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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MATTHIAS SCHROFF [1]

Appeal 2016-007660
Application 11/569,697
Technology Center 1600

Before TONI R. SCHEINER, ULRIKE W. JENKS, and ELIZABETH A. LAVIER, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) from the final rejection of claims 16 and 18–31, directed to a DNA construct for specific inhibition of gene expression by RNA interference. The claims have been rejected on the grounds of indefiniteness, anticipation, and obviousness.

We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] Appellant identifies the Real Party in Interest as Mologen AG of Berlin, Germany. Br. 2.

BACKGROUND

The Specification is directed to a DNA vector free of plasmid or viral components, which, when transcribed, results in expression of a small interference RNA (siRNA) sequence (Spec. 7:8–9), i.e., "a double-stranded RNA molecule in which the pairing strands are linked on one side by a non-complementary single strand" (*id.* at 4:7–9).

> [The DNA vector] is capped by hairpin loop-shaped oligodeoxynucleotides having arranged therebetween a promoter at the 5′ end and a termination signal at the 3′ end of a double DNA strand, said DNA double strand including a singular copy 19–23 bases in length of a gene sequence, once in 5′–3′ direction and once in a 3′–5′ direction, a sequence 8–12 bases in length of two single strands being arranged between each 5′–3′ and 3′–5′ orientation of the singular copy of the gene sequence, said single strands being selected such that opposite bases are by no means complementary to each other and the flanking double strand regions are thereby linked to each other by two DNA single strands.

Id. at 6:27–7:4.

"[F]ollowing transfection thereof in eukaryotic cells, [the vector is] suitable for targeted inhibition of formation of defined proteins therein by RNA interference." *Id.* at 1:9–11.

STATEMENT OF THE CASE

Claims 16 and 18–31 are on appeal.[2] Independent claim 16 is representative and reads as follows (emphasis added):

> 16. A vector which, following transfection thereof into eukaryotic cells, specifically inhibits formation of defined proteins therein by RNA interference comprising:

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[2] Claims 1–15 have been withdrawn from consideration, and claim 17 has been cancelled.

two hairpin loop-shaped oligodeoxynucleotides having arranged between said two hairpin loop-shaped oligodeoxynucleotides a promoter at a 5' end and a termination signal at a 3' end of a DNA double strand, said DNA

double strand comprising between said promoter and termination signal, a first gene sequence consisting of 19–23 bases, wherein said first gene sequence forms a first double stranded region in 5'–3' direction and a second gene sequence consisting of said 19–23 bases in 3'–5' direction, wherein said second gene sequence forms a second double stranded region, *wherein the vector further comprises two single DNA strands linking said first double stranded region with said second double stranded region comprising 8–12 bases, said two single DNA strands being not complementary to each other and not self-complementary* and wherein

said first double stranded region and second double stranded region have short protruding ends of single-stranded DNA at their ends, and

said hairpin loop-shaped oligodeoxynucleotides have short protruding ends of single-stranded DNA at their ends, and

said promoter has short protruding ends of single-stranded DNA,

a single-stranded 5' end of the promoter being capable of pairing with one of the hairpin loop-shaped oligodeoxynucleotides, and a single-stranded 3' end of the promoter being complementary to a single-stranded 5' end of the first double stranded region, and

a termination signal for RNA polymerases with short protruding ends of single-stranded DNA,

a 5' protrusion of the termination signal being capable of specific pairing with a 3' end of the second DNA double stranded region, and a 3' protrusion of the termination signal being capable of specific pairing with one of said hairpin loop-shaped oligodeoxynucleotides.

The claims stand rejected as follows:

Claims 16 and 18–31 under 35 U.S.C. §112, second paragraph, as indefinite;

Claims 16, 18–29, and 31 under pre-AIA 35 U.S.C. § 102(a) as anticipated by Taira;[3] and

Claims 16 and 18–31 under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Agami,[4] Blumenfeld,[5] Wittig,[6] Robbins,[7] and Baer.[8]

INDEFINITENESS

Claims 16 and 18–31 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner finds that "[t]he term 'short' in 'short protruding ends' is a relative term which renders the claims indefinite." Final Act. 3. According to the Examiner, "one of ordinary skill in the art would not be reasonably apprised of the scope of the invention" because "the specification does not provide a standard for ascertaining the requisite degree." *Id.*

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[3] Taira et al., U.S. Patent Application Publication US 2005/0048647 A1, published March 3, 2005.
[4] Agami et al., U.S. Patent Application Publication US 2003/0144239 A1, published July 31, 2003.
[5] Blumenfeld et al., European Patent Application EP 0 572 287 A2, Published December 1, 1993.
[6] Wittig et al, U.S. Patent No. 6,451,563 B1, issued September 17, 2002.
[7] Robbins et al., International Patent Application WO 2004/085623 A2, published October 7, 2004.
[8] Madeline Baer et al., *Structure and transcription of a human gene for H1 RNA, the RNA component of human RNase P*, 18 Nucleic Acids Research 97–103 (1989).

Appellant contends that "the interpretation of the claim term 'short protruding ends' does not rely on the exercise of subjective judgment without restriction." Br. 7. Appellant contends, for example, that "the skilled artisan would understand the 'short protruding ends' to be short compared to the total length of the components to which they are attached." *Id.* Moreover, Appellant contends that the Specification teaches that the purpose of the short protruding ends is to ligate the various components of the vector together (e.g., to ligate the promoter to the hairpin-loop shaped oligo), and "the specification provides concrete examples of the claimed 'short protruding ends,'" e.g., "the protrusions of the constructs shown in Fig. 1 and 2 are four bases long." *Id.*; *see* Spec. 10:31–11:5; Figs. 1 and 2.

We agree with Appellant that "the skilled artisan would understand the scope of the claim term 'short protruding ends'" (*id.* at 8), given the guidance in the Specification. Accordingly, the rejection of claims 16 and 18–31 as indefinite under 35 U.S.C. § 112, second paragraph is reversed.

ANTICIPATION

Claims 16, 18–29, and 31 stand rejected under 35 U.S.C. § 102(e) as anticipated by Taira.

Taira

Taira discloses "an intracellular siRNA expression system capable of producing [RNA interference]" comprising "an antisense code DNA coding for antisense RNA directed against a region of a target gene mRNA, a sense code DNA coding for sense RNA directed against the same region of said target gene mRNA, and one or more promoters." Taira ¶¶ 9, 11.

"[T]he antisense and sense code DNAs are arranged in the opposite orientation on the same DNA strand via a linker" and, once transcribed, "the

linker portion forms a loop and sense and antisense RNA on its both sides pair up (a stem structure)" (*id.* ¶ 83), i.e., "a stem-loop structure in which ends of one side of double-stranded RNA are connected by a [single-stranded] linker RNA" (*id.* ¶ 69; Fig. 28). Taira teaches that "the length of the double-stranded RNA region that is a final transcription product of siRNAs to be expressed is, for example, 15 to 49 bp" and "there is no particular limitation in the length of the linker as long as it has a length so as not to hinder the pairing of the stem portion." *Id.* Finally, Taira discloses at least one siRNA where the double stranded RNA is 19 base pairs in length, and the single-stranded linker is 11 bases in length. *Id.* ¶ 179; SEQ ID NO:21.

Discussion

The Examiner finds that Taira's siRNA expression system meets all the limitations of claim 16, including the requirement that the vector's first double stranded DNA region is linked to the second double stranded region by two 8–12 base single DNA strands, where the two single DNA strands are neither complementary to each other nor self-complementary.

The Examiner finds that Taira teaches that the "linker sequence [of its siRNA] forms a loop of a stem-loop dsRNA" (Final Act. 4 (citing Taira ¶ 83)), and the loop portion of the linker "is neither self-complementary nor double-stranded" (*id.* at 6 (citing Taira ¶ 179)). The Examiner specifically identifies the siRNA represented by Taira's SEQ ID NO:21 as anticipating claim 16, but acknowledges that the linker portion of SEQ ID NO:21 is single-stranded RNA, rather than double-stranded DNA, as required by the claim. Nevertheless, the Examiner contends that "it is *prima facie* apparent to any ordinarily skilled artisan that SEQ ID NO:21 . . . which is referred to

as the 'sequence of the stem-loop siRNA **transcribed**', is transcribed from a DNA sequence." Final Act. 6. Thus, the Examiner contends, "the mere fact that Taira et al. did not disclose the DNA sequence *per se* does not fail to anticipate the DNA sequence limitation." *Id.*

Appellant contends that claim 16 requires, in relevant part, "two single DNA strands linking said first double stranded region with said [second] double stranded region comprising 8–12 bases, said two single DNA strands being not complementary to each other and not self-complementary." Br. 8. Appellant contends that "the fact that the siRNA transcribed from the linker of Taira forms a stem-loop sequence is precisely because that sequence is self-complementary; if it were not, the transcribed sequence would not form the 'stem' of the 'stem-loop' sequence." *Id.* at 9. Appellant further contends that "Taira's failure to disclose the required DNA element is *precisely* why Taira fails to anticipate the rejected claims." *Id.* at 10.

We find that Appellant has the better position. We agree with the Examiner that Taira discloses an siRNA with an 11 base single-stranded non-self-complementary portion (the linking "loop"), and a 19 base pair double-stranded RNA portion (the sense/antisense "stem") targeting the gene to be inhibited. Nevertheless, claim 16 is directed to the vector from which an siRNA is transcribed, and explicitly requires *two single DNA linking strands*, wherein the two single DNA strands are *not complementary to each other and not self-complementary*. To the extent the Examiner finds that Taira discloses that its siRNA is transcribed from a double-stranded DNA expression system we agree, but the Examiner does not point to anything that indicates that the two DNA strands of the linker in Taira's

double-stranded DNA expression system are inherently "not complementary to each other and not self-complementary." It is well settled that "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). We agree with Appellant that "Taira's failure to disclose the required DNA element is *precisely* why Taira fails to anticipate the rejected claims." Br. 10.

Accordingly, we reverse the rejection of claim 16 as anticipated by Taira, as well as the rejection of dependent claims 18–29 and 31.

OBVIOUSNESS

Claims 16 and 18–31 stand rejected under 35 U.S.C. §103 as unpatentable over Agami, Blumenfeld, Wittig, Robbins, and Baer.

Agami

Agami discloses a "vector for expressing short interfering RNAs (siRNAs) to inhibit the expression of a target gene." Agami ¶ 3. Agami's vectors "are DNA molecules capable of integrating into the genome of the target cells allow[ing] for stable, long term expression of the siRNA and hence long term inhibition of the target gene." *Id.* ¶ 18. Agami teaches that the DNA vector "transcribed to generate the siRNA may be double or single stranded nucleic acid" (*id.* ¶ 119), and includes a promoter downstream of the transcription start site, as well as a transcriptional termination element (*id.* ¶¶ 89, 94).

Agami further teaches that the siRNA transcribed from the DNA vector is a short double stranded RNA molecule "compris[ing] a region identical to a region of the sense strand of the target gene and a second

region which corresponds to the antisense strand of the target gene." *Id.* ¶¶ 98, 102. "The two complementary regions are usually separated by a short spacer region such that when the two complementary regions hybridise a stem loop or hairpin structure is formed with the spacer forming the loop." *Id.* ¶ 102.

Discussion

The Examiner finds that Agami teaches "a vector comprising H1 promoter operably linked to a gene sequence in the 5′–3′ direction linked via a li[n]ker sequence to another gene sequence in the 3′–5′ direction" (Final Act. 7) and "a termination signal sequence" (*id.* at 8), "wherein the vector produces a hairpin dsRNA" (*id.* at 7). The Examiner cites Blumenfeld as teaching "that a closed dumbbell oligonucleotide comprising a double-stranded DNA is stabilized and 'resistant to degradation'" (*id.* at 8), and Wittig as teaching "a closed dumbbell construct 'essentially free from contamination by genomic DNA'" (*id.*).

The Examiner concludes that it would have been obvious for one of ordinary skill in the art "to utilize the closed 'dumbbell' oligonucleotide design when making the H1 promoter-containing shRNA [short hairpin RNA] vector of Agami" (*id.* at 9), in order "to make an shRNA vector that is 'resistant to degradation' and 'essentially free from contamination by genomic DNA'" (*id.*).

Appellant reiterates that "the rejected claims require, *inter alia*, 'two single DNA strands linking said first double stranded region with said [second] double stranded region comprising 8–12 bases, said two single DNA strands being not complementary to each other and not self-complementary.'" Br. 11. Appellant contends that "[n]one of the

publications cited by the Examiner disclose or suggest this limitation of the present claims," nor has the Examiner "pointed to any disclosure, either in the cited publications, or elsewhere in the art, that would lead the person of ordinary skill to modify the teachings of the publications . . . in order to incorporate this limitation." *Id.*

The Examiner responds that Agami "discloses the coding strand DNA and template strand DNA sequences in the 5′–3′ direction . . . wherein the linker sequence in each strand is indicated by underlining" (Ans. 9) as shown below:

5'gatccccGTTGGAGCTGTTGGCGTAGttcaagagaCTACGCCAACAGCTCCAACttttggaaa3'
and

5'agcttttccaaaaaGTTGGAGCTGTTGGCGTAGtctcttgaaCTACGCCAACAGCTCCAACggg3'

The above sequences are reproduced from Agami's Example 6, with underlining added by the Examiner. Agami ¶¶ 244–250. According to the Examiner, "Agami's expression system contains two DNA linker sequences (5′- TTCAAGAGA in the coding strand; 5′- TCTCTTGAA in the template strand), wherein the two separated strands of each linker are not complementary." Ans. 10.

According to Agami, however, the two oligonucleotides relied on by the Examiner "were annealed to generate an insert with compatible ends to a BgIII and HindIII digested pSUPER vector." Agami ¶ 245. That being the case, one of the two strands should be read in the 3′–5′ direction, while the other maintains the 5′–3′ direction. When one of the strands is read in the 3′–5′ direction, it is clear that the two linker sequences are perfectly complementary. Thus, the Examiner has not established that Agami discloses "two single DNA strands linking said first double stranded region with said second double stranded region comprising 8–12 bases, said two

single DNA strands being not complementary to each other and not self-complementary" as required by claim 16. Nor has the Examiner explained how the remaining references cited teach or suggest this particular limitation.

Accordingly, we reverse the rejection of claim 16 as unpatentable over Agami, Blumenfeld, Wittig, Robbins, and Baer, as well as the rejection of dependent claims 18–31.

SUMMARY

The rejection of claims 16 and 18–31 as indefinite under 35 U.S.C. § 112, second paragraph is reversed;

The rejection of claims 16, 18–29, and 31 under 35 U.S.C. § 102(e) as anticipated by Taira is reversed; and

The rejection of claims 16 and 18–31 under 35 U.S.C. § 103(a) as unpatentable over Agami, Blumenfeld, Wittig, Robbins, and Baer is reversed.

REVERSED