). Prelim. Resp. 25–28. On the record before us, we agree with Patent Owner.

Petitioner and Patent Owner agree that the effective filing date of the '264 patent is January 22, 2002. *See* Ex. 1001, 1; Pet. 4–5; Prelim. Resp. 28. Zamore issued from a non-provisional application filed on July 12, 2002, and claimed benefit of priority under 35 U.S.C. § 119(e) of the '185 provisional application, filed on July 12, 2001. Ex. 1003, [21], [22], [60], 1:5–7. Accordingly, Zamore is only available as prior art under § 102(e) if Petitioner can show that Zamore is entitled to the earlier filing date of the '185 provisional application. To make such a showing, Petitioner must demonstrate that the '185 provisional application provides written description support for at least one claim of the Zamore patent. *See, e.g.*, *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1381 (Fed. Cir. 2015) ("A reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with § 112 ¶ 1.").

The claims of the Zamore patent are generally directed to nucleic acids "capable of inducing RNA interference (RNAi) in a mammalian cell in vivo." *See* Ex. 1003, claim 1. Independent claims 1 and 41 require first and second stem portions comprising complementary RNA sequences of "about 18 to about 40 nucleotides." *Id*. at claim 1, 41. Various dependent claims further recite stem portions of "18 to 40 nucleotides" (*id*. at claim 20, 58),

"22 to 28 nucleotides" (*id*. at claim 21, 59), "18 to 30 nucleotides" (*id*. at claim 22), and "18 to 40 nucleotides" (*id*. at claim 58). The Zamore '185 provisional application, on the other hand, describes stem portions of "19 to 22," "21 or 22," and "21 or 40" nucleotides in length. Ex. 1004, 2, 7. For the reasons discussed on pages 25 through 27 of Patent Owner's Preliminary Response, we agree that these disclosures do not provide written description support for the ranges claimed in the issued patent.

Zamore was squarely before the Examiner during the prosecution leading to the issuance of the '264 patent (as it had been during prosecution of the closely related '864 patent). *See* Ex. 1002, 480; Ex. 2018, 1001–1009, 1019–1022, 1039–1052. Petitioner's position appears to be that the Examiner erred in allowing the '264 patent over Zamore because the '185 provisional application inherently discloses the minimum length of dsRNA known in the art to trigger the PK response. *See* Pet. 23, 26–30. In particular, at page 27 of the Petition, Petitioner cites a portion of the '185 provisional application, which reads as follows:

> Another defining feature of these engineered RNA precursors is that as a consequence of their length, sequence, and/or structure, they do not induce sequence non-specific responses such as induction of the interferon response or apoptosis, or that they induce a lower level of such sequence non-specific responses than long, double stranded RNA (>150 bp) currently used to induce RNAi.

Ex. 1004, 8:11–15.

In light of this statement, Petitioner argues that

> [O]ne of ordinary skill in view of the cited teachings and knowledge in the art would understand that in the '185 provisional (Ex. 1004[)], Zamore had possession of the means to avoid PKR when utilizing the gene silencing technology, based on his reference to the "length, sequence, and/or structure" of the

> constructs (Ex. 1004, 8:11) and their effect on "induction of the interferon response" (Ex. 1004, 8:13).

Pet. 26.

"[T]he hallmark of written description is disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Id.* No particular form of disclosure is required, but "a description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352. To find an element inherently disclosed demands that "the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added).

In the present case, Petitioner presents no expert opinion with respect to the understanding of one of ordinary skill in the art, much less with respect to the disclosure of the Zamore '185 provisional application. Petitioner's assertion that "Zamore had possession of the means to avoid PKR when utilizing the gene silencing technology, based on his reference to the 'length, sequence, and/or structure' of the constructs . . . and their effect on 'induction of the interferon response'" (Pet. 26) fails to convince us that one of ordinary skill in the art would understand that the '185 provisional application inherently discloses the ranges claimed in the Zamore patent. Accordingly, we are not persuaded that the Zamore patent qualifies as prior

art under 35 U.S.C. § 102(e). Absent such a showing, Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '264 patent based on this reference.

c. *Anticipation by Graham (Ex. 1005)*

Petitioner further contends that Graham anticipates claims 1–10 of the '264 patent under 35 U.S.C. § 102(b). Pet. 9–25; *see also id*. at 16 ("Petitioner asserts that all elements of claim 1 are described and inherently present in Graham.").

Graham discloses "synthetic genes and genetic constructs which are capable of repressing[,] delaying[,] or otherwise reducing the expression of . . . a target gene in an organism." Ex. 1005, Abstract; *see id*. at 2:8–22. Graham teaches that synthetic genes comprise at least one "structural gene component" that is substantially identical to at least about 30 contiguous nucleotides of an endogenous or other target gene. *Id*. 5:7–20, 6:18–24. Graham further states that "[p]referred structural gene components . . . comprise at least about 20–30 nucleotides in length derived from [a target gene]." *Id*. at 6:25–40.

Graham teaches that a synthetic gene may comprise multiple structural gene sequences that are "substantially identical to the nucleotide sequence of the target gene . . . or a complementary sequence thereto." *Id*. at 9:53–63.

> Accordingly, a multiple structural gene sequence may comprise a tandem repeat or concatemer of two or more identical nucleotide sequences or alternatively, a tandem array or concatamer of non-identical nucleotide sequences, the only requirement being that each of the structural gene sequences

> contained therein is substantially identical to the target gene sequence or a complementary sequence thereto.

Id. at 9:67– 10:7.

Patent Owner argues that Graham contains "no disclosure of a transgenic mouse nor any data regarding attenuating expression of a target gene in a mammalian cell" (Prelim. Resp. 15) and, thus, fails to disclose a transgenic mouse comprising a germline or somatic cell molecule wherein an shRNA molecule is "stably expressed in in said germline or somatic cell in an amount sufficient to attenuate expression of [a] target gene in a sequence specific manner" as required by independent claims 1 and 6. *See* Prelim. Resp. 16–17.

Graham discloses specific constructs designed to express synthetic genes using genetic elements known to be active in eukaryotic cells. *See, e.g.*, Ex. 1005, 17:39–51 ("Plasmid pEGFP.BEV.1 (FIG. 9) is capable of expressing the BEV polymerase structural gene as a GFP fusion polypeptide under the control of the CMV-IE promoter sequence."); *see id*. at 8:4–34. Petitioner, however, points to no evidence indicating that such constructs were introduced into mammalian cells; nor do we discern in Graham any evidence that the disclosed constructs were successfully expressed in mammalian cells, or that they subsequently produced a measurable effect on a target gene in accord with the claim language.

Based on our review of the record to date, we acknowledge the substantial complexity of the subject matter[17] and unpredictability of the art.

---

[17] *See e.g.*, Ex. 2005 ¶ 43 (cited in full, *supra*) ("Further evidence of the non-obviousness of the Hannon et al. invention is evidenced in the complicated nature of the methods provided in the cited references.").

See Mycogen Plant Sci. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001) (recognizing the unpredictability of the biological arts); *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) (2008) (contrasting predictable factors involving mechanical or electrical elements with "cases involving unpredictable factors, such as most chemical reactions and physiological activity"). Given this subject matter, and Petitioner's lack of testimonial evidence, we do not find that Petitioner has established that Graham expressly or inherently discloses a transgenic mouse comprising a germline or somatic cell molecule wherein an shRNA molecule is "stably expressed in in said germline or somatic cell in an amount sufficient to attenuate expression of [a] target gene in a sequence specific manner" as required by claims 1 and 6. For at least this reason, Petitioner has not established that Graham anticipates the challenged claims.

Patent Owner further argues that Graham fails to disclose "using a short hairpin RNA molecule to attenuate expression of a target gene in a mammalian cell," and fails to disclose "a double stranded region of a RNA hairpin molecule consisting of at least 20 nucleotides but not more than 29 nucleotides" complementary to a portion of the target gene. *See* Prelim. Resp. 15, 18–22. With respect to the limitations of the required hairpin RNA, we agree with Patent Owner's reasoning as set forth on pages 18–23 of the Preliminary Response. For the sake of brevity, however, we focus on Petitioner's assertion that "Graham discloses a silencing construct having short hairpin RNA, with duplex regions at least 20 [nucleotides] and not more than 29 [nucleotides] in length." Pet. 11. To support this assertion, Petitioner relies on statements in the following passage from Graham:

> The optimum number of structural gene sequences which may be involved in the synthetic gene of the present invention will vary considerably, depending upon the length of each of said structural gene sequences, their orientation and degree of identity to each other. For example, those skilled in the art will be aware of the inherent instability of palindromic nucleotide sequences in vivo and the difficulties associated with constructing long synthetic genes comprising inverted repeated nucleotide sequences, because of the tendency for such sequences to form ***hairpin*** loops and to recombine in vivo. Notwithstanding such difficulties, the optimum number of structural gene sequences to be included in the synthetic genes of the present invention may be determined empirically by those skilled in the art, without any undue experimentation and by following standard procedures such as the construction of the synthetic gene of the invention using recombinase deficient cell lines, reducing the number of repeated sequences to a level which eliminates or minimizes recombination events and by keeping the total length of the multiple structural gene sequence to an acceptable limit, preferably no more than 5–10 kb, more preferably no more than 25 kb and even more preferably no more than 0.5–2.0 kb in length.

Ex. 1005, 10:22–44 (emphasis added); *see* Pet. 11–12, 14.

The above passage contains Graham's sole reference to a "hairpin." Given the evidence of record, we agree with Patent Owner that Graham's discussion of "hairpin loops" refers to *a problem* that may occur when using inverted repeat sequences. *See* Prelim. Resp. 19–21. Thus, rather than disclosing the use of such structures for attenuating expression of a target gene, Graham teaches that hairpin loops should be avoided. Petitioner presents no evidence suggesting that one of ordinary skill in the art would read Graham in any other way. Accordingly, Petitioner fails to show that Graham discloses the use of a short hairpin RNA molecule comprising "a double-stranded region, wherein the double-stranded region consists of at

least 20 nucleotides but not more than 29 nucleotides" and "wherein the double-stranded region of the shRNA molecule comprises a sequence that is complementary to a portion of the target gene," as required by the challenged claims. This provides an independent reason why Petitioner has not established a reasonable likelihood that it would prevail in showing the at least one challenged claim of the '264 patent is anticipated by Graham.

d. *Obviousness in view Graham and/or Zamore, Tuschl, Fire, Harborth, Parrish, Sijen, Green, Tian, Svoboda, Zernicka-Goetz, and/or Wianny*

> Petitioner contends that claims 1–10 of the '264 patent
>
> are rendered obvious by a combination of Graham (Ex. 1005) and/or Zamore (Ex. 1003), in view of a combination of Tuschl (Ex. 1007), Fire (Ex. 1006), Harborth (Ex. 1012), Parrish (Ex. 1010), Sijen (Ex. 1011), Green (Ex. 1008), Tian (Ex. 1009), Svoboda (Ex. 1018) Zernicka-Goetz (Ex. 1019), and/or Wianny (Ex. 1020) in view of the knowledge of one skilled in the art pursuant to 35 U.S.C. § 103.

Pet. 3–4.

Zamore is discussed above in the context of anticipation. Because Petitioner does not persuade us that Zamore qualifies as prior art, we do not consider it further. With respect to the remaining references, Petitioner argues the obviousness of claims 1–10 of the '264 patent based on Graham (*id*. at 45–46); Graham and Tuschl (*id*. at 47–48); Graham and Fire (*id*. at 48–51); Graham, Tuschl, and/or Fire, Svoboda, Zernicka-Goetz, and/or Wianny (*id*. at 51–54), Graham, Tuschl, and/or Fire and Parish, Sijen, and Harborth (*id*. at 54–57); Graham, Tian, and/or Green (*id*. at 57); Graham, Tian, and/or Green, and Svoboda, Zernicka-Goetz, and/or Wianny, and Tuschl, Fire, Parrish, Sijen, and/or Harborth (*id*. at 58–59).

Patent Owner contends that Petitioner's "kitchen sink" approach

obscures the bases for the underlying obviousness challenge and, thus, requests that we deny the Petition as violating the particularity provisions of 35 U.S.C. § 312(a)(3) and 37 C.F.R. § 42.22(a)(2). Prelim. Resp. 35; *see also* 37 C.F.R. § 42.104(b)(4) and 42.104(b)(5). Patent Owner's position is not without merit. "Vague arguments and generic citations to the record are fundamentally unfair to an opponent and do not provide sufficient notice to an opponent and creates inefficiencies for the Board." 77 Fed. Reg. 48,620. We, nevertheless, address Petitioner's arguments to the extent we discern them.

i. Graham

Petitioner relies on Graham as teaching shRNAs, in particular, "short dsRNA constructs for gene silencing" (Pet. 45 (citing Ex. 1005, 6:25–40, 10:22–32)), and the "desirability of using short hairpin sequences to avoid unwanted cellular responses" (*id*. at 46 (citing Ex. 1005, 6:25–40)). As discussed above in the context of anticipation, however, Graham teaches that the potential of hairpin formation was a problem to be solved. Indeed, rather than teaching the "desirability" of using hairpin sequences, as Petitioner contends, Graham indicates that hairpins should be avoided and, thus, teaches away from the use of shRNAs for gene silencing in mammalian cells. Accordingly, Graham does not teach or suggest the use of "a sequence encoding a short hairpin RNA (shRNA) molecule . . . compris[ing] a double-stranded region, wherein the double-stranded region consists of at least 20 nucleotides but not more than 29 nucleotides," as required by claims 1 and 6.

As we understand the Petition, however, Petitioner additionally relies on Svoboda, Zernicka-Goetz, and Wianny as teaching gene silencing in transgenic animals using shRNAs (Pet. 41–43, 46–50), and further relies on

Tuschl, Fire, and Parrish as teaching the length of gene silencing shRNAs (*id.* at 41–43, 51–54).

ii. Svoboda (Ex. 1018), Zernicka-Goetz (Ex. 1019), and Wianny (Ex. 1020)

Petitioner contends that each of Svoboda, Zernicka-Goetz, and Wianny "itself renders obvious claim 1 and 6 with regards to teaching germline or somatic cells comprising a transgene, wherein the transgene comprises a sequence encoding a short hairpin RNA (shRNA) molecule wherein the cells are in transgenic mice." Pet. 51, 52, 53.

Svoboda discloses that "RNA interference (RNAi), the targeted mRNA degradation by double-stranded RNA (dsRNA), is a useful tool for studying gene function in several organisms." Ex. 1018, 1099. Svoboda further discloses that "experiments indicated that . . . hairpin dsRNA was just as effective as dsRNA (i.e., annealed sense and antisense RNA) in promoting the destruction of targeted mRNA." *Id.* Nevertheless, Petitioner does not explain sufficiently how Svoboda teaches or suggests a transgene comprising a "short" hairpin RNA molecule. Rather, according to Patent Owner, "Svoboda discloses a long hairpin RNA molecule with a double-stranded region of **535 base pairs**." PO Resp. 46 (citing Ex. 1018, 1099 ("An inverted repeat (IR) from the *mos* gene was created by self-ligating the previously described 535 bp *mos* PCR product.").

Zernicka-Goetz discloses inhibiting the expression of a target gene in a mammalian cell or transgenic mouse embryo by "introducing . . . an RNA comprising a double stranded structure having a nucleotide sequence which is substantially identical to at least a part of the target gene." Ex. 1019 ¶¶ 11–13. Again, Petitioner has not established sufficiently that Zernicka-

Goetz teaches or suggests a transgene comprising a short hairpin RNA molecule, as Petitioner does not explain how or why Zernicka-Goetz's "RNA comprising a double-stranded structure" (Pet. 53 (citing Ex. 1019 ¶¶ 11–13)) has a hairpin structure.

Wianny reports that double-stranded RNA "is effective as a specific inhibitor of the function of three genes in the mouse, namely maternally expressed c-*mos* in the oocyte and zygotically expressed *E-cadherin* or a *GFP* transgene in the preimplantation embryo." Ex. 1020, Abstract. Again, Petitioner has not established sufficiently that Wianny teaches or suggests a transgene comprising a short hairpin RNA molecule, as Petitioner does not explain how or why Wianny's dsRNA, comprising "anneal[ed] sense and antisense RNA[]" (*Id.* at 74) constitutes a hairpin structure.

Accordingly, we are not persuaded that Svoboda, Zernicka-Goetz, and Wianny remedy the deficiencies of Graham, even when considered in combination with Tuschl, Fire, and Parrish, discussed below.

iii. Parrish (Ex. 1010)

Petitioner contends that "Parrish (Ex. 1010) itself renders obvious claims 1–4 and 6–9 relative to the sizes of the dsRNA, silencing of homologous target genes, processing through the Dicer pathway, and the lack of use of a PK inhibitor." Pet. 55.

Nevertheless, Petitioner does not explain how Parrish teaches or suggests the use of short hairpin RNA in any context. Parrish teaches that double-stranded RNA molecules as short as 26 bp can trigger RNAi when injected into *Caenorhabditis elegans*, a non-mammalian organism that does not employ the PK response. *See* Ex. 1010, Abstract, 1 ("In mammalian cells, dsRNA is associated with a sequence-nonspecific response that

includes induction of interferon, phosphyorylation of translation initiation factor eIF2 (which leads to a general block in translation) an induction of a 2'-5' oligoadenylate synthase (which can stimulate the RNA degrading enzyme RNase I) [].").[18]

With respect to the claim limitation "a sequence encoding a short hairpin RNA (shRNA) molecule, wherein the shRNA molecule comprises a double-stranded region . . . consist[ing] of at least 20 nucleotides but not more than 29 nucleotides," Petitioner relies on, for example, the Abstract and page 2, lines 17–18 of Parish. Pet. 55. Although Petitioner's selected passages refer to the length of duplex RNA fragments that may trigger RNAi, none refer to or suggest shRNA. At best, Figure 2 of the reference, which Petitioner does not rely on, indicates that injecting *C. elegans* with stem-loop molecules having a very long double-stranded region ("corresponding to the entire 717 base *gfp* coding region") triggered the RNAi response. *See* Ex. 1010, Fig. 2, 1079.

In sum, Petitioner has not shown that Parrish teaches or suggests the use of shRNA in mammalian cells; or that one of ordinary skill in the art reading Parrish would have been motivated to use a stem-loop molecule of any dimension in mammalian cells as set forth in the challenged claims with a reasonable expectation of success.

iv. Tuschl (Ex. 1007)

Tuschl demonstrates that long double-stranded RNA molecules are

---

[18] Although we stop short of finding that Parrish teaches away from the use of dsRNA in mammalian cells, we disagree with Petitioner's unsupported assertion that "Parrish provides motivation to employ short dsRNA to avoid PKR." *See* Pet. 56.

processed to shorter sequences of 21 to 23 nucleotides in length, which can mediate RNAi in vitro. Ex. 1007, Abstract. Tuschl states that "[u]se of long dsRNAs in mammalian cells to elicit RNAi is usually not practical, presumably because of the deleterious effects of the interferon response," but suggests, instead, that these 21 to 23 nucleotide fragments may be used to inactivate gene function. *Id*. ¶ 53.

Tuschl demonstrates that the transfection of chemically synthesized 21 nucleotide siRNA duplexes into mammalian cells specifically suppressed reporter gene expression without activating the interferon response (*see id.* ¶ 145), which, as Patent Owner notes, pertains to post-Dicer RNA-mediated interference (*see* Prelim. Resp. 39–40). Petitioner does not convince us that Tuschl provides any guidance for using siRNA as "a substrate for Dicer-dependent cleavage" as required by the challenged claims. In addition, as with Parish, Tuschl does not teach or suggest use of "a sequence encoding a short hairpin RNA (shRNA) molecule, wherein the shRNA molecule comprises a double-stranded region . . . consist[ing] of at least 20 nucleotides but not more than 29 nucleotides," for attenuating expression of a target gene in a mammalian cell, as required by claims 1 and 6.

v. Fire (Ex. 1006)

Fire discloses sequence-specific inhibition of a target gene using double-stranded RNA "formed by a single self-complementary RNA strand or two complementary RNA strands." *See* Ex. 1006, Abstract, 4:41–46, 6:32–43, 7:42–52. Fire teaches that, "RNA containing a [sic] nucleotide sequences identical to a portion of the target gene are preferred for inhibition" (*id*. at 7:53–54) and that "[t]he length of the identical nucleotide sequences may be at least 25, 50, 100, 200, 300 or 400 bases" (*id*. at 8:5–6).

As we understand Petitioner's argument, Petitioner relies on these teachings to assert that Fire teaches or suggests the use of "a sequence encoding a short hairpin RNA (shRNA) molecule, wherein the shRNA molecule comprises a double-stranded region . . . consist[ing] of at least 20 nucleotides but not more than 29 nucleotides," for attenuating expression of a target gene in a mammalian cell. *See* Pet. 41–43, 48–51. In applying the reference, however, Petitioner's implication is that the Examiner was wrong to withdraw a rejection over Fire during the prosecution leading to the issuance of the '846 patent. We are not persuaded.

In distinguishing an obviousness rejection involving Fire during prosecution of the '846 patent, Applicants argued that

> Fire lacks any disclosure of a short hairpin RNA molecule as presently claimed, that is, a single-stranded RNA molecule comprising a double-stranded region having a length of at least 20 nucleotides but not more than 29 nucleotides. The Examiner erroneously alleges that Fire discloses the length of the dsRNA region "to be at least 25 bases in length." However, the language to which the Examiner expressly refers states only that "the length of *the identical nucleotide sequences* may be at least 25, 50, 100, 200, 300 or 400 bases." (Fire, 8:5-6, emphasis added.) The language makes no reference whatsoever to the length of the double-stranded region. The italicized phrase above refers back to sentence at 7:53-54 which recites "nucleotide sequences identical to a portion of the target gene ..." This sentence does not refer to the length of the double-stranded region of a hairpin, but rather refers to the sequence that is identical to a portion of the target gene.

Ex. 2018, 892–893.

Applicants further relied on the Hernandez Declaration,[19] which stated that, "a person of ordinary skill would have had no reasonable expectation that one could successfully carry out sequence specific gene silencing by using an expression vector encoding a short hairpin RNA molecule having a double stranded region consisting of 20 to 29 base pairs (bp)." Ex. 2018, 777–778, 893–895; *see also* Ex. 2005 ¶ 8 (same).[20, 21] Dr. Hernandez based this conclusion, in part, on "the leading literature in the field [, which] would have taught away from using an expressed short hairpin molecule, which to have gene silencing activity, must first be processed in the cell." Ex. 2018, 778; Ex. 2005 ¶ 8. Dr. Hernandez stated, for example, that "Elbashir et al. (2001) Genes Dev. 15:188–200 discourages the use of RNA precursors comprising double-stranded regions of shorter than 38 bp in length as a means of attenuating target genes through RNAi." Ex. 2018, 779. "In particular, the authors conclude that '[s]pecific inhibition of target RNA expression was detected for dsRNA as short as 38 bp, but dsRNAs of 29–36 bp were not effective in this process.'" *Id*. (quoting Ex. 2007 at 189).

---

[19] Declaration of Professor Nouria Hernandez, Ph.D., submitted under 37 C.F.R. § 1.132, dated October 29, 2009. Ex. 2018, 776–782.

[20] Second Declaration of Professor Nouria Hernandez, Ph.D., submitted under 37 C.F.R §1.132. Ex. 2005.

[21] As indicated in the second Hernandez Declaration (Ex. 2005), the Declaration was filed in App. No. 11/894,676, which issued as US 8,153,776 B2, and was before the Examiner in the prosecution leading to the issuance of the '846 patent as evidenced by repeated references to the document during prosecution (Ex. 2018, 958–959, 1040, 1045, 1047, 1048, 1050, 1051), including during the March 22, 2011, interview with Examiners from multiple related cases (*see id*. at 955, 958–959, 964, 968).

In a subsequent Declaration, Dr. Hernandez expanded on her understanding of the state of the art and the perspective of one of ordinary skill in the art, concluding that,

> the methods for attenuating target gene expression as recited in the claims of Hannon et al. would not have been obvious in view of the art. It would have been backwards and contrary to the Elbashir paper's text for a person of ordinary skill in the art to interpret the negative results in Elbashir, as somehow indicating the complete opposite, that is, as providing any reasonable expectation that a dsRNA shorter than 29 bp could serve as an RNAi trigger.

Ex. 2005 ¶ 13.

Petitioner does not directly address the Hernandez Declarations. At best, Petitioner attempts to counter Dr. Hernandez's evidence of teaching away by arguing that the Examiner overlooked that the patent claims are merely "reflective of an inherent property of the mammalian cellular response to dsRNA" (Pet. 40), and that Tuschl, Parrish, Sijen, Harborth, Zamore, and Graham taught that dsRNAs shorter than 29 bp in length were effective as pre-Dicer triggers (*id*. at 48).

Parrish, Zamore, and Graham, have been discussed above. Sijen observes gene silencing in response to dsRNA molecules injected into or fed to *C. elegans*. *See, e.g.*, Ex. 1011, Fig. 6B, 472. As Patent Owner points out, Petitioner's citations to statements in Sijen relate to *C. elegans*, which does not have a PK response. *See* Prelim. Resp. 49. Harborth notes that "[m]ammalian cells were until recently not amenable to RNAi since use of in vitro transcribed, long dsRNAs (> 30 bp) led to activation of a global, sequence unspecific response." Ex. 1012, 4557. Harborth avoids this problem by transfecting 21 nucleotide double-stranded RNAs into cultured cells to "knock down" the expression of target genes. *Id*. at Abstract, 4558.

To the extent Petitioner relies on the teachings of certain recited references, we are not convinced of their relevance as compared to, for example, Elbashir. In contrast to Petitioner's evidence, the Hernandez Declarations are based on the perspective of one of ordinary skill in the art and "the leading literature in the field." *See, e.g.*, Ex. 1002, 777–778; Ex. 2005 ¶¶ 5, 8. Accordingly, Petitioner presents insufficient evidence to convince us that the Examiner erred in relying on the Hernandez Declarations with respect to Fire and, more broadly, with respect to whether one of ordinary skill in the art would have been motivated to combine Fire with other asserted references with a reasonable expectation of success in arriving at the claimed invention. Petitioner has, therefore, failed to established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '264 patent based on the combination of Fire and any of the other cited references.

vi. Green (Ex. 1008) and Tian (Ex. 1009)

Petitioner generally cites Green (Ex. 1008) and Tian (1009) as evidence that "to avoid PKR, the prior art fully disclosed that fragment length must be kept shorter than 30 bases in length." Pet. 7, 42, 44, 53, 54, 57. Green teaches that the protein kinase DAI is an essential component of the PK response. Ex. 1008, Abstract. "DAI interacts with dsRNA in a length-dependent fashion: Duplexes of ≥85 bp bind DAI and activate the enzyme as efficiently as very long natural dsRNAs; short duplexes of ≤30 bp bind and activate the enzyme very weakly." *Id*. at 2483.

Tian teaches that myotonic dystrophy is caused by expanded CTG repeat sequences in the DMPK gene and notes that the CUG repeats in the resulting RNA bind to the dsRNA-binding domain of PKR. Ex. 1009,

Abstract. Although Petitioner states that "Tian is particularly notable as it describes hairpin RNA structures as PKR triggers" (Pet. 57), Petitioner's claim chart does not cite Tian as teaching or suggesting "a sequence encoding a short hairpin RNA (shRNA) molecule, wherein the shRNA molecule comprises a double-stranded region, wherein the double-stranded region consists of at least 20 nucleotides but not more than 29 nucleotides," as recited in claims 1 and 6 (*see id*. at 42, 43).

Petitioner argues that Tian, "renders obvious claims 1 and 6 with regards to PKR triggers [, and] the length of hairpin dsRNA required to initiate PKR." Pet. 58. With respect to these elements, Tian states that "[t]he threshold for *binding* to PKR is ~15 CUG repeats, and the affinity increases with longer repeat lengths." Ex. 1009, Abstract (emphasis added). In contrast, "the shortest [CUG] polymers that *activate* PKR were 105 [nucleotides] (35 repeats), and longer versions were increasingly effective (Fig. 6)." *Id*. at 83 (emphasis added). As Tian makes clear that binding does not equate to activation, we find unsupported Petitioner's conclusion that "Tian evidences from 2000 onward, short hairpin duplex RNAs greater than 30 bases in length were understood to be PKR triggers." Pet. 59.

Neither Green nor Tian are directed to the design of constructs for RNA interference, and Petitioner does not convince us that one of ordinary skill in the art would look to these articles in designing an shRNA having the characteristics set forth in the challenged claims. To the extent the skilled artisan would have done so, alone or in combination with other cited references, Petitioner provides no evidence of reasonable expectation of success in achieving the claimed invention.

In light of the above, we find that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the ’264 patent based on any combination of Graham and/or Zamore, Tuschl, Fire, Harborth, Parrish, Sijen, Green, Tian, Svoboda, Zernicka-Goetz, and/or Wianny.

CONCLUSION

Petitioner has failed to establish a reasonable likelihood that it would prevail in showing that any of claims 1–10 of the ’264 patent are unpatentable in view of the asserted references.

ORDER

Accordingly, it is

ORDERED that the Petition is *denied* as to all challenged claims of the ’264 patent.

PETITIONER:

Lisa A. Haile
John M. Garvey
DLA Piper LLP
Benitec-IPR@dlapiper.com

PATENT OWNER:

Michael Siekman
Patricia Granahan
Oona Johnstone
WOLF, GREENFIELD & SACKS, PC
MSiekman-PTAB@wolfgreenfield.com
PGranahan-PTAB@wolfgreenfield.com
OJohnstone-PTAB@wolfgreenfield.com