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Paper 8
Entered: March 31, 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 IPR2016-00016
Patent 8,153,776 B2

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

SNEDDEN, *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 8,153,776 B2 (Ex. 1001; "the '776 patent"). Cold Spring Harbor Laboratory ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 7 ("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 '776 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 B2 ("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 8,829,264 B2 ("the '264 patent") in IPR2016–00017.

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.

b. Technical Background

The '776 patent 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, 1:20–2:18; 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. 1002,[3] 722–727; Ex. 1001, 19:51–65, 20:17–30. The resulting fragments, known as short interfering RNAs ("siRNAs"), are themselves incorporated into an RNA-induced silencing complex ("RISC"). *See* Ex. 1002, 722–724. 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*, *id.* at 722–727; Ex. 1001, 20:37–46. As Petitioner points out, however, "PK binds dsRNA and initiates a type of post-transcriptional gene silencing different from RNAi." Pet. 6. "PK triggers interferon synthesis, initiates interferon-related cellular immune responses and causes cellular death through apoptotic pathways." *Id*. at 6–7.

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[1] Emily Bernstein et al., *Role for a Bidentate Ribonuclease in the Initiation Step of RNA Interference*, 409 NATURE 363 (2001).
[2] Sayda M. Elbashir et al., *RNA Interference Is Mediated by 21- and 22-Nucleotide RNAs*, 15 GENES & DEV. 188 (2001).
[3] Prosecution History of U.S. Patent No. 8,153,776.

c. The '776 patent and Representative Claim

The '776 patent discloses methods for attenuating gene expression in a mammalian cell using short hairpin RNA ("shRNA") molecules that are processed by Dicer, but do not trigger the PK response ("PKR"). *See* Ex. 1001, 19:9–50. Claim 1, the sole independent claim of the patent, recites:

> 1. A method for attenuating expression of a target gene in a mammalian cell, the method comprising
>
> introducing into mammalian cells a library of RNA expression constructs, each expression construct comprising:
>
> (i) an RNA polymerase promoter, and
>
> (ii) a sequence encoding 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,
>
> wherein the short hairpin RNA molecule is a substrate for Dicer-dependent cleavage and does not trigger a protein kinase RNA-activated (PKR) response in the mammalian cell,
>
> wherein the double-stranded region of the short hairpin RNA molecule comprises a sequence that is complementary to a portion of the target gene, and
>
> wherein the short hairpin RNA molecule is stably expressed in the mammalian cell in an amount sufficient to attenuate expression of the target gene in a sequence specific manner, and is expressed in the cell without use of a PK inhibitor, whereby expression of the target gene is inhibited.

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. 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] Waterhouse,[13] and/or Symonds,[14] in view of the knowledge of one skilled in the art

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*

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[5] Graham, US 6,573,099 B2, issued June 3, 2003. Ex. 1005.
[6] Tuschl et al., US 2002/0086356 A1, published Jul. 4, 2002. Ex. 1007.
[7] Fire et al., US 6,506,559 B1, issued Jan. 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 (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 (2000). Ex. 1010.
[10] Titia Sijen et al., *On the Role of RNA Amplification in dsRNA-Triggered Gene Silencing*, 107 CELL 465 (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 & DEV. 2478 (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 (2000). Ex. 1009.
[13] Peter M. Waterhouse et al., *Gene Silencing As an Adaptive Defense Against Viruses*, 411 NATURE 834 (2001). Ex. 1013.
[14] Symonds et al., US 7,345,025 B2, issued Mar. 18, 2008. Ex. 1015.

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