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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTOPHER E. BRADBURNE and LUCY M. CARRUTH

Appeal 2018-004487
Application 14/768,465
Technology Center 1600

Before ULRIKE W. JENKS, TIMOTHY G. MAJORS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as The Johns Hopkins University of Baltimore, Maryland. Appeal Br. 2.

STATEMENT OF THE CASE

"All influenzas, and many other (-) strand RNA viruses such as Hantaviruses, utilize a 'Cap-Snatching' mechanism to prime the synthesis of their own RNA." Spec. ¶ 7. "During this mechanism, the viral transcriptase cleaves m^7G-capped RNA leader sequences from host mRNAs to prime transcription of the viral genome." *Id.* ¶ 15.

> The Influenza A polymerase complex consists of three viral proteins, PB1, PB2 and PA, which are all required for viral mRNA synthesis. Whilst the role of PA is still unknown, PB2 binds to the 5' cap structure of cellular mRNAs . . . , which activates its endonuclease domain to cleave at a site 10-14 nucleotides downstream the 5' cap structure.

Id. ¶ 17.

RNA interference sequences (RNAi) "inhibit gene expression, typically by causing the destruction of specific mRNA molecules, or by binding complementary nucleotide sequences and inhibiting their transcription or translation by polymerases or ribosomes, respectively." *Id.* ¶ 24.

> Current RNAi technology involves activating the host RNAi machinery in both infected and non-infected host cells, exposing both types to potential toxicity and off-target effects that are common with RNAi-based therapies. The presently disclosed methods only allow for activation of RNAi machinery in infected cells and therefore allow for the treatment, prevention and/or diagnosis of virally-infected subjects and/or cells and tissues with minimal effects to the host since constructs are inactive unless in the presence of Cap-Snatching virus.

Id. ¶ 18.

Claims 1, 2, and 6–12 are on appeal,[2] and can be found in the Claims Appendix of the Appeal Brief. Claim 1, reproduced below, is illustrative of the claimed subject matter:

> 1. An expression vector comprising a polynucleotide coding sequence operably linked to a constitutive promoter, wherein the polynucleotide coding sequence encodes a precursor RNAi construct, wherein the precursor RNAi construct comprises an mRNA molecule comprising:
> (a) a 5' methylguanosine cap leader;
> (b) an 8 to 12 nucleotide sequence immediately downstream from the methylguanosine cap leader; and
> (c) an RNAi sequence immediately downstream from the 8 to 12 nucleotide sequence, the RNAi sequence comprising 20 to 25 nucleotides;
> wherein the mRNA molecule does not comprise a ribosomal binding site, and
> wherein in the presence of a Cap-Snatching virus, the 8 to 12 nucleotide sequence is removed and the RNAi sequence becomes activated.

Appeal Br. 8 (Claims Appendix).

REFERENCES

The prior art relied upon by Examiner is:

Name	Reference	Date
Chen et al. ("Chen")	US 2006/0160759 Al	July 20, 2006
Marisa B. Banasik et al., *Development of an Integrase Deficient Lentiviral Vector for Transient shRNA Expression in Respiratory Epithelia*, 458 Molecular Therapy S385 (2009) ("Banasik")		
Xuezhong Cai et al., *Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs*, 10 RNA 1957–66 (2004) ("Cai")		

[2] Claims 3–5 and 13–32 are withdrawn. Appeal Br. 2.

Alexandre Dias et al., *The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit*, 458 Nature 914–18 (2009) ("Dias")
KV Morris & JJ Rossi, *Lentiviral-mediated delivery of siRNAs for antiviral therapy*, 13 Gene Therapy 553–58 (2006) ("Morris")
Stephen J. Plotch et al., *A unique Cap(m^{7}GpppXm)-Dependent Influenza Virion Endonuclease Cleaves Capped RNAs to Generate the Primers That Initiate Viral RNA Transcription*, 23 Cell 847–58 (1981) ("Plotch")

REJECTION

Appellant requests review of the rejection of claims 1, 2, and 6–12 under 35 U.S.C. § 103 over Chen in view of Morris, Banasik, Dias, Plotch, and Cai.

Analysis

Appellant contends that the element of locating the RNAi sequence immediately downstream from the 8-12 nucleotide sequence is missing from the cited references. Appeal Br. 6. We agree with Appellant that Examiner has not articulated a sufficient rationale to support the conclusion that the claims are obvious.

"'[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."' *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). "[O]bviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Unigene Laboratories, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

To summarize, Examiner relies on Chen for teaching iRNA sequences targeting influenza and expressing these sequences using a viral vector. Ans. 4–5. Chen uses small interfering RNA (siRNA) to suppress influenza virus replication, and tests various influenza A virus siRNAs. Chen ¶ 345. Examiner finds that Chen's SEQ ID NO: 69 has 100% sequence similarity to claimed SEQ ID NO: 1. Ans. 7. Examiner relies on Morris and Banasik for teaching additional elements directed to the viral vector expression system. Ans. 4.

Examiner acknowledges that Chen does not teach "a mRNA comprising: (a) a 5'methylguanosine cap leader, (b) an 8-12 nucleotide sequence immediately downstream from the cap leader, and (c) an iRNA sequence immediately downstream from the 8 to 12 nucleotide sequence, wherein the mRNA molecule does not comprise a ribosomal binding site" as required by claim 1. Ans. 4.

Examiner relies on Dias and Plotch for teaching the cap-snatching mechanism utilized by influenza virus. Ans. 5. Specifically, Dias teaches that influenza virus polymerase (comprising PA, PB1, and PB2 subunits) is responsible for replication and transcription of the viral RNA. Dias Abstract. "The PB2 subunit binds the 5' cap of host pre-mRNAs[], which are subsequently cleaved after 10-13 nucleotides by the viral endonuclease." *Id.* Plotch teaches these eukaryotic RNA caps with their attached nucleotides act as primers for the synthesis of influenza viral mRNA and transfer their 5′-terminal methylated cap structure and short stretch of nucleotides (about 10-15) to the viral mRNA. Plotch 847. Both Dias and Plotch suggest that the target for inhibition is the polymerase involved in the host cap-snatching mechanism. Dias 918 ("These observations will be

helpful in developing potential new antivirals using a structure-based approach."); Plotch 856 ("[If] a cap-recognizing endonuclease is unique to influenza virions, it might be an ideal target for specific anti-influenza virus drugs"). Neither Dias, nor Plotch, suggests using the cap-snatching mechanism itself to activate the therapeutic molecule, i.e., the recited iRNA sequence. Because mRNA missing the 5' cap is more prone to degradation, one of ordinary skill in the art would not have recognized that removing protecting structures from cellular RNA would result in a new beneficial structure. Indeed the ordinary artisan would have expected the RNA to degrade and not be further available. Plotch 856 ("[I]nitial removal of the capped 5′ end of a mRNA by a cap-dependent endonuclease would facilitate subsequent RNA degradation.").

Finally, Examiner directs our attention to Cai for teaching "microRNA molecules [a type of iRNA that] can be derived from pri-miRNA transcripts that are capped with a 5' 7-methylguanosine (m7G) cap and a 3' poly(A) tail." Ans. 5.

Cai teaches that "[a] defining characteristic of almost all eukaryotic mRNAs is that they are terminally modified by addition of a 5' 7-methyl guanylate (m7G) cap and a 3' poly(A) tail." Cai 1958. "MicroRNAs (miRNAs) are ~22-nt noncoding RNAs expressed in a wide range of eukaryotic organisms." *Id.* 1957. According to Cai, the biological function of miRNAs in humans is not well known, but in other cell systems they have been shown to inhibit the expression of mRNAs bearing complementary sequences. *Id.* Cai teaches that "miRNAs are initially expressed as part of one arm of an imperfect ~80-nt RNA hairpin that, in turn, forms part of a longer transcript termed a primary miRNA (pri-miRNA)." *Id.* The pri-

miRNA can serve as a precursor for the embedded mature miRNA. *Id.* at 1959. Cai explains that the pri-miRNA is processed by two RNase III enzymes Drosha and Dicer to produce a 20 nucleotide duplex. *Id.* at 1957. Cai teaches that the 80 nt structure is first degraded to a 65 nt structure and ultimately degraded to a 20 nt miRNA structure. Cai, however, does not disclose limiting the distance between the cap structure and the miRNA sequence to 8-12 nt.

What is missing from Examiner's analysis is evidence that an ordinarily skilled person would have a reason to look to Cai's miRNA processing using cellular RNAase enzymes that differ structurally and functionally from the influenza polymerases to arrive at the mRNA structure as claimed. *See KSR*, 550 U.S. at 418 (obviousness rejections require "some articulated reasoning with some rational underpinning").

Accordingly, the evidence of record does not support Examiner's conclusion that the claimed mRNA structure is obvious.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 6–12	103	Chen, Morris, Banasik, Dias, Plotch, Cai		1, 2, 6–12

REVERSED